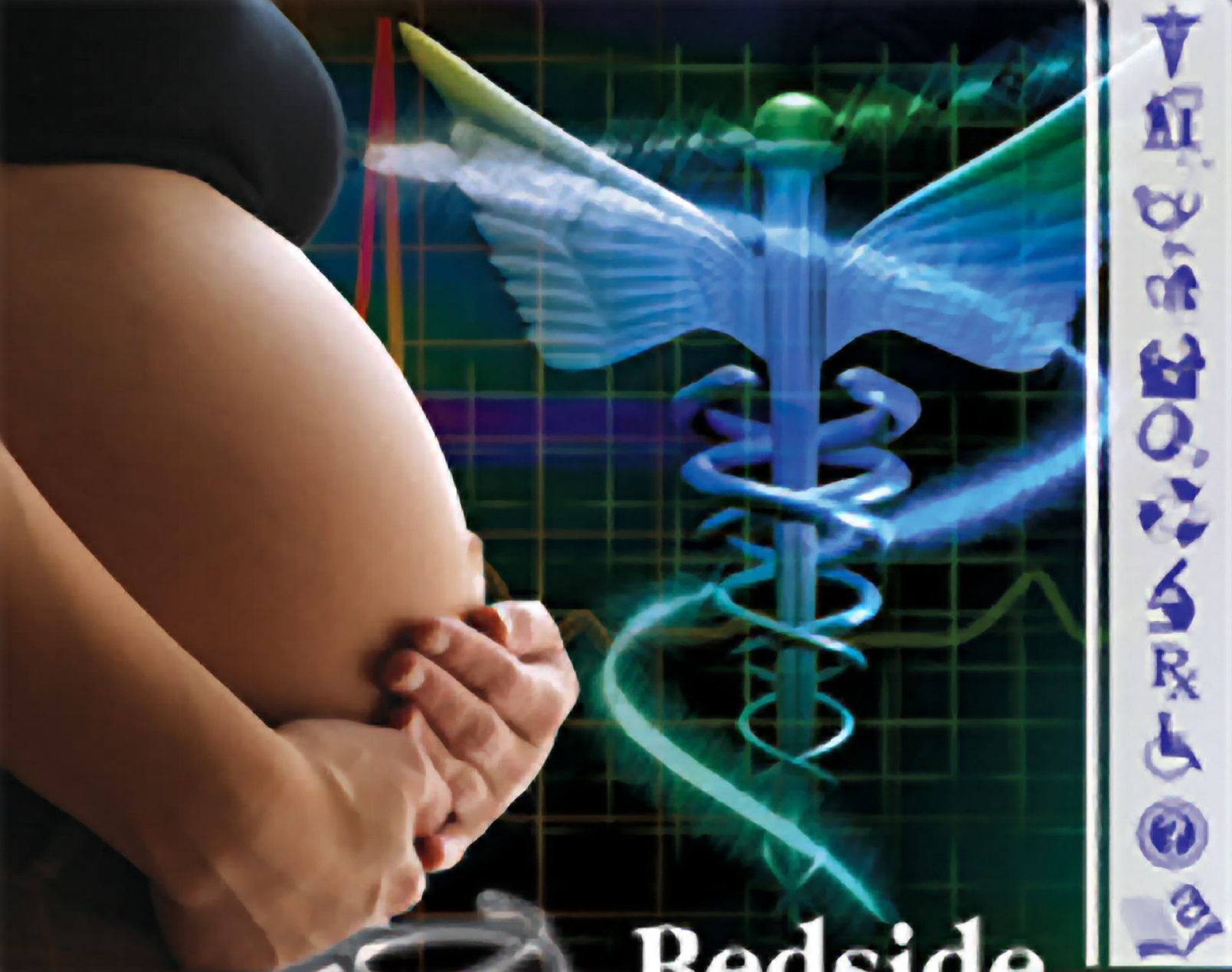


Bedside OBSTETRICS & GYNECOLOGY

Richa Saxena

JAYPEE

Bedside Obstetrics and Gynecology

Bedside Obstetrics and Gynecology

Richa Saxena
MBBS MD (Obstetrics and Gynecology)
PG Diploma in Clinical Research
New Delhi, India

JAYPEE BROTHERS MEDICAL PUBLISHERS (P) LTD

New Delhi • St Louis (USA) • Panama City (Panama) • London (UK) • Ahmedabad
Bengaluru • Chennai • Hyderabad • Kochi • Kolkata • Lucknow • Mumbai • Nagpur

Published by
Jitendar P Vij
Jaypee Brothers Medical Publishers (P) Ltd

Corporate Office
4838/24 Ansari Road, Daryaganj, **New Delhi** - 110002, India
Phone: +91-11-43574357, Fax: +91-11-43574314

Registered Office
B-3 EMCA House, 23/23B Ansari Road, Daryaganj, **New Delhi** - 110 002, India
Phones: +91-11-23272143, +91-11-23272703, +91-11-23282021
+91-11-23245672, Rel: +91-11-32558559, Fax: +91-11-23276490, +91-11-23245683
e-mail: jaypee@jaypeebrothers.com, Website: www.jaypeebrothers.com

Offices in India
- **Ahmedabad**, Phone: Rel: +91-79-32988717, e-mail: ahmedabad@jaypeebrothers.com
- **Bengaluru**, Phone: Rel: +91-80-32714073, e-mail: bangalore@jaypeebrothers.com
- **Chennai**, Phone: Rel: +91-44-32972089, e-mail: chennai@jaypeebrothers.com
- **Hyderabad**, Phone: Rel:+91-40-32940929, e-mail: hyderabad@jaypeebrothers.com
- **Kochi**, Phone: +91-484-2395740, e-mail: kochi@jaypeebrothers.com
- **Kolkata**, Phone: +91-33-22276415, e-mail: kolkata@jaypeebrothers.com
- **Lucknow**, Phone: +91-522-3040554, e-mail: lucknow@jaypeebrothers.com
- **Mumbai**, Phone: Rel: +91-22-32926896, e-mail: mumbai@jaypeebrothers.com
- **Nagpur**, Phone: Rel: +91-712-3245220, e-mail: nagpur@jaypeebrothers.com

Overseas Offices
- **North America Office, USA,** Ph: 001-636-6279734
  e-mail: jaypee@jaypeebrothers.com, anjulav@jaypeebrothers.com
- **Central America Office, Panama City, Panama,** Ph: 001-507-317-0160
  e-mail: cservice@jphmedical.com, Website: www.jphmedical.com
- **Europe Office, UK,** Ph: +44 (0) 2031708910
  e-mail: info@jpmedpub.com

Bedside Obstetrics and Gynecology

First Edition : **2010**

ISBN 978-81-8448-988-0

Typeset at JPBMP typesetting unit

Printed at Ajanta Offset & Packagings Ltd., New Delhi

Dedicated to

My Mother, Mrs Bharati Saxena

and all the Mothers

Who have undergone much pain and sufferings for their children.

A mother is the most trusted friend we have, when trials, heavy and sudden, fall upon us;
When adversity takes the place of prosperity; when friends who rejoice with us in our sunshine, desert us;
When troubles thicken around us, still she will cling to us
and counsel to dissipate the clouds of darkness, causing peace to return to our hearts;
and has proven time and time again that no matter whatever circumstances may come between mother and her children, their lives are interwoven forever.

— Washington Irving

Preface

Father, lead me day by day, ever in thy own sweet way.
Teach me to be pure and good and tell me what I ought to do.
—Amen

I strongly believe that no task whatsoever in this world can be accomplished without His permission and divine intervention. With this in mind, I have started this preface with a small prayer of thanks to the Almighty, which I was taught in my childhood.

The concept of a bedside book is not new, but is a novel one and unique in itself. It may sound funny, but when I told a non-medical editor from a reputed publishing house that I was writing a book titled, "Bedside Obstetrics and Gynecology", he laughed asking whether the book is meant to remain at the bedside of the patient or the doctor? Jokes apart, who else other than the medical personnel would know the importance of the education which takes place at the patient's bedside. In today's world of scientific advancement and technology, the clinical art of medicine is sadly dying off ...

The doctors today do not believe in auscultating the patient's chest or merely palpating the patient's abdomen. A stethoscope can diagnose a consolidated lung suggestive of Kochs at a much earlier stage than a chest X-ray or even a bronchoscopic-guided biopsy. Hence, it is important for the medical personnel to become acquainted with the skills of taking history and performing a clinical examination. The purpose of the book is to promote the art of good history taking and clinical examination, and reaching the final diagnosis by obtaining only a few selective investigations or special evaluations. The book highlights the classical and systematic approach towards diagnosis of the disease. Each case study has been carefully designed to simulate the clinical practice scenarios as far as possible in order to evoke the right patient approach and clinical decision making. Unlike the small clinical vignettes described in most other books, detailed explanation of the pathology relevant to the case study in question has been described in all the chapters. One of the key features of this book is its versatility. Not only will the book be useful to the undergraduates who are required to get acquainted with the clinical examination skills but also for the busy postgraduates who are in the rush to go through the clinical scenarios.

I believe that writing a book involves a continuous learning process. Though extreme care has been taken to maintain accuracy while writing this book, constructive criticism shall be greatly appreciated. Please e-mail me your comments at *richasaxena@womanhealthsimplified.com.* Also, please feel free to refer your patients to my website titled *www.womanhealthsimplified.com* for obtaining information related to various health-related issues of women.

I wish to express my thanks and appreciation to all the related authors and publishers whose references have been used in this book. It is needless to say that this book would not have been possible without the encouragement and support of Shri Jitendar P Vij (Chairman and Managing Director) and Mr Tarun Duneja (Director-Publishing) of M/s Jaypee Brothers Medical Publishers (P) Ltd, New Delhi. Last but not the least, I would like to thank the entire team of Jaypee Brothers Medical Publishers who worked sincerely on this book, especially the production manager and coordinators, who streamlined the process of publishing and the entire team of creative designers, artists, operators and the editorial board who worked hard on this book. May God bless them all!

Richa Saxena
e-mail: richasaxena@womanhealthsimplified.com
website: www.womanhealthsimplified.com

Contents

PART I: OBSTETRICS

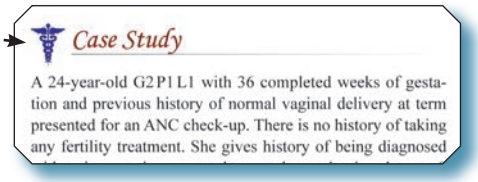
PART II: GYNECOLOGY

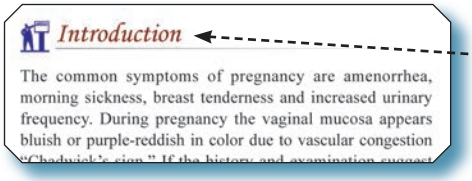
Introduction

As previously described, this book emphasizes the patient rather than the disease. For example, a patient may be presenting with jaundice, fever, and malaise, but the actual diagnosis may turn out to be hepatitis. So simply knowing about hepatitis is not enough, one needs to have the ability to diagnose the condition based on the findings of history and clinical examination. Promoting clinical acumen is the basic purpose of this book. Each chapter has been written keeping in mind the clinical presentation of the patient. Various clinical scenarios have been divided into seven sections in all, out of which the first three deal with obstetrics and last four with gynecology. All the chapters have been divided into various subparts with the help of the symbols as described below:

Case Presentation

A typical patient presenting with a relevant pathology



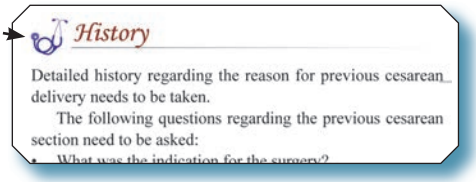


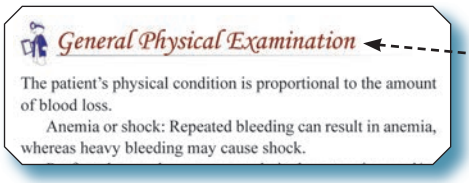
Introduction

A brief introduction related to etiology and pathogenesis of the disease in consideration

History

The distinctive clinical features, complaints and the probable risk factors with which the patient presents



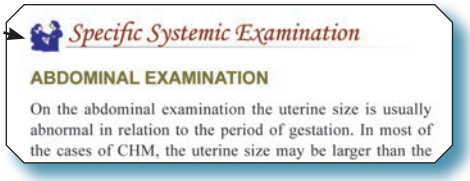


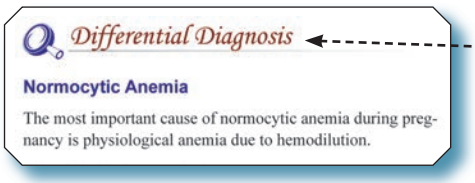
General Physical Examination

The typical clinical findings of the relevant disease on general physical examination (GPE)

Specific Systemic Examination

The typical findings of the relevant disease on specific systemic examination, particularly abdominal and pelvic examination



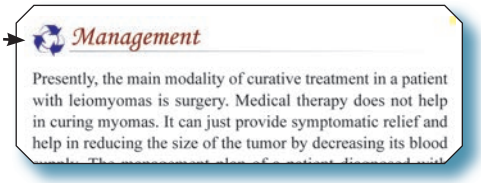


Differential Diagnosis

Other diseases which must be ruled out before arriving at the exact diagnosis

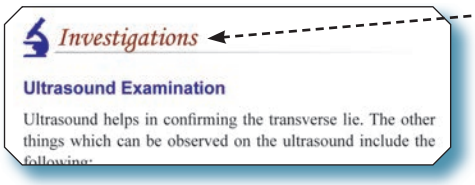
Management

Plan of management of the relevant disease



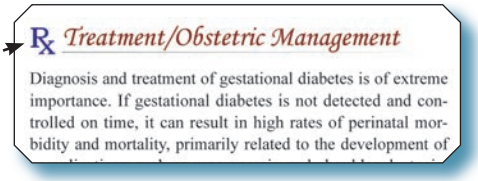
Investigations

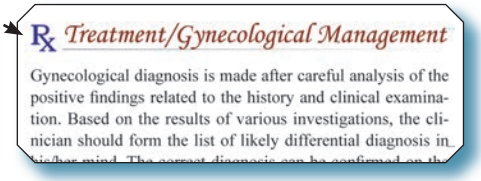
The investigations which may be ordered to confirm the correct diagnosis



Treatment

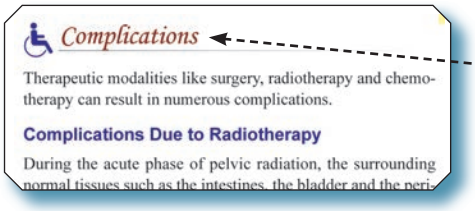
Most appropriate treatment strategy for the diagnosed disease





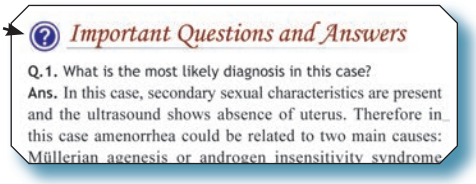
Complications

The complications which are likely to occur if the disease remains untreated



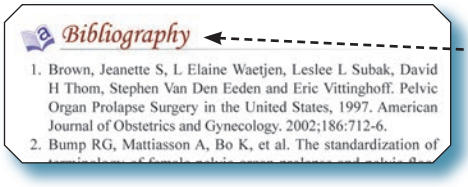
Important Questions and Answers

Relevant information which could not be included in the above mentioned sub-headings



Bibliography

List of references to enable the readers gain deeper insight of the subject

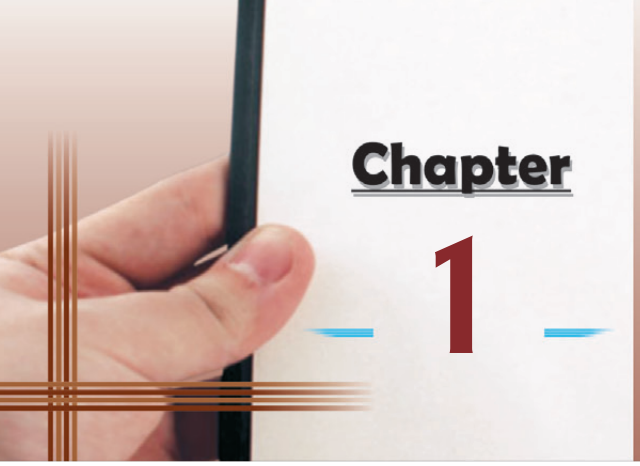


Obstetrics

Section 1

Normal and Abnormal Presentations

- Normal Pregnancy
- Breech Presentation
- Transverse Lie



Chapter 1

Normal Pregnancy

Case Study

A 34-year-old primigravida patient is seen at the antenatal clinic at 37 weeks gestation. She is clinically well and reports normal fetal movements. The fetal heart rate is 144 beats per minute. The S-F height which was 35 cm at the time of previous antenatal visit, last week, is presently 34 cm. Also at the time of previous visit, the fetal head was freely ballotable above the pelvic brim and presently is just 2/5 above the brim. The patient is reassured that she and her fetus are healthy and she is asked to attend the antenatal clinic again in a week's time.

Introduction

The common symptoms of pregnancy are amenorrhea, morning sickness, breast tenderness and increased urinary frequency. During pregnancy the vaginal mucosa appears bluish or purple-reddish in color due to vascular congestion "Chadwick's sign." If the history and examination suggest that a patient is pregnant, the diagnosis is easily confirmed by urine pregnancy test. The test becomes positive by the time the first menstrual period is missed.

Table 1.1: Differentiating between intrauterine and extrauterine pregnancy

	Intrauterine pregnancy	*Extrauterine pregnancy*
Size of the uterus	Appropriate for the duration of pregnancy	Uterine size is smaller than the period of gestation
Pain abdomen	Absent	Present
Vaginal bleeding	Absent	Present
Vaginal/abdominal tenderness	Absent	Present
Bimanual vaginal examination	No adnexal tenderness or mass	Tender, vague adnexal mass, thickening or fullness is present
Cervical excitation	Absent	Present

It is customary to divide the entire period of gestation into three trimesters: First trimester (until 14 weeks); second trimester (15–28 weeks); third trimester (29–42 weeks).

A positive pregnancy test is, however, produced by both an intrauterine and an extrauterine pregnancy. Extrauterine pregnancy if undiagnosed can present as an obstetric emergency. Therefore, it is important to establish whether the pregnancy is intrauterine or not on the clinical examination (table 1.1). If the clinical examination appears to be suggestive of extrauterine pregnancy, the diagnosis needs to be confirmed by ultrasound examination.

History

Frequency of Antenatal Visits

There is no fixed timing or frequency for antenatal visits. The number of antenatal visits may vary from center to center. Increased number of visits may be required in a patient with high risk of complications. Nevertheless there should be at least four antenatal visits during normal pregnancy: First visit at 16 weeks, second visit between 24–28 weeks, third visit at 32 weeks and fourth visit at 36 weeks.

History at the Time of First Antenatal Visit

The aim of history taking is to determine the period of gestation and thereby expected date of delivery. History taking also helps in determining if the pregnancy is associated with any high risk factors. Taking appropriate history helps the obstetrician determine the further management and mode of delivery. A full history comprising of the following needs to be elicited:

- Menstrual history
- Previous obstetric history
- Present obstetric history
- Medical history
- Treatment history
- Surgical history
- Family history

- Social history
- Personal history

Menstrual History

It is important to elicit the proper history regarding the last normal menstrual period (LMP).

It is also important for the obstetrician to find out if the previous cycles were normal and regular or not. It may be difficult to establish the LMP accurately when the woman had been previously experiencing irregular cycles. The obstetrician must also enquire about the length of periods and amount of bleeding. Excessive amount of menstrual blood loss in previous cycles may be associated with anemia.

LMP can be used for calculating the expected date of delivery (EDD). To calculate the expected date of deliver, seven days are added to the first day of LMP and then nine months are added to this date. For example, if the LMP was on 2-2-2009, the EDD will be on 9-11-2009. If the LMP was 27-10-2008, the EDD will be 3-8-2009. This method of estimating EDD is known as the Naegele's rule. This rule can also be applied by adding seven days to the first day of LMP, subtracting three months and then adding one year to this. The rule should be used to measure the duration of pregnancy, only if the patient had been having regular menstrual cycles previously.

The history of using steroidal contraception prior to conception is important as in this case EDD may not be accurately determined with help of Naegele's rule. This is so as ovulation may not immediately resume following withdrawal bleeding; there may be a delay of 2–3 weeks.

Previous Obstetric History

The woman's past obstetric history must be denoted by the acronym GPAL, where G stands for gravida, P for parity, A for number of abortions and L for number of live births. It is also important to ask the woman, how long she has been married.

Gravida: This refers to the number of pregnancies, including the present pregnancy the woman has ever had. This is irrespective of the fact whether the pregnancies were viable at the time of birth or not.

Nulligravida: This implies a woman who has never been pregnant.

Primigravida: This stands for a woman who is pregnant for the first time (Gravida 1).

Multigravida: This stands for a woman who has had at least one previous pregnancy, irrespective of whether was viable or not (depending on the number of previous pregnancies, she could be gravida 2, 3, or more). For example, a woman has had three previous pregnancies and is now pregnant for the fourth time will be gravida 4.

Abortions: Number of the pregnancies which have terminated before reaching the point of viability. The obstetrician must give their exact gestational period and also mention whether they were spontaneous or induced abortions; the reason for the induced abortion also needs to be asked.

Viabality: Refers to the ability of the fetus to live outside the uterus after birth.

Parity: Refers to the number of previous viable pregnancies (including infants who were either stillborn or born alive). Parity is determined by the number of viable pregnancies and not by the number of fetuses delivered. Thus parity does not change even if twins or triplets are born instead of a singleton fetus. Previous multiple viable pregnancies are shown as twins +1, triplets +2; etc.

For example, if one of the viable pregnancies of this female produced twins, alive or still born, she will be gravida 4, para 2+1.

If the first viable pregnancy produced twins and the second viable pregnancy produced quadriplet, she will be gravida 4 para 2+1+3.

Nullipara: A women who has never carried a previous pregnancy to a point of viability (para 0).

Primipara: Woman who has had one previous viable pregnancy (para 1). For example if the woman is gravida 4 and only 2 of the previous pregnancies of this woman were viable, she would be gravida 4, para 2.

Multipara: Woman who has had two or more previous viable pregnancies (para 2, 3, or more).

Grand multipara: Woman who has had 5 or more previous viable pregnancies (para 5, 6 or more)

A woman is considered as a high risk mother, if she is either a primigravida or nullipara over the age of 30 or if she is a young teenaged primigravida or if she is a grand multipara.

It is important to take the history of previous pregnancies including history of previous abortions (period of gestation < 24 weeks), precipitate labor, preterm pregnancies (period of gestation < 37 completed weeks), abnormal presentations, preeclampsia or eclampsia, cesarean section, retained placenta, postpartum hemorrhage, stillbirths, history of episiotomies, perineal tears, and history of receiving epidural anesthesia during the previous pregnancies. History about any episodes of hospitalization during previous pregnancies can be helpful. History of complications during previous pregnancy such as preeclampsia, placenta previa, abruption placenta, IUGR, polyhydramnios or oligohydramnios is important because many complications in previous pregnancies tend to recur in subsequent pregnancies. For example,

patients with a previous history of perinatal death or spontaneous preterm labor are at high risk of perinatal death or preterm labor during their future pregnancies respectively. Patients who develop preeclampsia before 34 weeks gestation have a greater risk of preeclampsia in further pregnancies. Multiple pregnancy, especially the previous history of nonidentical twins tend to recur in subsequent pregnancies. It is also important to take the history of previous pregnancy losses. A history of three or more successive first trimester miscarriages suggest a possible genetic abnormality in the father or mother. Previous mid trimester miscarriages could be associated with cervical incompetence. Patient may often forget to give the history about previous miscarriages and ectopic pregnancies. Therefore the obstetrician needs to ask specifically about the history of previous miscarriages and ectopic pregnancies. Approximate birth weights of previous children and the approximate period of gestation, especially if the infant was low-birth weight or preterm, are useful. Low-birth weight at the time of birth is indicative of either intrauterine growth restriction or preterm delivery. On the other hand, large sized infants point towards the possibility of maternal diabetes.

It is important to know if the woman has had a long labor during her previous pregnancy, as this may indicate cephalopelvic disproportion. History of previous birth in form of assisted delivery, including forceps delivery, vacuum application and cesarean section, suggest that there may have been cephalopelvic disproportion. In case of previous cesarean delivery, a detailed history of the previous surgery needs to be taken. The patient should always be asked if she knows the reason for having had a cesarean section. She should be asked to show the hospital notes related to the surgery. This may help provide some information regarding the type of incision made in the uterus, any complications encountered during the surgery, etc. Detailed history of the previous live births as well as of previous perinatal deaths is important. The following points need to be elicited:

The birth weight of each infant born previously

This is important as previous low birth weight infants or spontaneous preterm labors tend to recur during future pregnancies. Also, history of delivering a large sized baby in the past is suggestive of maternal diabetes mellitus or gestational diabetes, which may recur during subsequent pregnancies.

Method of delivery of each previous infant

The type of previous delivery is also important because a forceps delivery or vacuum extraction may suggest that some degree of cephalopelvic disproportion may have been present. If the patient had a previous cesarean section, the indication for the cesarean section must be determined.

History of previous perinatal deaths

Previous history of having had one or more perinatal deaths in the past places the patient at high risk of further perinatal deaths. Therefore, every effort must be made to find out the cause of any previous deaths. If no cause can be found, then the risk of a recurrence of perinatal death is even higher.

The Present Obstetric History

Regarding the present pregnancy, the following points need to be considered:

- The first day of the last normal menstrual period must be determined as accurately as possible. The obstetrician must ask the patient how long she had been married or has been in relationship with the present partner. The obstetrician must also ask the women if she had previously received any treatment for infertility. The patient must be asked if the present pregnancy is a planned one; and since how long she had been planning this pregnancy. Did she ever use any contraceptive agents in the past?
- The obstetrician needs to take the history of any medical or obstetric problems which the patient has had since the start of this pregnancy, for example, pyrexial illnesses (such as influenza) with or without skin rashes; symptoms suggestive of a urinary tract infection and history of any vaginal bleeding.
- Enquiry must be also made regarding normal symptoms related to pregnancy, which the patient may be experiencing, for example, nausea and vomiting, heartburn, constipation, etc.

Medical History

Patients must be specifically asked about the previous medical history of diabetes, epilepsy, hypertension, renal disease, rheumatic disease, heart valve disease, epilepsy, asthma, tuberculosis, psychiatric illness or any other significant illness she may have had in the past. She should also be asked if she had any allergies (specifically allergy to penicillin) in the past.

Treatment History

The woman must be asked if she has previous history of allergy to any drugs, history of receiving immunization against tetanus or administration of Rh immune globulins during her previous pregnancies. The patient must be asked if she had received any treatment in the past (e.g. hypoglycemic drugs, antihypertensive drugs, etc). Certain drugs may be

teratogenic to the fetus during the first trimester of pregnancy, e.g. retinoids, which are used for acne and anticoagulant drugs like warfarin. Also certain drugs which the women may be regularly taking prior to pregnancy are relatively contraindicated during pregnancy, e.g. antihypertensive drugs like ACE inhibitors, β-blockers, etc.

History regarding any previous hospital admission, surgery, blood transfusion, etc also needs to be taken. It is important to elicit the patient's medical history as some medical conditions may become worse during pregnancy, e.g. a patient with heart valve disease may go into cardiac failure, while a hypertensive patient is at high risk of developing preeclampsia.

Surgical History

The woman must be enquired if she ever underwent any surgery in the past such as cardiac surgery, e.g. heart valve replacement; operations on the urogenital tract, e.g. cesarean section, myomectomy, cone biopsy of the cervix, operations for stress incontinence and vesicovaginal fistula repair, etc.

Family History

Family history of medical condition such as diabetes, multiple pregnancy, bleeding tendencies or mental retardation increases the risk of development of these conditions in the patient and her unborn infant. Since some birth defects are inherited, it is important to take the history of any genetic disorder, which may be prevalent in the family.

Social History

It is important to elicit information regarding the patient's social circumstances. The patient should be specifically asked if she has been smoking or consuming alcohol. Smoking and alcohol both may cause intrauterine growth restriction. Additionally, alcohol may also cause congenital malformations. The mother should be asked if she has social or family support to help her bring up the baby, for example a working mother may require assistance to help her plan the care of her infant. Social problems like, unemployment, poor housing and overcrowding increase the risk of mother developing medical complications like tuberculosis, malnutrition and intrauterine growth restriction. Patients living in poor social conditions need special support and help. Sometimes it may become difficult to ask the patient directly regarding her socio-economic status. In these cases taking the history regarding the occupation of the husband or partner is likely to give clues regarding the patient's socio-economic history. Classification of the women based on their socio-economic status is usually done using the Kuppuswamy Prasad's classification system (1961), which is based on the per capita monthly income.

Personal History

Behavioral factors (smoking or tobacco usage, alcohol usage, utilization of prenatal care services, etc).

Family Planning

The patient's family planning needs and wishes should be discussed at the first antenatal visit. If she is a multipara having at least two live babies, she should be counseled and encouraged for postpartum sterilization. In case the woman is not willing to undergo permanent sterilization procedure, the patient's wishes should be respected; she can be offered temporary methods of contraception like OCP's, cu-T, etc.

General Physical Examination

The general appearance of the patient is of great importance as it can indicate whether or not she is in good health. A woman's height and weight may reflect her past and present nutritional status.

The signs which must be carefully looked for in a pregnant woman include the following:

- Pallor
- Edema
- Jaundice
- Enlarged lymph nodes (neck, axillae and inguinal areas)
- The thyroid gland: The obstetrician must look for an obviously enlarged thyroid gland (goiter).

In case, there is obvious enlargement of the thyroid gland or it feels nodular, the patient must be referred for further investigations.

Examination of the Breasts

The breasts should be examined with the patient both sitting and lying on her back, with her hands above her head.

Inspection

Both the breast must be inspected for the presence of any obvious gross abnormalities. The obstetrician must particularly look for any distortion of the breasts or nipples. The nipples should be specifically examined with regard to their position and deformity (if any), discharge, inversion and areola. Presence of any eczema of the areola must also be noted.

Palpation

Both the breasts must be palpated with the palm of the hand rather than fingers for the presence of any lumps, masses, etc.

In case there is presence of a breast lump or a blood stained discharge from the nipple, the patient must be sent for a surgical referral and further investigations for diagnosis of a likely malignancy.

Whenever possible, all HIV negative pregnant women must be advised and encouraged to breast feed. The clinician must make special efforts to emphasize the importance of breastfeeding and to teach its advantages to the women.

Hoffman's exercises

In case the nipples are found to be inverted or flat, this condition must be treated as soon as possible so that the patient may be able to breast feed successfully in future. The easiest way of correcting inverted nipples involves the use of Hoffman's exercises, which are performed as described below:

- The thumbs are placed on either side of the base of the nipple
- The thumbs are then moved towards the periphery of the areola. This is done in both vertical and horizontal directions.

This exercise must be repeated several times per day throughout pregnancy in order to bring the nipples in their normal position. The patient should be taught to do these exercises herself.

Specific Systemic Examination

During pregnancy a detailed abdominal and vaginal examination may be required. Besides this, the other body systems like the respiratory system and the cardiovascular system must also be briefly examined. In case any pathological sign is observed, a detailed examination of the respective body system must be carried out.

ABDOMINAL EXAMINATION IN ANTENATAL PERIOD

General Examination of the Abdomen

Even in the present time of technological advancements, the obstetricians must not underestimate the importance of clinical abdominal examination. In the Western countries technological gadgets like ultrasound and cardiotocography have largely replaced the abdominal examination. In developing countries, many hospitals do not have facilities for electronic monitoring. When intermittent auscultation is used to monitor the baby, the contractions are not constantly monitored, as they would be with continuous electronic monitoring. In these cases, the clinician needs to assess the abdominal contractions through the method of abdominal palpation. The abdominal examination should comprise of the following:

- Estimation of height of uterine fundus
- Obstetric grips (Lepold's maneuvers)
- Uterine contractions
- Estimation of fetal descent
- Auscultation of fetal heart

Each of these would be described below in details:

Preparation of the Patient for Examination

- Before starting the abdominal examination, the clinician should ensure that the patient's bladder is empty; she should be asked to empty her bladder in case it is not empty.
- The patient must lie comfortably on her back with a pillow under her head. She should not lie in a left lateral position.

Inspection of the Abdomen

The following should be specifically looked for at the time of abdominal inspection:

The shape and size of the distended abdomen

- In case of a singleton pregnancy and a longitudinal lie, the shape of the uterus is usually oval.
- The shape of the uterus will be round with a multiple pregnancy or polyhydramnios.
- The flattening of the lower part of the abdomen suggests a vertex presentation with an occipito-posterior position (ROP or LOP).
- A suprapubic bulge is suggestive of a full bladder.

The presence or absence of scars

In case scar marks as a result of previous surgery are visible, a detailed history must be taken. This should include the reasons of having the surgery and the type of surgery performed (myomectomy or previous LSCS). In case the scar is related to previous LSCS, detailed history as described in chapter 7 needs to be taken.

Presence of stria gravidarum and linea nigra

In many pregnant women, a black-brownish colored line may sometimes develop in the midline of the abdomen. This is known as linea nigra. In many woman, in later months of pregnancy, stretch marks called stria gravidarum may develop over the skin of abdomen, breast or thighs.

Abdominal Palpation

Besides the fetal and uterine palpation, other abdominal organs like the liver, spleen and kidneys must also be specifically palpated. Presence of any other abdominal mass should also be noted.

The presence of an enlarged organ, or a mass, should be appropriately followed up.

Examination of the Uterus and the Fetus

- The clinician must firstly check whether the uterus is lying in the midline of the abdomen or it is dextroratotated either to the right or the left. In case the uterus is dextrorotated, it needs to be centralized.

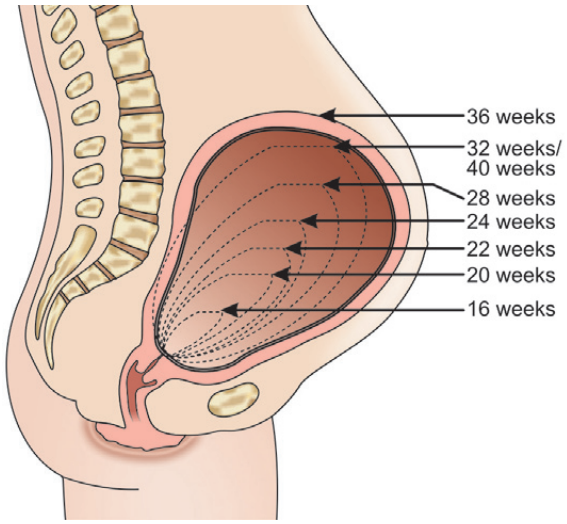


Fig. 1.1: Abdominal measurement of period of gestation

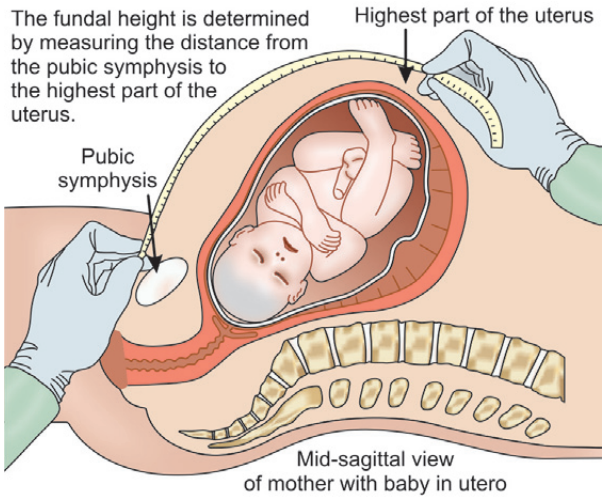


Fig. 1.2: Measurement of sympysio-fundal height

- The wall of the uterus must be palpated for the presence of any irregularities. An irregular uterine wall may be suggestive of either the presence of myomas or a congenital abnormality such as a bicornuate uterus. Uterine myomas may enlarge during pregnancy and become painful.

Determining the Fundal Height

In the first few weeks of pregnancy, there is primarily an increase in the anterior posterior diameter of the uterus. By 12 weeks, the uterus becomes globular and attains a size of approximately 8 cm. On the bimanual examination, the uterus appears soft, doughy and elastic. In the initial stages of pregnancy the cervix may appear firm. However with increasing period of gestation, the cervix becomes increasingly softer in consistency. From the second trimester onwards, the uterine height starts corresponding to the period of gestation. The rough estimation of fundal height with increasing period of gestation is shown in figure 1.1.

Measurement of Symphysio-Fundal Height (Figure 1.2)

After centralizing the dextrorotated uterus, the upper border of the fundus is located by the ulnar border of left hand and this point is marked by placing one finger there. The distance between the upper border of the symphysis and the marked point is measured in cm with help of a measuring tape. After 24 weeks, the symphysio-fundal height, measured in centimeters corresponds to the period of gestation up to 36 weeks. Though a variation of 2 cm (more or less) is regarded as normal, there are numerous conditions where the height of uterus may not correspond to the period of gestation.

However estimation of period of gestation from the fundal height is not a fool proof method as there are certain conditions where height of the uterus can be more than the period of gestation as well as the conditions where height of the uterus is less than the period of gestation.

Determining the size of the uterus through estimation of fundal height

- After centralizing the dextrorotated uterus with right hand, the upper border of the uterus is estimated with the ulnar border of the left hand. Anatomical landmarks used for determining the size of uterus through estimation of fundal height mainly include the symphysis pubis and the umbilicus:
  - If the fundus is palpable just above the symphysis pubis, the gestational age is probably 12 weeks.
  - If the fundus reaches half way between the symphysis and the umbilicus, the gestational age is probably 16 weeks.
  - If the fundus is at the same height as the umbilicus, the gestational age is probably 22 weeks (one finger under the umbilicus = 20 weeks and one finger above the umbilicus = 24 weeks).
  - The distance between the xiphisternum and umbilicus is divided into three equal parts. Upper one-third corresponds to 28 weeks; upper two-third corresponds to 32 weeks whereas the tip of xiphisternum corresponds to 36 weeks. At 40 weeks due to the engagement of fetal head, the height of the uterus reduces slightly and corresponds to the level of 32 weeks.

At every antenatal visit from 28 weeks gestation onwards, the wellbeing of the fetus must be assessed. Having

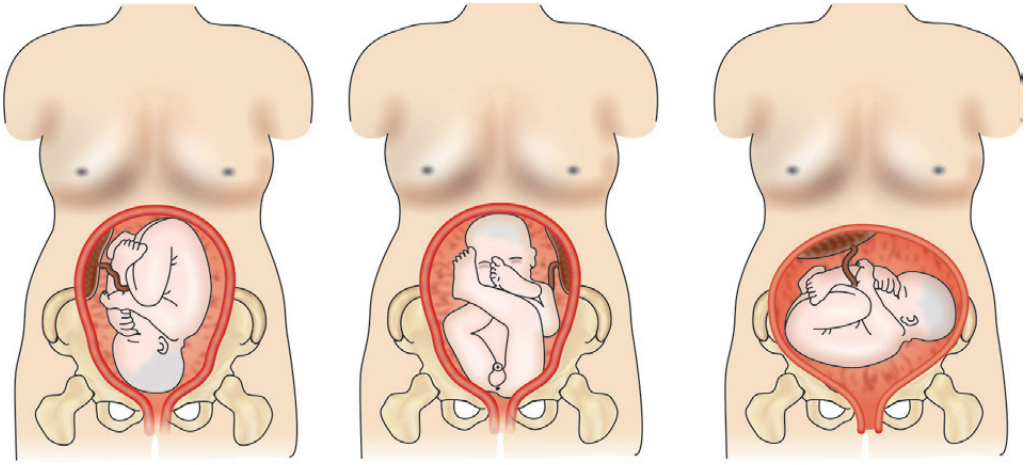


Fig. 1.3: Types of fetal lie

determined the height of the fundus, the clinician needs to assess whether the height of the fundus corresponds to the patient's dates and to the size of the fetus. From 18 weeks, the S-F height must be plotted on the S-F growth curve to determine the gestational age. This method is, therefore, only used once the fundal height has reached 18 weeks. In other words when the S-F height has reached two fingers width under the umbilicus.

Palpation of the Fetus

The lie and presenting part of the fetus only becomes important when the gestational age reaches 34 weeks. The following must be determined:

Fetal lie

Fetal lie refers to the relationship of cephalocaudal axis or long axis (spinal column) of fetus to the long axis of the centralized uterus or maternal spine. The lie may be longitudinal, transverse, or oblique (table 1.2, figure. 1.3).

Longitudinal lie: The fetal lie can be described as longitudinal when the maternal and fetal long axes are parallel to each other.

Transverse: The fetal lie can be described as transverse when the maternal and fetal long axes are perpendicular to each other.

Oblique lie: The fetal lie can be described as oblique when the maternal and fetal long axes cross each other obliquely or at an angle of 45°. The oblique lie is usually unstable and becomes longitudinal or transverse during the course of labor.

Fetal presentation

Fetal presentation can be described as the fetal body part which occupies the lower pole of the uterus and thereby first enters the pelvic passage. Fetal presentation is determined by fetal lie and may be of three types: Cephalic, podalic (breech), or shoulder (table 1.3 and figure 1.4 A).

Table 1.2: Types of fetal lie

Type of fetal lie	*Description*
Longitudinal lie	Spinal columns of mother and fetus are parallel to each other
Transverse lie	Spinal columns of mother and fetus are perpendicular to each other
Oblique lie	Spinal columns of mother and fetus cross each other obliquely at an angle of 45°.

Table 1.3: Types of fetal presentation

Type of fetal presentation	*Presenting part*
Cephalic presentation	Fetal head
Breech presentation	Fetal podalic pole (either buttocks or lower extremities)
Shoulder presentation	Fetal shoulders

Cephalic or the head presentation is the commonest and occurs in about 97% of fetuses. Breech and shoulder presentations are less common and may pose difficulty for normal vaginal delivery. Thus, these two presentations are also known as malpresentations. As described previously, in cephalic presentation, the fetal head presents first. Depending on the part of fetal head presenting first, cephalic presentation can be divided as follows (table 1.4).

Vertex or occiput presentation: When the head is completely flexed onto chest, smallest diameter of the fetal head (suboccipitobregmatic diameter) presents. In these

Table 1.4: Fetal presenting parts

Fetal presentation	*Fetal presenting part*
Cephalic	Vertex: completely flexed fetal head Sinciput: Deflexed fetal head
	Brow: Partially extended fetal head
	Face: Completely extended fetal head
Breech	Sacrum
Shoulder	Fetal back

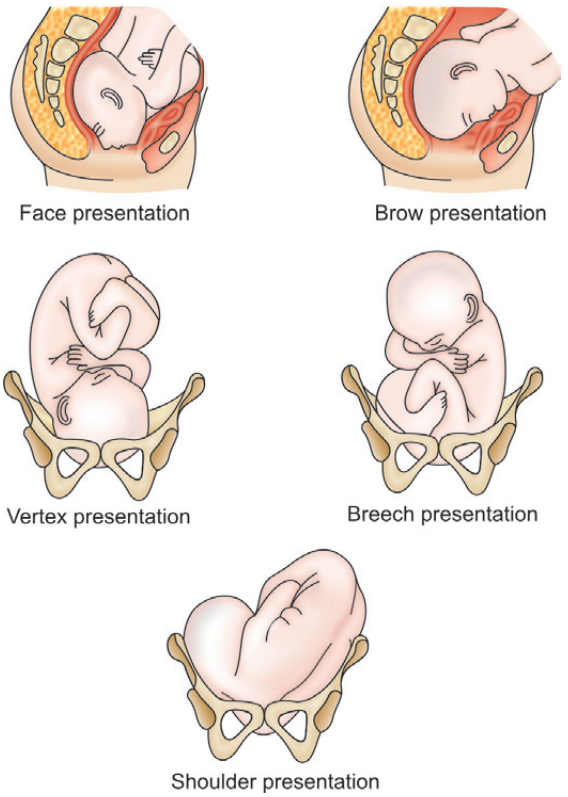


Fig. 1.4A: Various types of fetal presentation

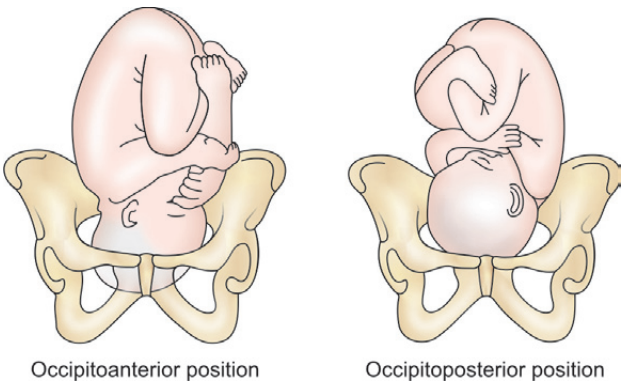


Fig. 1.4B: Occipitoposterior position

cases, the occiput is the presenting part. Usually the occiput presents anteriorly. In some cases occiput may be present posteriorly (figure 1.4B). This type of presentation is known as occipitoposterior position. Though most of the cases with occipitoposterior position undergo normal vaginal delivery, labor is usually prolonged in these cases. In some cases with occipitoposterior presentation, cesarean delivery may be required.

Face presentation: When the fetal head is sharply extended, occiput and the back are in contact with one another. In these cases face is the foremost part of fetal head inside the birth canal and it presents first.

Brow presentation: When the fetal head is only partially extended, fetal brows are the foremost part of fetal head inside the birth canal and they present first. Brow presentation is usually transient because with the progress of labor, as further extension of neck takes place, brow presentation almost invariably gets converted into face presentation. If the brow presentation remains pesistent, the labor gets arrested and a cesarean section is invariably required.

Sinciput presentation: When the fetal head is only partially flexed, the anterior fontanelle or bregma is the foremost inside the birth canal and it presents. With progress of labor, as the flexion of neck takes place, sinciput presentation almost invariably gets converted into vertex presentation.

Compound presentation: Compound presentation is a term used when more than one part of the fetus presents (figure 1.4C). For example, presence of fetal limbs alongside the head in case of a cephalic presentation or one or both arms

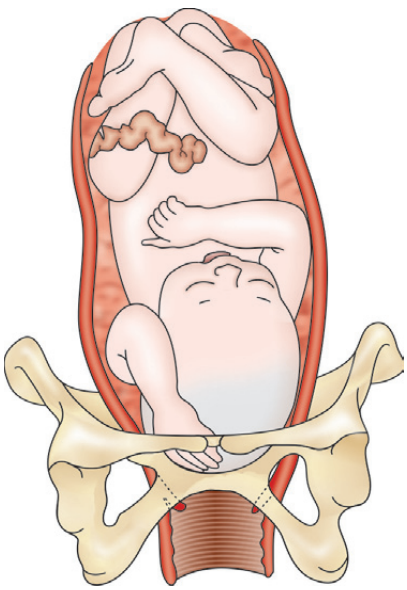


Fig. 1.4C: Compound presentation

in case of breech presentation. This can commonly occur in case of preterm infants.

Presenting part

This can be defined as the part of fetal presentation which is foremost within the birth canal and is therefore first felt by the obstetrician's examining fingers (table 1.4).

Fetal attitude

Fetal attitude refers to the relationship of fetal parts to each another. The most common fetal attitude is that of flexion in which the fetal head is flexed over the fetal neck; fetal arms are flexed unto chest and the fetal legs are flexed over the abdomen.

Denominator

Denominator can be described as an arbitrary fixed bony point on the fetal presenting part (table 1.5).

Fetal position

Fetal position can be defined as the relationship of the denominator to the different quadrants of maternal pelvis (anterior, transverse and posterior). Since the presenting part would be either directed to the left or right side of maternal pelvis, six positions would be possible for each of the fetal presentation (table 1.6 and figure 1.5). For e.g. with vertex position, the six positions that would be possible are left occiput anterior (LOA), right occiput anterior (ROA), left occiput transverse (LOT), right occiput transverse (ROT), left occiput posterior (LOP) and right occiput posterior (ROP). The fetal position give an idea regarding whether the presenting is part directed towards the front, back, left or right of the birth passage.

Table 1.5: Fetal denominators in relation to fetal presenting parts

Fetal presenting part	*Denominator*
Vertex	Occiput
Face	Mentum
Brow	Frontal eminence
Breech	Sacrum
Shoulder	Acromion

Table 1.6: Various fetal positions in relation to the fetal denominator

Fetal denominator	*Fetal positions*
Occiput	Left occiput anterior, right occiput anterior, left occiput transverse, right occiput transverse, left occiput posterior and right occiput posterior
Mentum	Left mentum anterior (LMA); RMA; LMT; RMT; LMP; RMP
Sacrum	Left sacral anterior (LSA); RSA; LST; RST; LSP; RSP
Acromion	Dorso-anterior (R or L); Dorso-posterior (R or L); Dorso-superior (R or L) and Dorso-inferior (R or L)

Diagnosis of Fetal Presentation and Position

It is most important for the obstetrician to correctly identify the fetal presentation and position. This is usually done by performing Lepold's maneuvers on abdominal examination or via vaginal examination.

Obstetric Grips or Lepold's Maneuvers of Abdominal Palpation (Figure 1.6)

Obstetric grips which help in determining fetal lie and presentation are also known as Lepold's maneuvers. Lepold's maneuvers basically include four steps and must be performed while the woman is lying comfortably on her back. The examiner faces the patient for the first three maneuvers and faces towards her feet for the fourth. Obstetric grips must be conducted when the uterus is relaxed and not when the woman is experiencing contractions.

Maternal position

The mother should be comfortable lying in supine position and her abdomen is to be bared. She should be asked to semi-flex her thighs in order to relax the abdominal muscles.

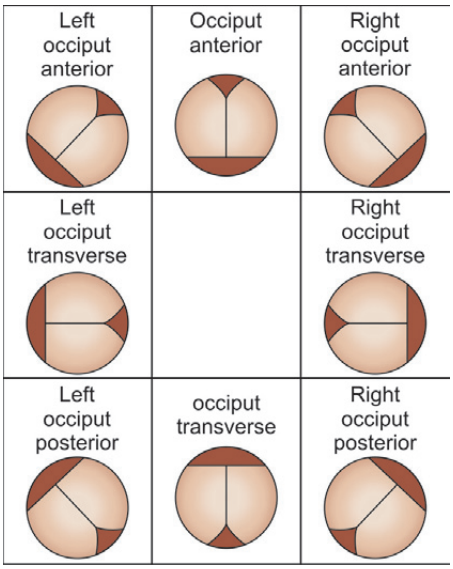


Fig. 1.5: Various positions possible in case of vertex presentation

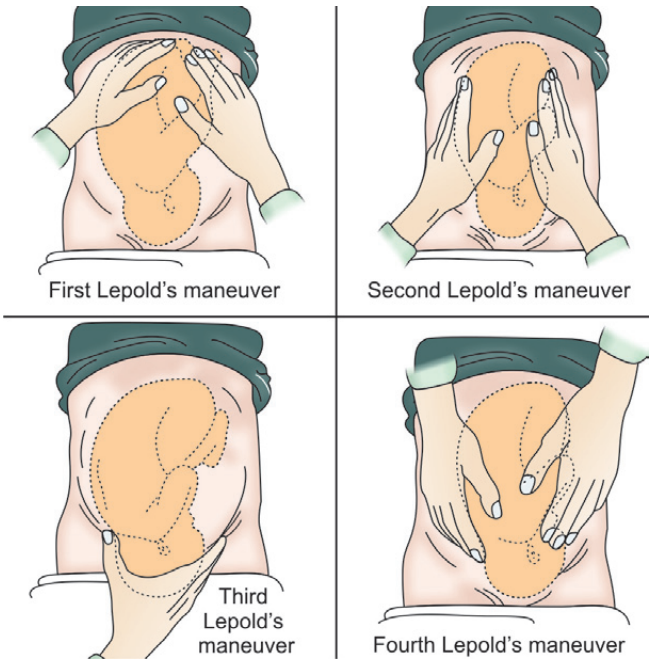


Fig. 1.6: Lepold's maneuvers

These maneuvers can be performed throughout the third trimester and between the contractions, when the patient is in labor. These grips help in determining fetal lie and presentation. The head feels hard and round, and is easily movable and ballotable. The breech feels soft, board and irregular and is continuous with the body. Besides estimating the fetal lie and presentation, many an experienced obstetricians are also able to estimate fetal size and weight through these maneuvers. These maneuvers can be used by experienced clinicians as an effective screening tool for detecting fetal malpresentation, particularly in settings where ultrasound may not be readily available. However, it may be difficult to feel the fetus well when the patient is obese, when there is a lot of liquor or when the uterus is tight, as in some primigravidas. The following obstetric grips/Lepold's maneuvers are carried out:

Fundal grip (Lepold's first maneuver)

This is conducted while facing the patient's face. This grip helps the obstetrician to identify which of the fetal poles (head or breech) is present at the fundus. The fundal area is palpated by placing both the hands over the fundal area. Palpation of broad, soft, irregular mass is suggestive of fetal legs and/or buttocks, thereby pointing towards head presentation. Palpation of a smooth, hard, globular, ballotable mass at the fundus is suggestive of fetal head and points towards breech presentation.

Lateral grip (Lepold's second maneuver)

This grip is also conducted while facing the patient's face. The hands are placed flat over the abdomen on the either side of the umbilicus. Lateral grip helps the clinician in identifying the position of fetal back, limbs and shoulder in case of vertex or breech presentation. The orientation of the fetus can be determined by noting whether the back is directed vertically (anteriorly, posteriorly) or transversely. In case of transverse lie, hard round globular mass suggestive of fetal head can be identified horizontally across the maternal abdomen. The fetal back can be identified as a smooth curved structure with a resistant feel. The position of the fetal back on the left or right side of the uterus would help in determining the position of the presenting part. The fetal limbs would be present on the side opposite to the fetal back and present as small, round, knob like structures. After identifying the back, the clinician should try to identify the anterior shoulder, which forms a well-marked prominence just above the fetal head.

Pelvic grips

Second pelvic grip (Pawlik's grip) or Third Leopold's maneuver: This examination is done while facing the patient's face. The clinician places the outstretched thumb and index finger of the right hand keeping the ulnar border of the palm on the upper border of the patient's pubic symphysis. If a hard globular mass is gripped, it implies vertex presentation. A soft broad part is suggestive of fetal breech. If the presenting part is not engaged, it would be freely ballotable between the two fingers. If the presenting part is deeply engaged, the findings of this maneuver simply indicate that the lower fetal pole is in the pelvis. Further details would be revealed by the next maneuver. In case of transverse presentation the pelvic grip is empty. Normally the size of head in a baby at term would fit in the hand of the examining clinician.

First pelvic grip (Fourth Leopold's maneuver): The objective of the step is to determine the amount of head palpable above the pelvic brim in case of a cephalic presentation. First pelvic grip is performed while facing the patient's feet. Tips of three fingers of each hand are placed on the either side of the midline in downwards and backwards direction in order to deeply palpate the fetal parts present in the lower pole of the uterus. The fingers of both the hands should be placed parallel to the inguinal ligaments and the thumbs should be pointing towards the umbilicus on both the sides. In case of vertex presentation a hard smooth globular mass suggestive of fetal head can be palpated on pelvic grip. In case of breech presentation broad soft, irregular mass is palpated.

Special Points about the Palpation of the Fetus

Assessment of fetal size

While palpating the fetus, the obstetrician must try to assess the size of the fetus itself. A note should be made regarding the expected fetal weight. This should be later compared with the actual weight of the baby at the time of delivery. Regular use of this practice greatly helps in improving the accuracy of fetal weight estimation. The obstetrician should observe if the uterus appears to be full with fetus or the fetus feels smaller than what is expected for the particular period of gestation. A fetus which feels smaller than expected could be indicative of intrauterine growth retardation or oligohydramnios or wrong dates. A fetus which feels larger than expected could be indicative of fetal macrosomia (particularly in association with gestational diabetes); polyhydramnios or multifetal gestation. In multifetal gestation, though the uterine size is larger than the period of gestation the size of individual fetuses per se is small.

If the clinician feels that the size of the head appears to be smaller in relation to the period of gestation, he/she must try to assess the size as well as hardness of the fetal head. The fetal head feels harder as the pregnancy gets closer to term. A relatively small fetal head with a hard feel is suggestive of intrauterine growth retardation rather than prematurity.

Engagement

With the progress of second stage of labor, there is progressive downwards movement of the fetal head in relation to the pelvic cavity. Engagement is said to have occurred when largest diameter of presenting part passes through pelvic inlet. Engagement of the fetal presenting part is of great importance as it helps in ruling out feto-pelvic disproportion. Engagement of fetal presenting part is evident from abdominal and vaginal examination. Vaginal examination reveals the descent of fetal head in relation to the ischial spines (would be described with the vaginal examination).

Abdominal assessment of fetal descent (figures 1.7A and B)

The assessment of fetal descent through the abdominal examination is done by using the Fifth's formula. In this method, number of fifths of fetal head above the pelvic brim is estimated. The amount of fetal head that can be palpated per abdominally is estimated in terms of finger breadth which is assessed by placing the radial margin of the index finger above the symphysis pubis successively. Depending upon the amount of fetal head palpated per abdominally, other fingers of the hand can be placed in succession, until all the five fingers cover the fetal head.

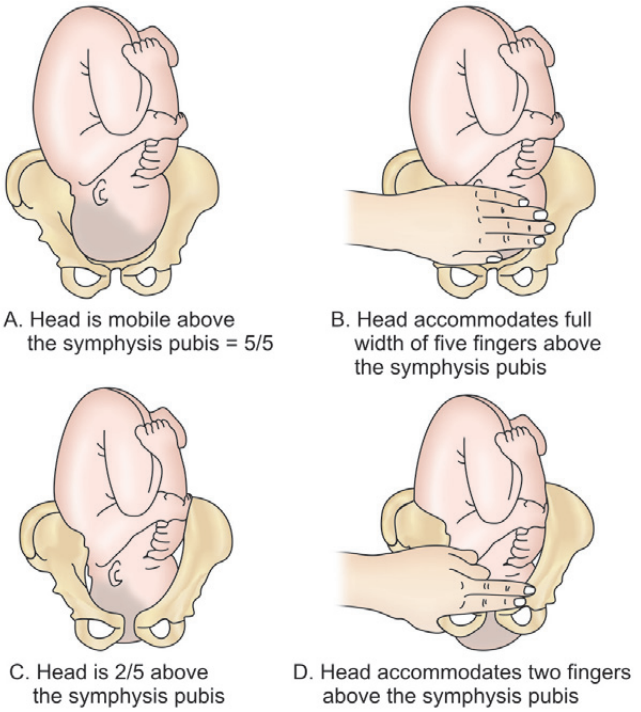


Fig. 1.7A: Abdominal examination for fetal descent

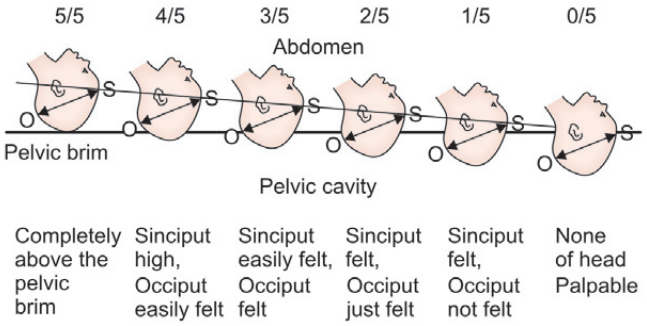


Fig. 1.7B: Stages of fetal descent through the pelvic cavity

A free floating head would be completely palpable per abdomen. This head accommodates full width of all the five fingers above the pubic symphysis and can be described as 5/5. A head which is fixing but not yet engaged may be three fifths palpable per abdominally and is known as 3/5. A recently engaged fetal head may be two fifths palpable per abdominally and is known as 2/5, while a deeply engaged fetal head may not be palpable at all per abdominally and may be described as 0/5.

Assessment of the Amount of Liquor Present

Under normal circumstances, the amount of liquor decreases as the pregnancy approaches term. The amount of liquor can be clinically assessed by feeling the way that the fetus can be

Table 1.7: Causes of polyhydramnios

Multiple gestation
Maternal diabetes
Twin to twin transfusion syndrome
Fetal Parvovirus B19 infection
Rh blood incompatibilities between the mother and the fetus
Fetal congenital abnormalities (e.g. birth defects involving the gastrointestinal tract and central nervous system (e.g. esophageal atresia, spina bifda, anencephaly, etc).

Table 1.8: Causes of oligohydramnios

Intrauterine growth retardation
Placental dysfunction: Presence of amnion nodosum (squamous metaplasia of amnion) on the placenta
Premature rupture of the membranes
Birth defects, especially those involving the kidneys and urinary tract, e.g. renal agenesis or obstruction of the urinary tract (posterior urethral valves)
Postterm pregnancy (> 40 weeks)
Chronic maternal disorders including gestational diabetes mellitus, preeclampsia, chronic hypertension, systemic lupus erythematosus (SLE), etc.
Medications including angiotensin-converting enzyme (ACE) inhibitors (like captopril); prostaglandin inhibitors (aspirin, etc).

balloted while being palpated. Reduced degree of fetal ballotment at the time of abdominal palpation is indicative of reduced amount of amniotic fluid or oligohydramnios. On the other hand, increased degree of fetal ballotment at the time of abdominal plapation is suggestive of increased amount of amniotic fluid or polyhydramnios. Some of the causes for polyhydramnios and oligohydramnios are enumerated in tables 1.7 and 1.8 respectively. In both the cases an ultrasound examination needs to be performed by a trained person to exclude multiple gestation, a congenital abnormality in the fetus or IUGR.

Uterine Contractions

Typically by placing hands on the patient's abdomen and feeling her uterus contract, the clinician will get an idea regarding her uterine contractions. The parameters to be assessed include, number of uterine contractions in a 10 minutes period, duration of contractions, regularity of contractions and intensity of contractions. Another important parameter to assess is whether the contractions result in dilatation of the cervix. One way to determine the intensity of a contraction is by comparing the firmness of the uterus to areas on the clinician's face. For example, the cheek could be considered as mild, the tip of the nose as moderate and forehead as strong. In the early stages of labor, the frequency of the uterine contractions may be after every 10–15 minutes, lasting for about 30–60 seconds. However as the labor progresses, the frequency and duration of uterine contractions greatly increases with contractions occurring after every 1–2 minutes and lasting for about 60–120 seconds.

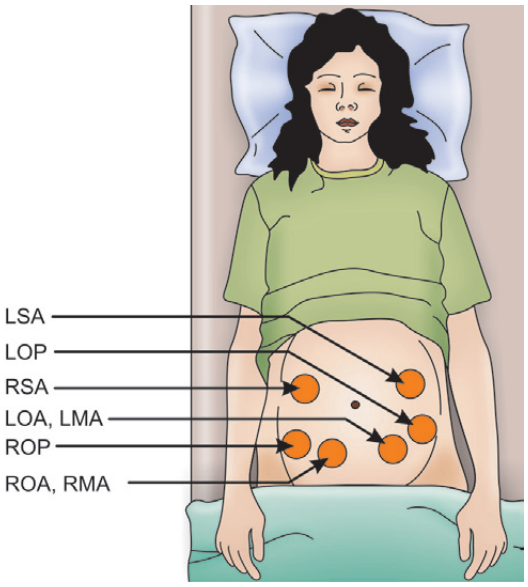


Fig. 1.8A: Location of fetal heart rate

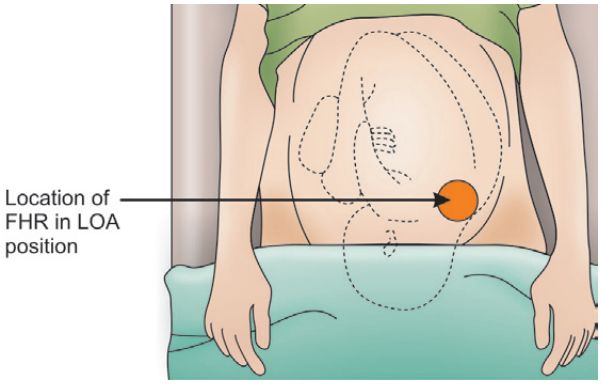


Fig. 1.8B: Location of fetal heart rate in LOA position

Auscultation of Fetal Heart

The fetal wellbeing is usually assessed by listening to the fetal heart. The auscultation of fetal heart will also give some idea regarding the fetal presentation and position. The region of maternal abdomen where the heart sounds are most clearly heard would vary with the presentation and extent of descent of the presenting part (figures 1.8A and B). The fetal heart is most easily heard by listening over the back of the fetus. The fetal heart rate can be monitored either through electronic fetal monitoring, using an external fetal monitor or through intermittent auscultation, using a Doppler instrument or

Pinard's fetoscope or even an ordinary stethoscope. Normal fetal heart rate varies from 100 to 140 beats per minute with the average being 120 beats per minute.

Auscultation of fetal heart rate is particularly important in cases whether the woman is unable to perceive the fetal movements. To make sure that the clinician is not accidentally listening to mother's heart instead of fetal heart, the maternal pulse must also be simultaneously palpated. In normal cases the fetal heart rate must be auscultated as described:

- During the first stage of labor: Every thirty minutes, followed by every 15 minutes during the second stage of labor.
- In high risk cases (e.g., preeclampsia), the fetal heart rate must be auscultated every 15 minutes during first stage and every 5 minutes during the second stage of labor.

EXAMINATION OF THE PATIENT IN LABOR

Abdominal Examination in Labor

The abdominal examination forms an important part of every complete physical examination in labor. The abdominal examination must be done at the time of admission and each time before a vaginal examination is performed. The parameters to be assessed at the time of abdominal examination of a patient who is in labor is similar to those observed at the time of antenatal examination and have been described before. Aditionally, descent and engagement of the fetal head, assessment of fetal position and uterine contractions is especially important when the patient is in labor. The amount of descent and engagement of the head is assessed by feeling how many fifths of the head are palpable above the brim of the pelvis (figures 1.7A and B).

Uterine Contractions

Uterine contractions usually follow a rhythmic pattern, with periods of contractions followed by periods of relaxation in between, which would allow the woman to rest. During the phase of relaxation, restoration of placental circulation occurs, which is important for the baby's oxygenation. The uterus appears to be hard during the strong uterine contractions and it may be difficult to palpate the fetal parts. Causes for abnormal hardness of the uterus are enumerated in table 1.9. Commonest causes for abnormal hardness and tenderness of the uterus, include abruption placenta or a ruptured uterus. Some of the features of uterine contractions which need to be assessed are described below:

Duration of uterine contractions

Length of the uterine contractions is assessed by placing a hand on the abdomen and feeling when the uterus becomes hard and when it relaxes. Depending upon the time duration for which the contractions last, they can be classified as strong, moderate and weak contractions. Grading of the duration of uterine contractions is described in table 1.10.

Table 1.9: Causes for abnormal hardness of the uterus

Some primigravidas
At the time of strong uterine contractions
Abruption placenta
Rupture of the uterus

Table 1.10: Grading the duration of contractions

Duration of contraction	*Grading of contractions*
Contraction lasting less than 20 seconds	Weak contractions
Contractions lasting for 20–40 seconds	Moderate contractions
Contractions lasting more than 40 seconds	Strong contractions

Strength of contractions

The strength of contractions or intensity is assessed by measuring the degree of hardness, the uterus undergoes at the time of contraction. Experienced obstetrician can estimate the intensity of uterine contractions by palpating the uterine fundus during the contractions. During a mild contraction, the uterine wall can be indented, whereas during a strong contraction, it cannot be indented.

Frequency of uterine contractions

This measures the number of times, the uterine contractions occurs in a period of 10 minutes.

Commonest causes for abnormal hardness and tenderness of the uterus include abruption placenta or a ruptured uterus.

VAGINAL EXAMINATION

Prerequisites for a Vaginal Examination

- The patient must be carefully explained about the examination, prior to performing the examination.
- Adequate permission must be taken from the patient.
- There should be a valid reason for performing the examination.
- A vaginal examination must always be preceded by an abdominal examination.

Indications for a Vaginal Examination in Pregnancy

Indications for performing a vaginal examination during the various periods of pregnancy are enumerated in table 1.11.

Table 1.11: Indications for a vaginal examination in pregnancy

At the time of first ANC visit	*Subsequent antenatal visits*	*At the time of labor*
Diagnosis of pregnancy	Investigation of a threatened abortion	Assessment of the ripeness of the cervix prior to induction of labor
Assessment of the gestational age	Confirmation of preterm rupture of the membranes with a sterile speculum	Performance of artificial rupture of the membranes to induce labor
Detection of abnormalities in the genital tract	Confirmation of the diagnosis of preterm labor	Detection of cervical effacement and/or dilatation
Investigation of a vaginal discharge	Identification of the fetal presenting part in the pelvis	Identification of the fetal presenting part
Cervical examination	Performance of a pelvic assessment	Performance of a pelvic assessment

Contraindications to a Vaginal Examination in Pregnancy

Antepartum hemorrhage (see chapter 4) and preterm rupture of the membranes without contractions are conditions in which the vaginal examination is contraindicated. In these cases a sterile speculum examination can be done to confirm or exclude rupture of the membranes.

Preparation for Vaginal Examination

- The patient's bladder must be empty.
- The procedure must be carefully explained to the patient.
- The patient must be placed in either the dorsal or lithotomy position. In clinical practice, dorsal position is most commonly used because it is more comfortable and less embarrassing than the lithotomy position. Also the lithotomy position usually requires equipment like lithotomy poles and stirrup, which is not the case with dorsal position.
- If the membranes have not ruptured or are not going to be ruptured during the examination, an ordinary surgical glove can be used and there is no need to swab the patient with antiseptic solution. However, if the membranes have ruptured or are going to be ruptured during the examination, vaginal examination in labor should be performed as a sterile procedure. Therefore, in these cases a sterile tray which contains sterile swabs, sterile gloves, sterile instruments for performing ARM (preferably Kocher's forceps), an antiseptic vaginal solution (betadine) or sterile lubricant (savlon) is required.
- The clinicians before performing the vaginal examination must either scrub or thoroughly wash their hands and wear sterile gloves. The patient's vulva and perineum must be swabbed with savlon or betadine solution. This is done by first swabbing the labia majora and groin on both sides and then swabbing the introitus while keeping the labia majora apart with the thumb and forefinger.
- A vaginal examination must be preceded by the inspection of the external and internal genitalia, for signs of sexually transmitted diseases (STD) such as presence of single or multiple ulcers, a purulent discharge or enlarged inguinal lymph nodes. The vulva must also be carefully inspected for any abnormalities, e.g. scars, warts, varicosities, congenital abnormalities, ulcers or discharge. Vagina and cervix can be inspected by performing a per speculum examination. The vagina must be assessed for the presence or absence of the following features: Vaginal discharge; a full loaded rectum, vaginal stricture or septum or prolapse of the umbilical cord through the vaginal introitus.
- Presence of a wart-like growth or an ulcer on the cervix may be suggestive of cervical carcinoma. The cervical surface can also be assessed while performing a vaginal examination. A bimanual examination helps in assessing the cervical dilatation and effacement, the size of the uterus and masses in the adnexa (ovaries and fallopian tubes).

In the first trimester of pregnancy, a bimanual examination helps in assessment of the uterine size in comparison with the period of amenorrhea. After the first trimester the uterine size is primarily assessed on abdominal examination. Lastly, the fornices are palpated to exclude any masses, the commonest of which is an ovarian cyst or tumor.

Special care must be taken, when performing a vaginal examination late in pregnancy, especially in the presence of a high presenting part. The non engagement of the presenting part could due to an undiagnosed placenta previa. If this is suspected, the finger must not be inserted into the cervical canal. Instead, the presenting part is gently palpated through all the fornices. If any bogginess is noted between the fingers of the examining hand and the presenting part, the examination must be immediately abandoned and the patient must be referred urgently for an ultrasound examination.

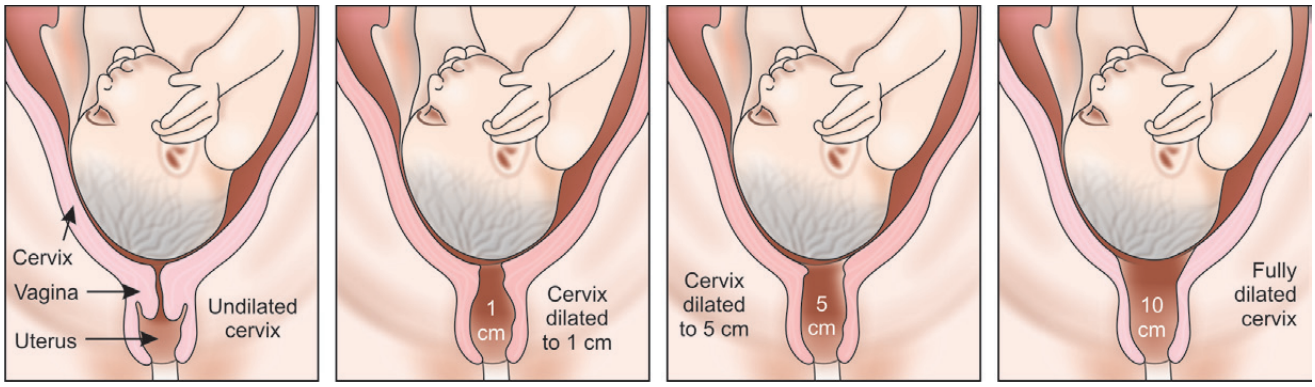


Fig. 1.9: Cervical dilatation

Parameters to be Observed during Vaginal Examination

The parameters to be observed while performing a vaginal examination are described below in table 1.12.

Cervical dilatation (figure 1.9) must be assessed in centimeters and is best measured by assessing the degree of separation of the fingers on vaginal examination.

The cervix undergoes progressively shortening or effacement in early labor (figure 1.10). The cervical effacement is measured by assessing the length of the endocervical canal.

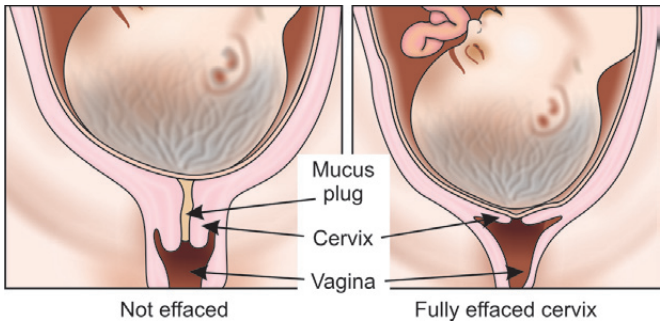


Fig. 1.10: Cervical effacement

Table 1.12: Parameters to be observed while performing a vaginal examination

Consistency of cervix
Cervical dilatation
Cervical effacement
Fetal presentation
Position
Assessment of fetal membranes
Assessment of liquor
Fetal descent (Station of fetal head)
Molding of fetal skull
Pelvic assessment

This refers to the distance between the internal os and the external os on digital examination. In an uneffaced cervix, the endocervical canal is approximately 3 cm long. However, when the cervix becomes fully effaced there will be no endocervical canal, only a ring of thin cervix. The cervical effacement is measured as a percentage.

Fetal Presentation

An abdominal examination performed earlier helps in determining the fetal lie and the presenting part. The presenting part of the fetus can be confirmed on vaginal examination. The presenting part could be head, breech or shoulder. If the head is presenting, the exact fetal presentation, e.g. vertex, brow or face needs to be determined.

Features of a vertex presentation

The posterior fontanelle is normally felt. It is a small triangular space. In contrast, the anterior fontanelle is diamond shaped. If the head is well flexed, the anterior fontanelle will not be felt. If the anterior fontanelle can be easily felt, the head is deflexed.

Features of a face presentation

On abdominal examination the presenting part is the head. However, on vaginal examination:

- Instead of a firm skull, something soft is felt.
- The gum margins distinguish the mouth from the anus.
- The cheek bones and the mouth form a triangle.
- The orbital ridges above the eyes can be felt.
- The ears may be felt.

Features of a brow presentation

The presenting part is high. The anterior fontanelle is felt on one side of the pelvis, the root of the nose on the other side and the orbital ridges may be felt laterally.

Features of a breech presentation

On abdominal examination the presenting part is the breech. (Soft and triangular). On vaginal examination:

- Instead of a firm skull, something soft is felt.
- The anus does not have gum margins.
- The anus and the ischial tuberosities form a straight line.

Features of a shoulder presentation

On abdominal examination the lie will be transverse or oblique. Features of a shoulder presentation on vaginal examination will be quite easy if the arm has prolapsed. The shoulder is not always that easy to identify, unless the arm can be felt. The presenting part is usually high.

Fetal Position

Fetal position refers to relationship of the designated landmark on the fetal presenting part with the left or right side of the maternal pelvis. Fetal position has been described in details before in the text (figure 1.5).

Assessment of the Membranes

Drainage of liquor indicates that membranes have ruptured. However, even if the liquor is obviously draining, the obstetrician must always try to feel for the presence of membranes overlying the presenting part. If the presenting part is high, it is usually quite easy to feel intact membranes. However, it may be difficult to feel the membranes, if the presenting part is well applied to the cervix. In this case, one should wait for a contraction, when some liquor often comes in front of the presenting part, allowing the membranes to be felt. If the membranes are intact, and the patient is in the active phase of labor, the membranes should be ruptured. However, if the presenting part is high, there is always the danger that the umbilical cord may prolapse, with the artificial rupture of membranes (ARM). Following precautions should therefore be taken while performing an ARM in a patient with high presenting part:

- Before doing an ARM, the fetal head must be stabilized using the abdominal hand in order to minimize the chances of cord prolapse.
- Fetal heart rate should be heard following the ARM. Decline in fetal heart rate could be indicative of fetal distress resulting from cord prolapse.
- A vaginal examination must be performed following ARM, in order to exclude the possibility of cord presentation.

Membranes are normally not ruptured in HIV positive patients unless there is poor progress of labor.

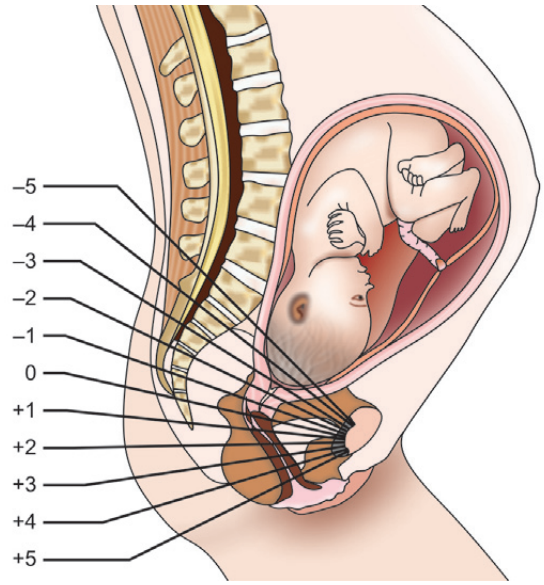


Fig. 1.11: Fetal descent

The Condition of the Liquor When the Membranes Rupture

An important parameter which must be assessed at the time of assessing the membranes is the condition of liquor following the rupture of membranes. Clear colored liquor following the rupture of membranes is indicative of a normal healthy fetus. Greenish colored liquor is suggestive of presence of meconium. The presence of meconium may change the management of the patient as it indicates the presence of fetal distress. In these cases, it may be required to expedite the delivery.

Determining the Descent and Engagement of the Head

The engagement of the fetal head is assessed on abdominal and not on vaginal examination. However the vaginal examination does help in assessing the descent of fetal presenting part. The level of the fetal presenting part is usually described in relation to the ischial spines, which is halfway between the pelvic inlet and pelvic outlet. When the lower most portion of the fetal presenting part is at the level of ischial spines, it is designated as "zero" station. The ACOG has devised a classification system that divides the pelvis above and below the spines into fifths. This division represents the distance in centimeters above and below the ischial spine. Thus, as the presenting fetal part descends from the inlet towards the ischial spine, the designation is –5, –4, –3, –2, –1, then 0 station. Below the ischial spines, the fetal head passes through +1, +2, +3, +4 and + 5 stations till delivery (figure 1.11). +5 station represents that the fetal head is visible at the introitus. If the leading part of the fetal head is at the zero station or below, the fetal head is said to be engaged. This implies that

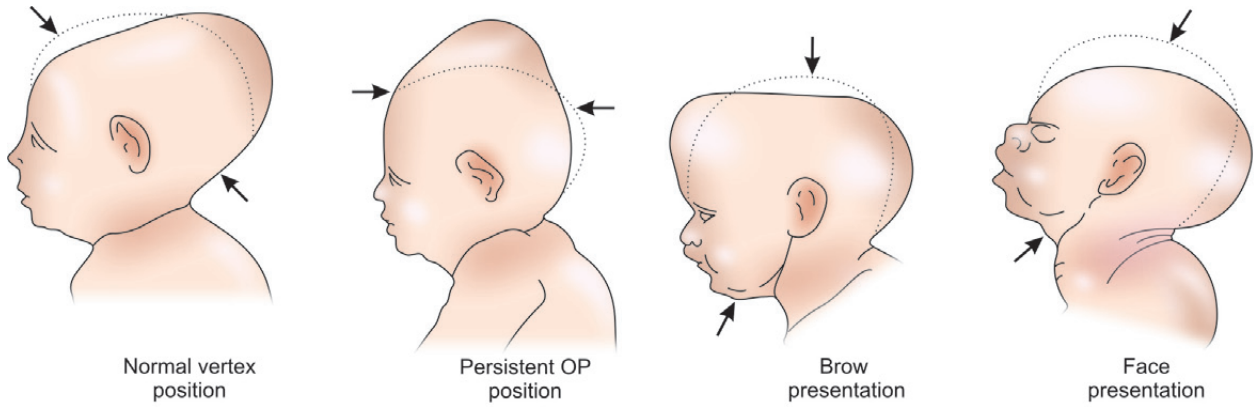


Fig. 1.12: Pattern of molding in different types of cephalic presentations

the biparietal plane of the fetal head has passed through the pelvic inlet. However in the presence of excessive molding or caput formation, engagement may not have taken place even if the head appears to be at zero station.

Molding

Molding is the overlapping of the fetal skull bones at the regions of the sutures, which may occur during labor due to the head being compressed as it passes through the pelvis of the mother. Molding results in the compression of the engaging diameter of the fetal head with the corresponding elongation of the diameter at right angles to it (figure 1.12). For example, if the fully flexed fetal head engages in the suboccipitobregmatic diameter, this diameter gets compressed. At the same time, the mentovertical diameter (which is at right angles to the suboccipitobregmatic diameter) gets elongated.

The diagnosis of molding

In a cephalic (head) presentation, molding is diagnosed by feeling overlapping of the sutures of the skull on vaginal examination and assessing whether or not the overlap can be reduced (corrected) by pressing gently with the examining finger.

The presence of caput succedaneum (soft tissue edema of fetal scalp) can also be felt as a soft, boggy swelling, which may make it difficult to identify the presenting part of the fetal head clearly. With severe caput, the sutures may be impossible to feel.

Grading the degree of molding (figure 1.13)

The occipitoparietal and the sagittal sutures are palpated and the relationship or closeness of the two adjacent bones is assessed. The degree of molding is assessed according to the scale described in table 1.13.

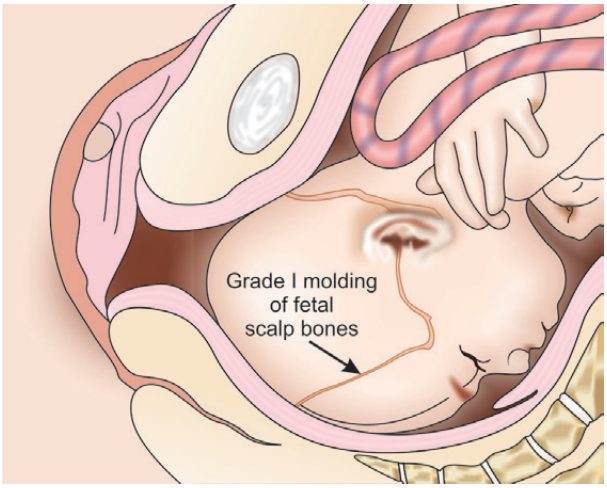


Fig. 1.13: Grade I molding of fetal scalp bones

Table 1.13: Degree of molding of fetal skull

Degree of molding	*Description*
0 (normal)	Normal separation of the bones with open sutures
1+ (mild molding)	Bones touching each other
2+ (moderate molding)	Bones overlapping, but can be separated with gentle digital pressure
3+ (severe molding)	Bones overlapping, but cannot be separated with gentle digital pressure

PELVIC ASSESSMENT

While assessing the pelvis, it is important to adopt a step-by-step method to assess the pelvis i.e. first assessing the size and shape of the pelvic inlet, then the midpelvis and lastly the pelvic outlet.

Assessment of Pelvic Inlet

For assessment of pelvic inlet, the sacral promontory and the retropubic area are palpated.

Assessment of Midpelvis

For assessment of the midpelvis, the curve of the sacrum, the sacrospinous ligaments and the ischial spines are palpated.

Assessment of the Pelvic Outlet

For assessment of the pelvic outlet, the subpubic angle, intertuberous diameter and mobility of the coccyx are determined.

The obstetrician must begin the pelvic assessment by starting with the sacral promontory and then following the curve of the sacrum down the midline. In an adequate pelvis, the promontory cannot be easily palpated, the sacrum is well curved and the coccyx cannot be felt. In case of an inadequate pelvis, the sacral promontory is easily palpated and prominent, the sacrum is straight and the coccyx is prominent and/or fixed. After assessing the sacrum, the obstetrician must move his/her fingers lateral to the midsacrum where the sacrospinous ligaments can be felt. If these ligaments are followed laterally, the ischial spines can be palpated. In an adequate pelvis, the sacrospinous ligaments are three cm or longer, i.e. at least two of the obstetrician's fingers can be placed over the sacrospinous ligaments. In case of an inadequate pelvis, it may not be possible to place two fingers over the sacrospinous ligaments; the ligaments usually allow less than 2 fingers. Also, the ischial spines may appear sharp and prominent. Next the retropubic area is palpated. For this the obstetrician must put two examining fingers with the palm of the hand facing upwards, behind the symphysis pubis. The hand is then moved laterally to both sides. In case of an adequate pelvis, the retropubic area is flat. In case of an inadequate pelvis, the retropubic area is angulated. To measure the subpubic angle, the examining fingers are turned so that the palm of the hand faces downwards. At the same time, the third finger is also held out at the vaginal introitus and the angle under the pubis is felt. If three fingers can be placed under the pubis, the subpubic angle is approximately 90°, which can be considered as adequate (figure 1.14). If the subpubic angle allows only 2 fingers, the subpubic angle is about 60°, which is indicative of an inadequate pelvis. Finally, as the obstetrician's hand is withdrawn from the vaginal introitus, the intertuberous diameter is measured with the knuckles of the closed fist of the hand placed between the ischial tuberosities. If the pelvis is adequate, the intertuberous diameter allows 4 knuckles. In case of an inadequate pelvis the intertuberous diameter allows less than four knuckles.

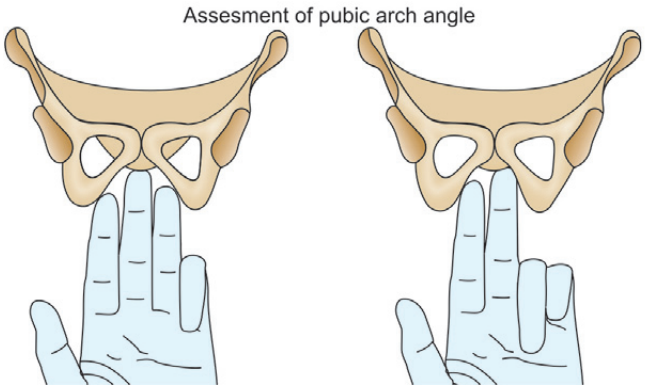


Fig. 1.14: Assessment of pubic angle

Abdominal Method for Assessment of Pelvic Disproportion

In case the pelvis appears to be inadequate at the time of vaginal examination, the abdominal method can be used for assessment of pelvic disproportion. In this method, the patient is placed in dorsal position with the thighs slightly flexed and displaced. The obstetrician grasps the fetal head using the left hand. The index and middle fingers of the right hand are then placed above the pubic symphysis, while keeping the inner surface of the fingers in line with the anterior surface of the pubic symphysis. As the left hand pushes the fetal head downwards and backwards, any degree of overlapping of the head over the symphysis pubis is noted. The following conclusions can be reached depending upon the findings on abdominal examination:

- *No disproportion*: If the head can be pushed down the pelvis without any overlapping of the parietal bones on the symphysis pubis, feto-pelvic disproportion can be ruled out.
- *Moderate disproportion*: If the head can be pushed down a little, but there is a slight overlapping (approximately 0.5 cm) of the parietal bones evidenced by the touch on the under surface of the fingers.
- *Severe disproportion*: Head cannot be pushed down and instead the parietal bones overhang the symphysis pubis, displacing the fingers.

Abdominal Vaginal Method (Muller Munrokerr Method)

Muller Munrokerr method is a bimanual method (figure 1.15) for assessing the pelvis and is superior to the abdominal method alone.

Procedure

- The patient is asked to empty her bladder.
- She is then placed in the lithotomy position

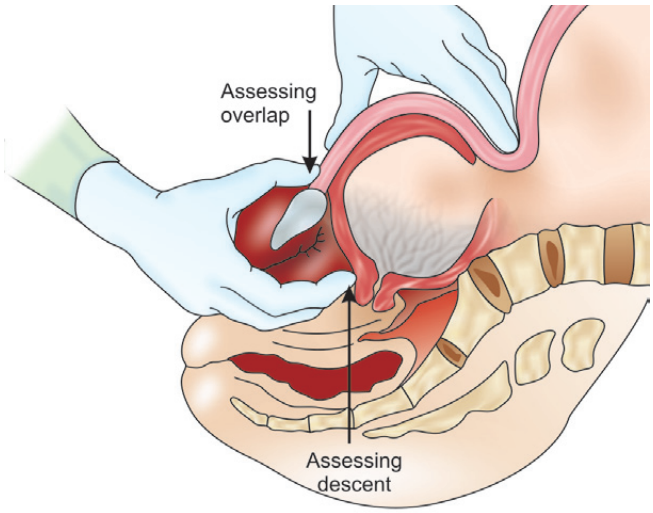


Fig. 1.15: Muller Munrokerr method

- After taking all aseptic precautions an internal examination is done.
- The obstetrician introduces two fingers of the right hand inside the vagina with tips of the fingers placed at the level of ischial spines and thumb above the symphysis pubis.
- The fetal head is then grasped by the left hand and pushed in a downwards and backwards direction into the pelvis. If the head can be pushed down upto the level of ischial spines and there is no overlapping of the parietal bones over the symphysis pubis, it implies that there is no disproportion.

  The following conclusions can be reached depending upon the findings on abdominal vaginal examination:
- *No disproportion:* Fetal head can be pushed down up to the level of ischial spines without any overlapping of the parietal bones.
- *Slight or moderate disproportion*: The head can be pushed down a little but not up to the level of ischial spines and there is only a slight overlapping of the parietal bones.
- *Severe disproportion*: The fetal head cannot be pushed down and instead the parietal bone overhangs the symphysis pubis displacing the thumbs.

Management

Management comprising of investigations and definitive obstetric management is discussed below.

Investigations

The investigations which need to be done at the time of first antenatal visit have been enumerated in table 1.14.

Table 1.14: Routine investigations to be done during the first antenatal visit

Determination of the patient's blood group (ABO and Rh)
Hemoglobin estimation
Urine test for protein and glucose is to be done at every visit
A serological screening test for syphilis
A rapid HIV screening test after pretest counseling and written consent
Wet smear of any symptomatic vaginal discharge (i.e. itching, burning or offensive) must be examined under a microscope

Pregnancy Test

The test is based on the detection of human chorionic gonadotrophin (hCG) in the patient's urine. hCG is a glycoprotein hormone produced by the trophoblastic cells and prevents the involution of corpus luteum during early pregnancy. Corpus luteum is the principal site of progesterone production during the first six weeks of gestation. In normal pregnancy β hCG levels start increasing from the day of implantation and reach their peak by 60–70 days. Thereafter, the levels start decreasing until a nadir is reached by 14–16 weeks of gestation. During early pregnancy, the doubling time of β hCG is nearly 1.4–2.0 days. The earliest that the β hCG test can be expected to be positive is 8–10 days following ovulation. The test normally becomes positive by the time a pregnant woman first misses her period. If the test is negative and the woman is not having her period yet, the test should be repeated after 48 hours.

The pregnancy test must be performed on a fresh urine specimen (first morning specimen).

The pregnancy test can be considered as negative if only the control band nearest the upper blue part of the test strip becomes pink. It can be considered as positive if two pink bands are visible and as uncertain if none of the pink bands are seen. Uncertain test implies that either the test was not performed correctly or the test strip is damaged. In these cases, the test must be repeated with another test strip.

If possible, all patients should have a midstream urine specimen examined for asymptomatic bacteriuria.

Ultrasound Examination

With the advent of transvaginal ultrasound, the gestational sac can be visualized as early as 4–5 weeks of gestation. A first trimester ultrasound examination helps in estimation the period of gestation. Ultrasound screening at 11 to 13 weeks may also be useful for the measurement of nuchal thickness, which may be a useful screening test for Down syndrome.

A second trimester ultrasound examination performed between 18–22 weeks is helpful in excluding multiple

pregnancy, placental localization, period of gestation and screening for gross fetal abnormalities.

An ultrasound examination done after the second trimester is too unreliable to be used to estimate the duration of pregnancy. However it may help in confirming the fetal presentation, placental localization, amount of liquor, etc.

Rx Treatment/Obstetric Management

Factors Important for the Normal Progress of Labor

Five important factors are responsible for the normal progress of labor. These include the passage, the fetus, the relationship between the passage and the fetus, the forces of labor and psychosocial considerations. This can be remembered by the mnemonic called the 5 "P"s of Labor: **P**assageway, **P**assenger (fetus), **P**ower (uterine contractions), **P**osition and **P**sychologic responses.

The Maternal Pelvis (Passageway)

The birth passage comprises of three parts: Namely the pelvic inlet, pelvic cavity (midpelvis), and the pelvic outlet. The bony pelvis can be classified into four types: Gynecoid, android, anthropoid, and platypelloid. Of these, the gynecoid type of pelvis is most common, with the diameters favorable for vaginal delivery. The anterior view of maternal gynecoid pelvis is shown in figure 1.16. Gynecoid pelvis is an ideal type of pelvis and is characterized by the presence of the following features:

- The pelvic brim is almost round in shape, but slightly oval transversely.
- Ischial spines are not prominent.
- Sub-pubic arch is rounded and measures at least 90° in size.
- Obturator foramen is triangular in shape
- Sacrum is wide with average concavity and inclination.
- Sacro–sciatic notch is wide.

The pelvic brim (figure 1.17) divides the pelvis into two: False pelvis and true pelvis. The boundaries of the pelvic brim or inlet include the following: Sacral promontory, sacral alae, sacro-iliac joints, ileopectineal lines, ileopectineal eminence, upper border of superior pubic rami, pubic tubercles, pubic crest and upper borders of pubic symphysis.

False pelvis: False pelvis lies above the pelvic brim and has no obstetrical significance.

True pelvis: True pelvis lies below the pelvic brim and plays an important role in the childbirth and delivery. The true pelvis forms a bony canal through which the fetus passes at the time of labor. It is formed by the symphysis pubis anteriorly and sacrum and coccyx posteriorly. The true pelvis can be divided into three parts: Pelvic inlet, cavity and outlet.

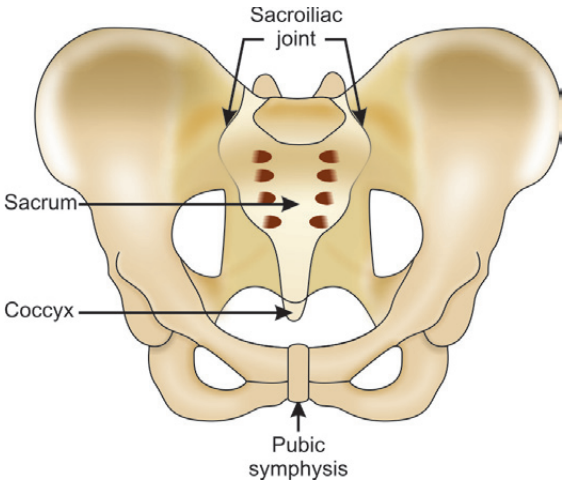


Fig. 1.16: Anterior view of maternal pelvis

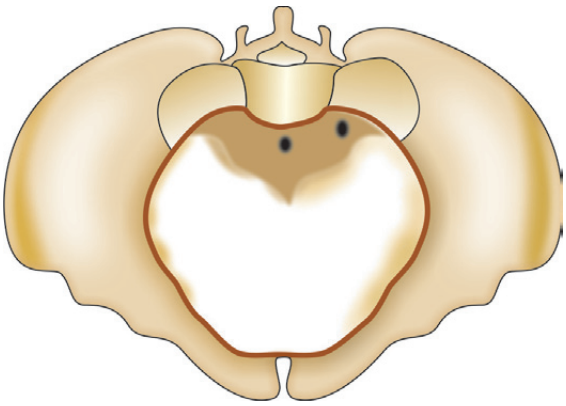


Fig. 1.17: Boundaries of the pelvic brim

Pelvic inlet

Pelvic inlet is round in shape and is narrowest Anterior posteriorly and widest in the transverse diameter. The fetal head enters the pelvic inlet with the longest diameter of the fetal head (A-P diameter) in the widest part of the pelvic inlet (transverse diameter) (figure 1.18).

The plane of the pelvic inlet (also known as superior strait) is not horizontal, but is tilted forwards. It makes an angle of 55° with the horizontal. This angle is known as the angle of inclination. Radiographically this angle can be measured by measuring the angle between the front of the vertebra L5 and plane of inlet and subtracting this from 180°. Increase in the angle of inclination has obstetric significance as this may result in delayed engagement of the fetal head and delay in descent of fetal head. Increase in the angle of inclination also favors occipitoposterior position. On the other hand, the reduction in the angle of inclination may not have any obstetric significance.

The axis of the pelvic inlet is a line drawn perpendicular to the plane of inlet in the midline (figure 1.19). It is in

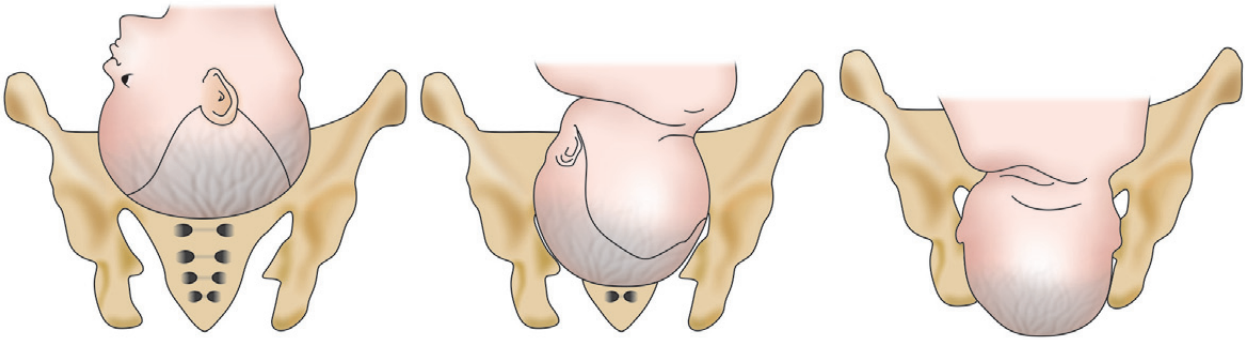


Fig. 1.18: Entry of fetal head into the maternal pelvis

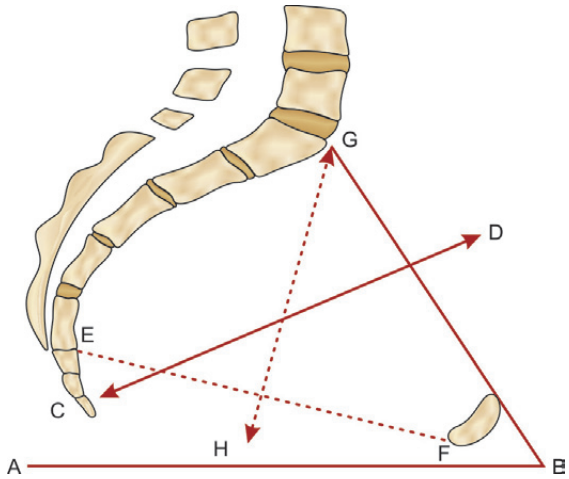


Fig. 1.19: Different planes and axes of the pelvis

AB – Horizontal line; GB – Plane of inlet; FE – Plane of obstetric outlet; DC – Axis of the inlet; GH – Axis of obstetrical outlet

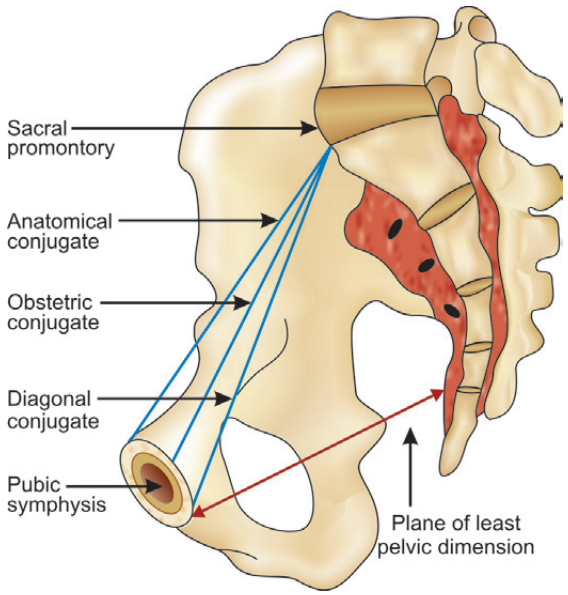


Fig. 1.20: Medial view of maternal pelvis (from left)

downward and backward direction. Upon extension, this line passes through the umbilicus anteriorly and through the coccyx posteriorly. For the proper descent and engagement of fetal head, it is important that the uterine axis coincides with the axis of inlet.

Diameters of the pelvic inlet

Anterior posterior (AP) diameter (figure 1.20):

- Anterior posterior diameter (true conjugate or anatomical conjugate = 11 cm): This is measured from the midpoint of sacral promontory to the upper border of pubic symphysis.
- Obstetric conjugate (10.5 cm): The obstetric conjugate is measured from the midpoint of sacral promontory to the most bulging point on the back of symphysis pubic. This is the shortest anterior posterior diameter of the pelvic inlet and measures about 10.5 cm.
- Diagonal conjugate (12.5 cm): It is measured from the tip of sacral promontory to the lower border of pubic symphysis.

Out of three AP diameters of pelvic inlet, only diagonal conjugate can be assessed clinically during the late pregnancy or at the time of the labor. Obstetric conjugate can be calculated by subtracting 1.5–2 cm from the diagonal conjugate. Also the true conjugate can be inferred by subtracting 1.2 cm from the diagonal conjugate.

Measurement of the diagonal conjugate

After placing the patient in dorsal position and taking all aseptic precautions two fingers are introduced into vagina. The clinician tries to feel the anterior sacral curvature with these fingers (figure 1.21). In normal cases it will be difficult to feel the sacral promontory. The clinician may be required to depress the elbow and wrist while mobilizing the fingers upwards in order to reach the promontory. The point at which the bone recedes from the finger is sacral promontory. A marking is placed over the gloved index finger by the

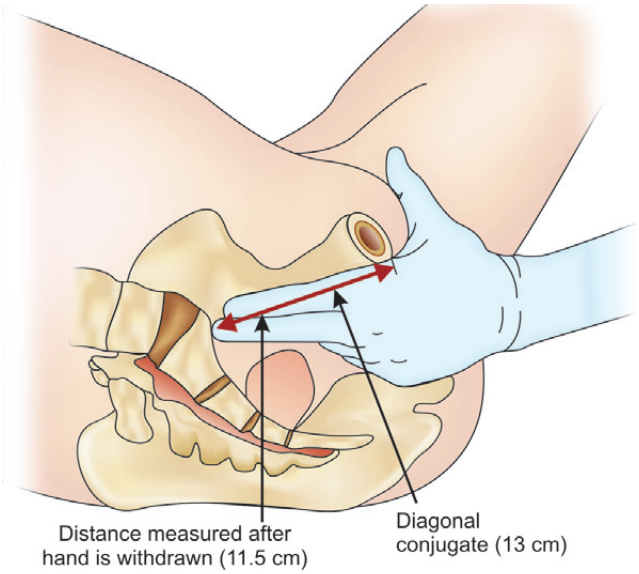


Fig. 1.21: Measurement of diagonal conjugate

index finger of the other hand. After removing the fingers from the vagina, the distance between the marking and the tip of the middle finger is measured in order to obtain the measurement of diagonal conjugate. In clinical situations it may not always be feasible to measure the diagonal conjugate. In these cases if the middle finger fails to reach the sacral promontory or reaches it with difficulty, the diagonal conjugate can be considered as adequate. Under normal circumstances, an adequate pelvis would be able to allow an average-sized fetal head to pass through.

Transverse diameter of pelvic inlet

- Anatomical transverse diameter (13 cm): It is the distance between the farthest two points on the ilio-pectineal line (figure 1.22). It is the largest diameter of the pelvic inlet and lies 4 cm anterior to the promontory and 7 cm behind the symphysis.
- Obstetric transverse diameter: This diameter passes through the midpoint of true conjugate and is therefore slightly shorter than the anatomical transverse diameter.

Oblique diameters of pelvic inlet

There are two oblique diameters, right and left (12cm). The right oblique diameter passes from right sacro-iliac joint to the left ilio-pubic eminence, whereas the left diameter passes from left sacro-iliac joint to the right ilio-pubic eminence.

Pelvic cavity

This is bounded above by the pelvic brim and below by the plane of least pelvic dimension, anteriorly by the symphysis pubis and posteriorly by sacrum. The plane of least pelvic

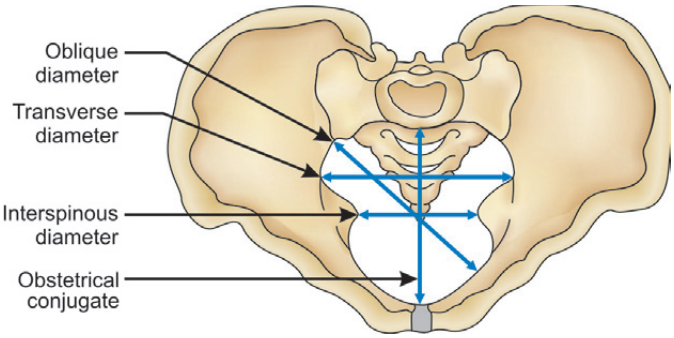


Fig. 1.22: Superior view of pelvic inlet

dimension extends from the lower border of pubic symphysis to the tip of ischial spines laterally and to the tip of 5th sacral vertebra posteriorly.

Plane of cavity (Plane of greatest pelvic dimensions): This plane passes between the middle of the posterior surface of the symphysis pubis and the junction between 2nd and the 3rd sacral vertebra. Laterally it passes through the center of acetabulum and the upper part of greater sciatic notch. Since this is the roomiest plane of pelvis, it is also known as the plane of greatest pelvic dimensions. This is almost round in shape. Internal rotation of the fetal head occurs when the biparietal diameter of the fetal skull occupies this wide pelvic plane while the occiput is on the pelvic floor i.e. at the plane of least pelvic dimensions.

Diameters of pelvic cavity

Anterior posterior diameter (12 cm): It measures from the midpoint on the posterior surface of pubis symphysis to the junction of second and third sacral vertebra.

Transverse diameter (12 cm): It is the distance between two farthest points laterally. Since there are no bony landmarks, the diameter cannot be exactly measured and can be roughly estimated to be about 12 cm.

Pelvic outlet

Anatomical outlet: It is a lozenge shaped cavity bounded by anterior border of symphysis pubis, pubic arch, ischial tuberosities, sacrotuberous ligaments, sacrospinous ligaments and tip of coccyx.

Plane of anatomical outlet: It passes along with the boundaries of the anatomical outlet and consists of two triangular planes with a common base which is the bituberous diameter.

Anterior sagittal plane: Its apex is at the lower border of the symphysis pubis.

Anterior sagittal diameter (6-7 cm): It extends from the lower border of the pubic symphysis to the center of bituberous diameter.

Posterior sagittal plane: Its apex lies at the tip of the coccyx.

Posterior sagittal diameter (7.5-10 cm): It extends from the tip of the sacrum to the center of bituberous diameter.

Obstetric outlet: It is bounded above by the plane of least pelvic dimensions, below by the anatomical outlet, anteriorly by the lower border of symphysis pubis, posteriorly by the coccyx and laterally by the ischial spines.

Diameters of pelvic outlet

Anterior posterior diameters of pelvic outlet include the following:

- *Anatomical anterior posterior diameter (11 cm):* It extends from tip of the coccyx to the lower border of symphysis pubis.
- *Obstetric anterior posterior diameter (13 cm):* It extends from the lower border of symphysis pubis to the tip of coccyx (as it moves backwards during the second stage of labor).

Transverse diameter of the pelvic outlet inlude the following:

- *Bituberous diameter (11cm):* It extends between the inner aspects of ischial tuberosities
- *Bispinous diameter (10.5 cm):* It extends between the tips of ischial spines.

Summary of the measurement of the diameters of the pelvis

Important diameters of pelvis are summarized in table 1.15.

Pelvic axis

Anatomical axis: This is an imaginary line joining the central points of the planes of inlet, cavity and outlet. This axis is C-shaped with concavity directed forwards. It has no obstetric significance.

Obstetric axis: It is an imaginary line which represents the direction in which the head passes during the labor. It is J-shaped and passes downwards and backwards along the axis of the inlet till the ischial spines are reached after which it passes downwards and forwards along the axis of pelvic outlet (figure 1.23).

Table 1.15: Summary of the measurement of the diameters of the pelvis

Diameter	*Pelvic brim*	*Pelvic cavity*	*Pelvic outlet*
Anterior posterior	11 cm	12 cm	13 cm
Oblique	12 cm	12 cm	-
Transverse	13 cm	12 cm	11 cm

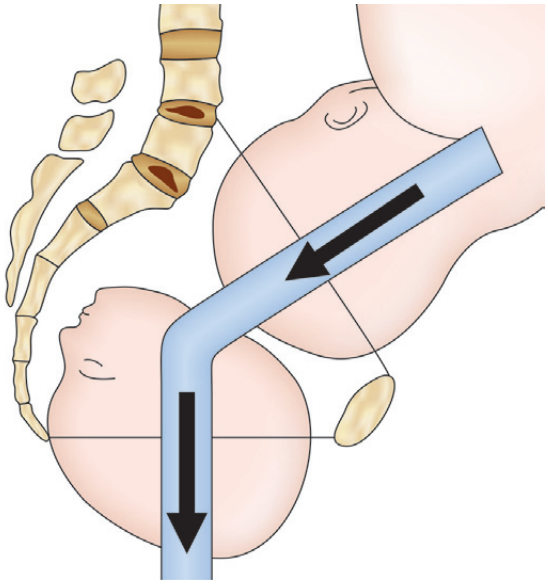


Fig. 1.23: Obstetric axis

Midpelvis

Midpelvic plane: This plane is bounded anteriorly by the lower margin of symphysis pubis. It extends through the ischial spines to the junction of S4 and S5 or the tip of fifth sacral piece, depending upon the structure of the sacrum. If this plane meets at the tip of the S5 sacral piece, this plane becomes same as that of the plane of least pelvic dimensions; otherwise it forms a wedge posteriorly.

Diameters of midpelvis

Anterior posterior diameter (11.5 cm): It is measured from the lower border of the symphysis pubis to the junction of S4 and S5 or the tip of S5, which ever is applicable.

Bispinous or transverse diameter (10.5 cm): It is the distance between two ischial spines.

Subpubic angle: It is the angle between two pubic rami. It varies from 85 ± 5°.

Waste space of Morris

Normally the width of the pubic arch is such that a round disc of 9.4 cm (diameter of a well flexed head) can pass through the pubic arch at a distance of 1 cm from the midpoint of the inferior border of the symphysis pubis. This distance is known as the "waste space of Morris" (figure 1.24). In case of an inadequate pelvis with narrow pubic arch, the fetal head would be pushed backwards and the waste space of Morris would increase. As a result, reduced space would be available for fetal head to pass through, due to which the fetal head would be forced to pass through a smaller diameter termed

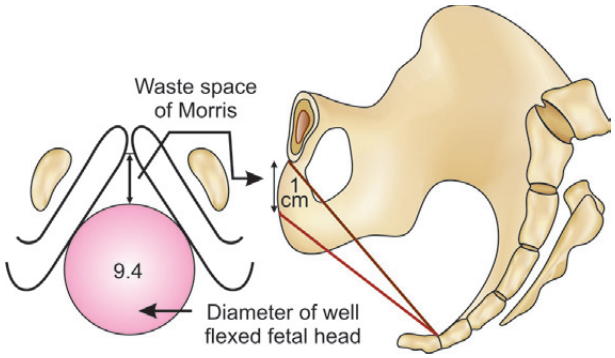


Fig. 1.24: Waste space of Morris

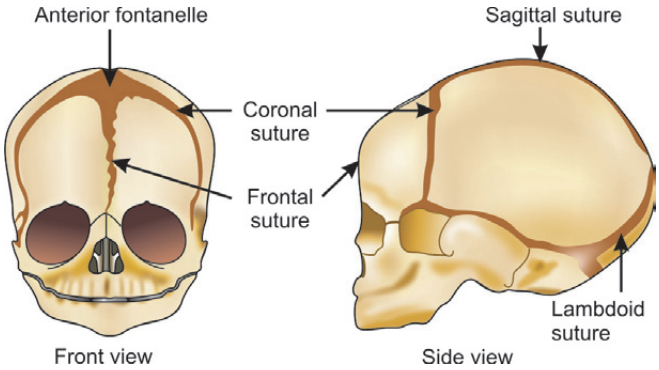


Fig 1.26: Important sutures and fontanelle in the fetal skull

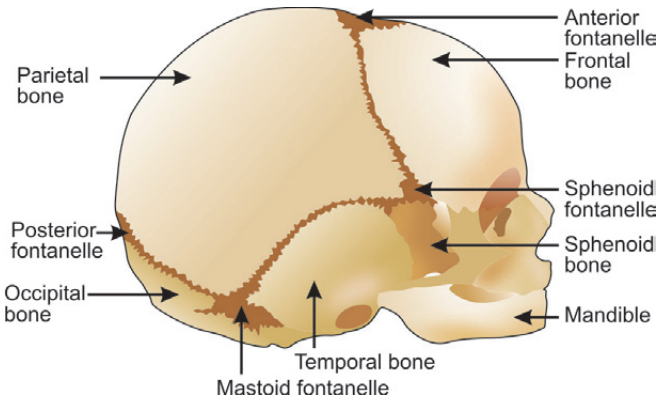


Fig. 1.25: Important sutures and bones of fetal skull

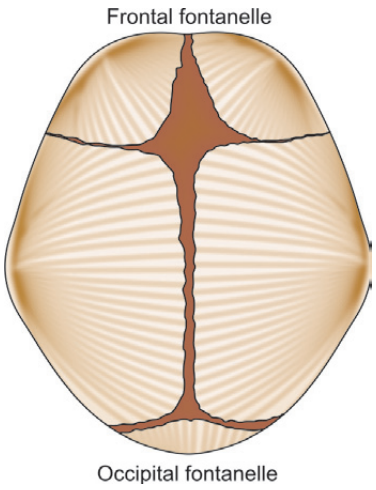


Fig 1.27: Anterior and posterior fontanelle in fetal head

as the "available anterior posterior diameter." This is likely to injure the perineum or sometimes cause the arrest of fetal head.

Passenger: Fetus

Obstetrically, the head of fetus is the most important part, since an essential feature of labor is an adaptation between the fetal head and the maternal bony pelvis. Only a comparatively small part of the head of the fetus at term is represented by the face; the rest is composed of the firm skull, which is made up of two frontal, two parietal and two temporal bones, along with the upper portion of the occipital bone and the wings of the sphenoid. The bones are not united rigidly but are separated by membranous spaces, the sutures. The fetal skull has four main sutures (figures 1.25 and 1.26) and are as follows:

- *Sagittal or longitudinal suture:* Lies longitudinally across the vault of the skull in midline. It lies between the two parietal bones.
- *Coronal suture:* These sutures are present between the parietal and frontal bones and extend transversely on either side from the anterior fontanelle.
- *Lambdoid suture:* This suture separates the occipital bone from the two parietal bones and extends transversely both on the right and left side from the posterior fontanelle.
- *Frontal suture:* This suture is present between the two halves of the frontal bone in the skull of infants and children and usually disappears by the age of six.

Where several sutures meet, an irregular space is formed, which is enclosed by a membrane and is designated as a fontanelle. The greater or anterior fontanelle is a lozenge-shaped space situated at the junction of the sagittal and coronal sutures (figures 1.26 and 1.27). The lesser, or posterior fontanelle is represented by a small triangular area at the intersection of the sagittal and lambdoid sutures. Both may be felt readily during labor, and their recognition gives important information concerning the presentation and position of the fetus. The two main fontanelles having obstetric significance in the fetal head are anterior fontanelle (bregma) and posterior fontanelle (lambda). Anterior fontanelle is formed by joining of four sutures: Frontal suture (anteriorly); sagittal suture

Table 1.16: Obstetric significance of the anterior fontanelle

Palpation of anterior fontanelle indicates degree of flexion of fetal head
It facilitates molding of fetal head
The membranous nature of anterior fontanelle helps in accommodating the rapid growth of brain during neonatal period
Floor of the anterior fontanelle reflects the intracranial status: The floor may be depressed in case of dehydration and elevated in case of hydrocephalus or other conditions with raised intracranial tension.

(posteriorly) and coronal sutures on the two sides (laterally). The palpation of anterior fontenelle on vaginal examination is of great obstetric significance (table 1.16). On the other hand, posterior fontanelle is formed by the joining of three sutures: Sagittal suture (anteriorly) and lambdoid sutures on the two sides.

Presenting Parts of Fetal Skull (Figure 1.28)

These include the following:

Vertex: This is a quadrangular area bounded anteriorly by bregma (anterior fontanelle) and coronal sutures; posteriorly by lambda (posterior fontanelle) and lambdoid sutures; and laterally by arbitrary lines passing through the parietal eminences. When vertex is the presenting part, fetal head lies in flexion.

Face: This is an area bounded by the root of the nose along with the supraorbital ridges and the junction of the chin or floor of mouth with the neck. Fetal head is fully extended during this presentation.

Brow: This is an area of forehead extending from the root of nose and superaorbital ridges to the bregma and coronal sutures. The fetal head lies midway between full flexion and full extension in this presentation.

Some other parts of fetal skull, which are of significance, include the following:

Sinciput: Area in front of the anterior fontanelle corresponding to the forehead.

Occiput: Area limited to occipital bone.

Mentum: Chin of the fetus.

Parietal eminences: Prominent eminences on each of the parietal bones.

Subocciput: This is the junction of fetal neck and occiput, sometimes also known as the nape of the neck.

Submentum: This is the junction between the neck and chin.

Important Diameters of Fetal Skull

Anterior posterior diameters

The important anterior posterior diameters of the fetal skull are suboccipitobregmatic (9.4 cm); suboccipitofrontal (10 cm); occipitofrontal (11.2 cm); mentovertical (13.9 cm); submentovertical (11.3 cm) and submentobregmatic (9.4 cm). These diameters are described in table 1.17 and figure 1.29.

Transverse diameters

Biparietal diameter (9.5 cm): It extents between the two parietal eminences. This diameter nearly always engages.

Supersubparietal diameter (8.5 cm): It extents from a point placed below one parietal eminence to a point placed above the other parietal eminence of the opposite side

Bitemporal diameter (8 cm): Distance between the anteroinferior ends of the coronal sutures.

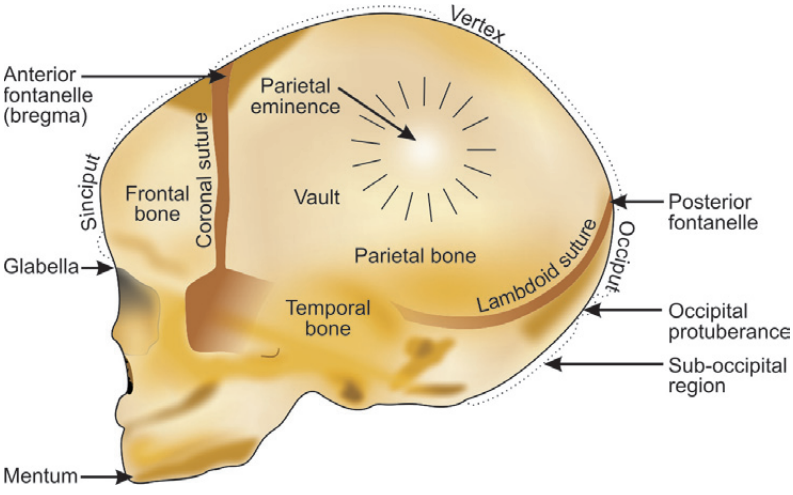


Fig. 1.28: Important landmarks of fetal skull

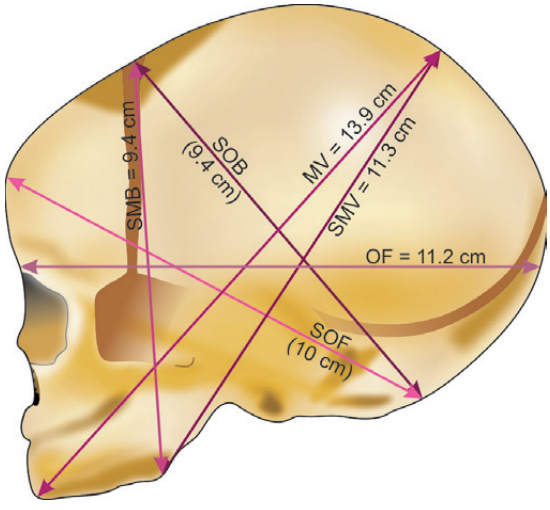


Fig. 1.29: Diameters of fetal skull

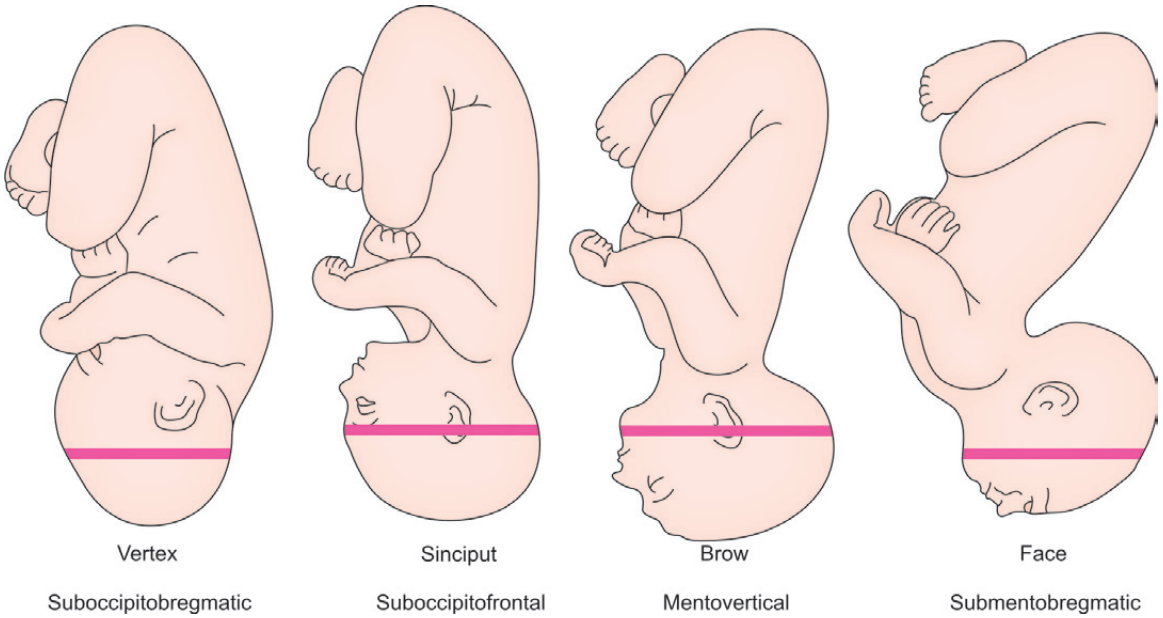


Fig. 1.30: Engaging diameters of fetal head depending on the position of presenting part

Table 1.17: Anterior posterior diameters of the fetal head which may engage

Diameter	*Extent*	*Length*	*Attitude of head*	*Presentation*
Suboccipitobregmatic	Extends from the nape of the neck to the center of bregma	9.4 cm	Complete flexion	Vertex
Suboccipitofrontal	Extends from the nape of the neck to the anterior end of anterior fontenelle or center of sinciput	10 cm	Incomplete flexion	Vertex
Occipitofrontal	Extends from the occipital eminence to the root of nose (glabella)	11.2 cm	Marked deflexion	Vertex
Mentovertical	Extends from midpoint of the chin to the highest point on sagittal suture	13.9 cm	Partial extension	Brow
Submentovertical	Extends from the junction of the floor of the mouth and neck to the highest point on sagittal suture	11.3 cm	Incomplete extension	Face
Submentobregmatic	Extends from the junction of the floor of the mouth and neck to the center of bregma	9.4 cm	Complete extension	Face

Bimastoid diameter (7.5 cm): Distance between the tips of the mastoid process. This diameter is nearly incompressible.

The fetal head is said to be engaged when maximum transverse diameter of fetal head can pass through the pelvic brim. The shape and the diameter of the circumference of the fetal skull varies with the degree of flexion and hence the presentation. A normal pelvis would be easily able to permit the engagement of the fetal skull in vertex and face presentations. This is so as in case of vertex and face presentations, the engaging anterior posterior diameters of fetal skull are respectively suboccipitobregmatic (9.4 cm) and submentobregmatic (9.4 cm) (table 1.18). However the passage of the fetal head in brow presentation would not be able to take place in a normal pelvis as the engaging anterior posterior diameter of fetal skull is mentovertical (13.9 cm) in this case. Therefore arrest of labor occurs when the fetal head is in brow presentation (figure 1.30).

Table 1.18: Plane of engagement of fetal head depending upon its attitude

Attitude of head	*Plane of shape*	*Engagement*
Complete flexion	Biparietal-suboccipito-bregmatic	Almost round
Deflexion	Biparietal-occipitofrontal	Oval
Incomplete extension	Biparietalmentovertical	Bigger oval
Complete extension	Biparietal-submentobregmatic	Almost round

Table 1.19: Four stages of labor

Stage of labor	*Time of onset*
First stage	Occurs between onset of true labor and the point of complete cervical dilation and effacement
Second stage	The expulsion of the fetus
Third stage	Delivery of placenta
Fourth stage	1st hour following delivery of placenta

LABOR AND ITS STAGES (TABLE 1.19)

First Stage

The first stage of labor begins with the onset of regular uterine contractions and ends with complete dilatation and effacement of cervix. The obstetrician needs to determine whether the woman is having true or false uterine contractions. True uterine contractions are regular; tend to become stronger with the passage of time, are usually experienced at lower back and radiate to abdomen, and tend to become more intense with walking, cervical changes, and with fetus moving to lower pelvis.

On the other hand, false contractions comprise of irregular contractions which stop with walking, and other measures used for providing comfort (e.g. hot fomentation, etc) and are usually experienced in the abdominal region. First stage is divided into two phases:

Latent phase (preparatory phase): It begins with onset of regular contractions, with contractions occurring after every 15 – 20 min, lasting 20 – 30 seconds. Gradually the frequency of contractions increase and they can occur after every 5 – 7 min, lasting for 30 – 40 seconds duration. This phase ends when cervix becomes about 3 – 5 cm dilated. The latent phase lasts for approximately 8 to 9 hours in the primi, and less than 6 hours in multigravida. Prolonged latent phase can be defined as greater than 20 hours in primigravida and greater than 14 hours in the multigravida.

Active phase: This phase begins when the cervix is about 4 cm dilated and ends when it becomes fully dilated. The normal rate of cervical dilatation during this stage is approximately 1 to 1.5 cm /hour. The intensity of contractions increases with the contractions occurring after every 2 to 3 minutes and lasting for about 40 – 60 seconds. This stage lasts for an average of 4.6 hours in a primigravida and approximately 2.4 hours in multigravidas.

There could be two types of problems in the active phase: Protraction disorders and arrest disorders. Protraction disorders can be defined as slow rate of cervical descent or dilatation which is < 1.2 cm dilatation per hour or less than 1 cm descent per hour in primigravidas. For multiparas, protraction can be defined as dilatation of less than 1.5 cm per hour or descent of less than 2 cm per hour. Arrest is defined as complete cessation of dilatation or descent. Arrest of dilatation is considered when two hours pass without any accompanying cervical changes. Arrest of descent is considered when one hour passes without any fetal descent. In both cases of protraction or arrest disorders, a feto-pelvic examination must be done to diagnose CPD. Recommended therapy for protracted disorders is expectant management, whereas oxytocin infusion must be used in cases of arrest disorders in absence of CPD.

Second Stage of Labor

The second stage of labor begins when the cervical dilatation and effacement is complete and ends with the delivery of the fetus. Its mean duration is 50 minutes for nullipara and 20 minutes for multipara. During this stage, the woman begins to bear down. The abdominal muscles contract, which help in the descent of fetal head. When the crowing of fetal head has occurred at vulvar opening, birth of the baby is imminent.

Mechanism of Normal Labor (Figure 1.31)

In normal labor the fetal head enters the pelvic brim most commonly through the available transverse diameter of the pelvic inlet. This is so as the most common fetal position is occipitolateral (transverse) position. In some cases the fetal head may enter through one of the oblique diameters. The fetal head with left occipitioanterior position enters through right oblique diameter, whereas that with right occipitoanterior position enters through left oblique diameter of the pelvic inlet. Left occipitoanterior position is slightly more common than the right occipito anterior position as the left oblique diameter is encroached by the rectum. The engaging AP diameter of the fetal head is suboccipitobregmatic (9.4 cm) in position of complete flexion. The engaging transverse diameter of the fetal head is biparietal diameter (9.5 cm). As the occipitolateral position of the fetal head is the commonest, the mechanism of labor in this position would be discussed. The cardinal fetal movements during the occipitolateral position comprise of the following: Engagement, flexion, descent, internal rotation, crowning, extension, restitution, external rotation of the head and expulsion of the trunk.

Engagement: In primigravida, the engagement of fetal head usually occurs before the onset of labor, while in multigravida, it may occur only during the first stage of labor, following rupture of membranes.

Descent: Descent of the fetal head is a continuous process that occurs throughout the second stage of labor in such a way that towards the end of second stage crowning of fetal head occurs.

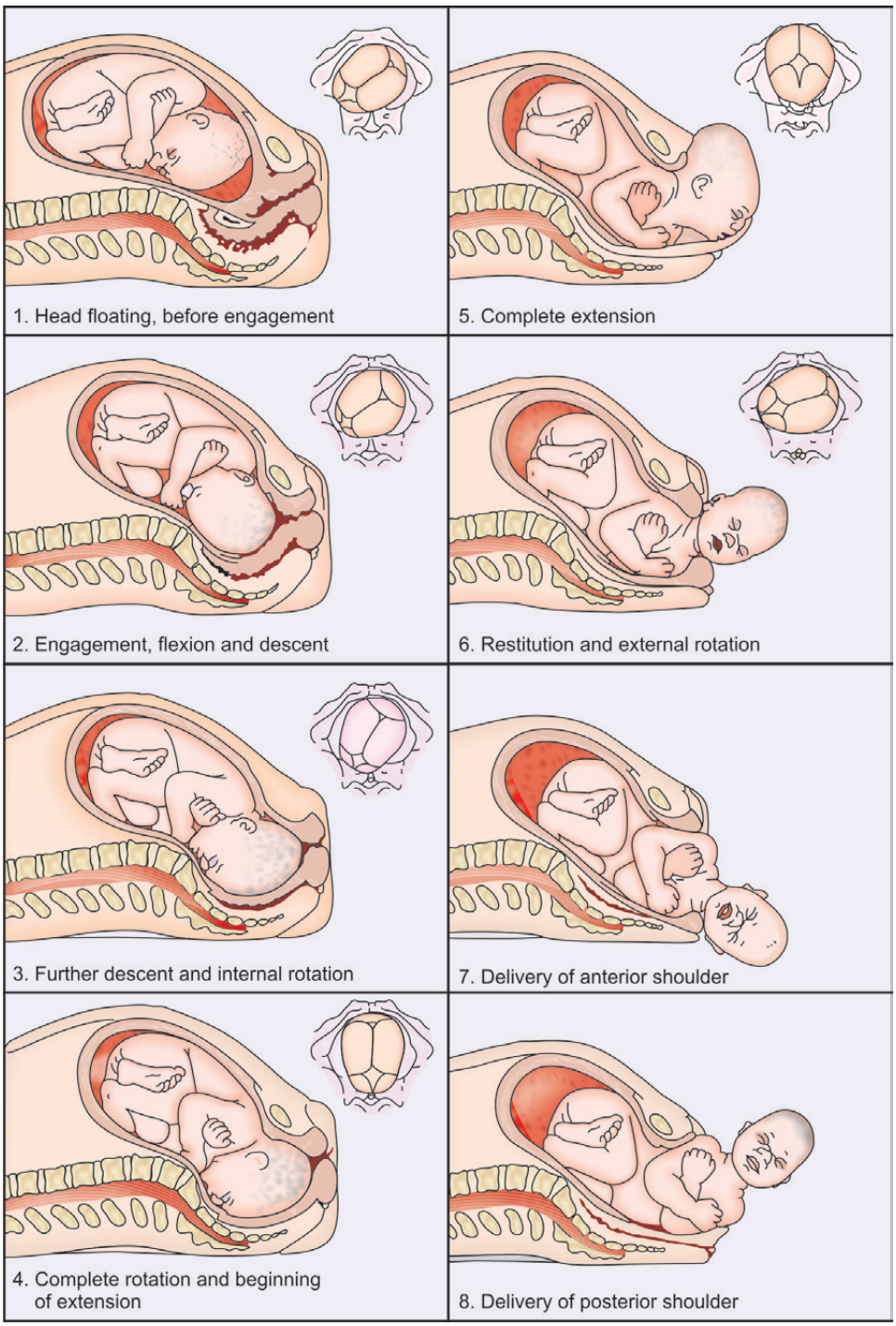


Fig. 1.31: Mechanism of normal labor

Flexion: In normal cases, increased flexion of fetal chin against chest, help in presenting the smallest fetal diameter. Flexion of the head occurs as it descends and meets the pelvic floor, bringing the chin into contact with the fetal thorax. Adequate flexion of the fetal head produces the smallest diameter of presentation, i.e. the suboccipitobregmatic diameter, which may change to the larger occipitofrontal diameter, when the fetal head is deflexed.

Internal rotation: Fetal head must rotate to accommodate the pelvis. The head rotates as it reaches the pelvic floor. In the occipitolateral position, there is anterior rotation of the fetal head by 2/8th of the circle in such a way that the occiput

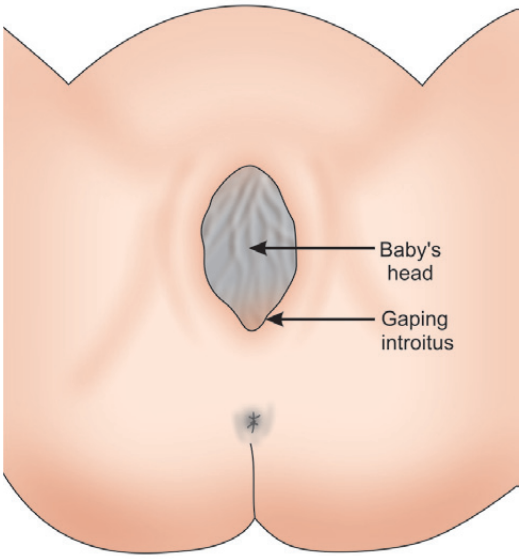


Fig. 1.32A: Baby's head visible through the vaginal introitus

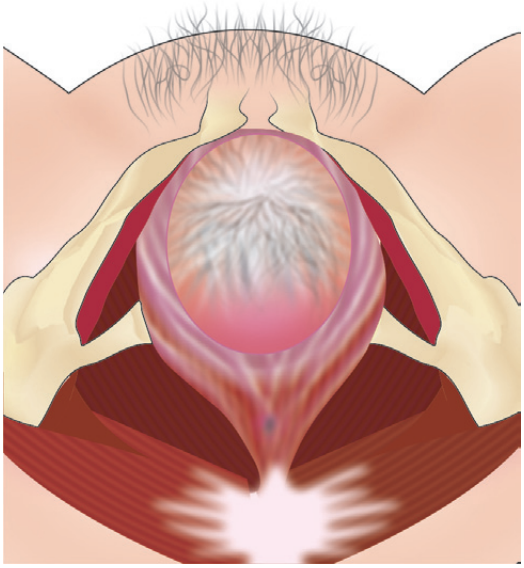


Fig. 1.32B: Crowning of the fetal head

rotates anteriorly from the lateral position towards the pubic symphysis. In case of anterior oblique position, rotation will be by 1/8th of the circle placing the occiput behind the pubic symphysis. There always occurs some descent with internal rotation. Torsion of fetal neck is a phenomenon which will inevitably occur during internal rotation of the fetal head. In case of occipitolateral position, the internal rotation of the fetal head by 2/8th of the circle is likely to cause the torsion of fetal neck by 2/8th of the circle. Since the neck would not be able to sustain this much amount of torsion, there would be simultaneous rotation of the fetal shoulders in the same direction by 1/8th of the circle. This would cause the torsion on the fetal neck to get reduced to 1/8th of the circle and would place the shoulders in an oblique diameter, i.e. right oblique with right occipitolateral and left oblique with left occipitolateral.

Crowning: With the increasing descent of the fetal head, crowning occurs. During this stage, the biparietal diameter of the fetal head stretches the vaginal introitus. Even as the uterine contractions cease, the head would not recede back during the stage of crowning (figures 1.32A and B).

Extension: Fetal head pivots under symphysis pubis and emerges out through extension, followed by occiput, then the face, and finally the chin.

Restitution: Following the delivery of fetal head (figure 1.32C), the neck which had undergone torsion previously, now untwists and aligns along with the long axis of the fetus.

External rotation of the head: As the undelivered shoulders rotate by 1/8th of the circle to occupy the anterior posterior diameter of the pelvis, this movement is visible outside

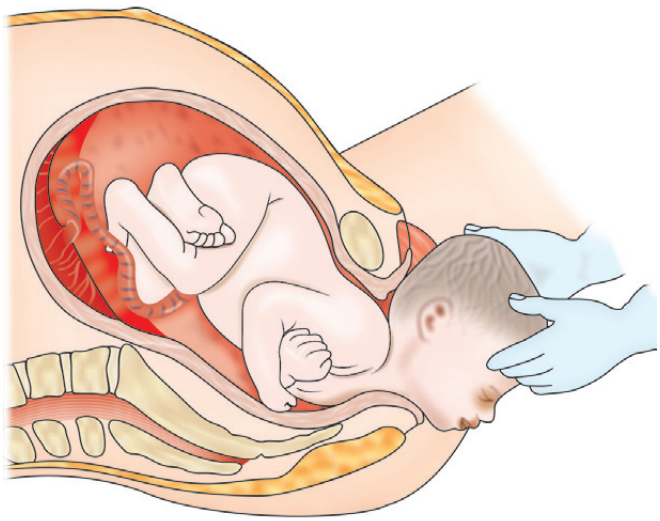


Fig. 1.32C: Delivery of the fetal head

in form of the external rotation of fetal head (figure 1.32D), causing the head to further turn to one side.

Following the engagement of the fetal shoulders in the anterior posterior diameter of the pelvis anterior shoulder slips under symphysis pubis, followed by posterior shoulder (figures 1.32E and F). Once shoulders have delivered, the rest of the trunk is delivered by lateral flexion.

- During normal labor, in absence of any complications, the following vital signs must be regularly monitored at every four hourly intervals: Pulse, blood pressure, temperature and frequency, duration and intensity of uterine contractions, fetal heart rate, fetal presentation,

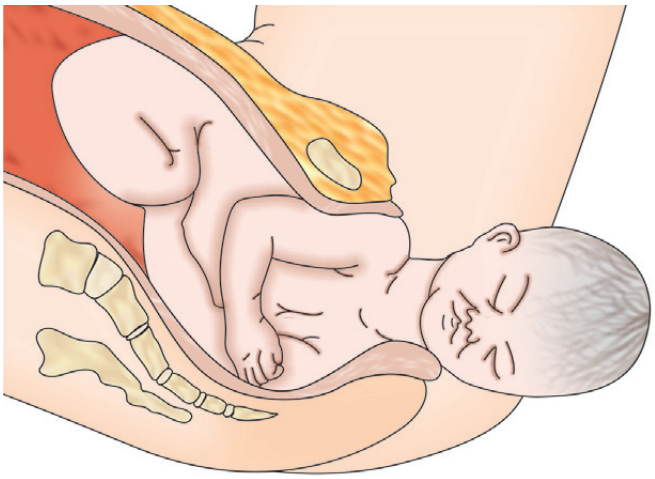


Fig. 1.32D: External rotation of head allowing delivery of shoulders

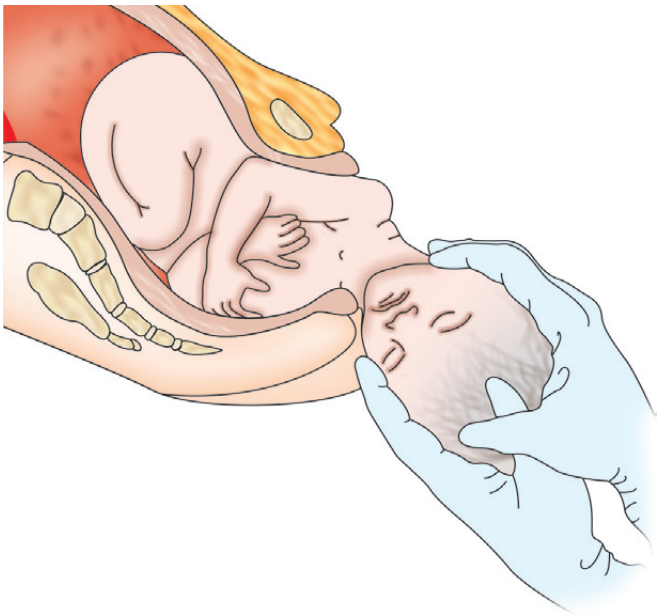


Fig. 1.32E: Delivery of anterior shoulder

presence or absence of fetal membranes and any vaginal bleeding.

- In normal pregnancy, there is no need to keep the patient confined to bed during the first stage of labor. She should be encouraged to move about in the labor room or sit on a birthing ball. She can assume any position in which she is comfortable in the bed.
- Bladder distension must be avoided as it can hinder the normal progress of labor. This can subsequently lead to bladder hypotonia and infection. If at any time during the abdominal examination, the bladder is palpable, the patient must be encouraged to void. If despite of distended bladder, the patient is unable to void, catherization is indicated.
- Rupture of fetal membranes is important due to three reasons:
  - If the presenting part is not fixed in the pelvis, there is a possibility of umbilical cord prolapse and cord compression.
  - Labor is likely to begin soon following the rupture of membranes.
  - If delivery is delayed for more than twenty four hours following rupture of membranes, there is a high possibility of intrauterine infection. If membranes have ruptured for more than 18 hours, antimicrobial therapy must be administered in order to reduce the risk of infection.
- During the second stage of labor, the woman must be encouraged to push down with each uterine contraction and then relax at the time the contractions stop. During this period of active bearing down, the fetal heart rate must be auscultated following each uterine contraction. Though FHS may be slow immediately following a contraction, it must recover in the time interval before the next contraction begins.

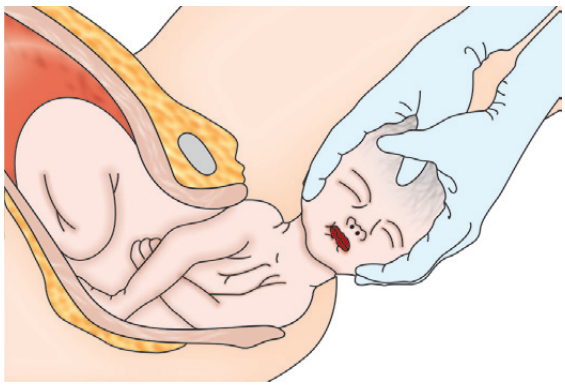


Fig. 1.32F: Delivery of posterior shoulder

Preparation for Normal Vaginal Delivery

- The most commonly adopted position at the time of delivery is dorsal lithotomy position.
- Vulvar and perineal cleaning and draping with antiseptic solution must be done.
- The sterile drapes must be placed in such a way that only the area immediately around the vulva and perineum is exposed.
- *Delivery of fetal head*: With the increasing descent of the head, the perineum bulges and thins out considerably. As

the largest diameter of the fetal head distends the vaginal introitus, the crowning is said to occur (figures 1.32A and B).

- As the head distends the perineum and it appears that tears may occur in the area of vaginal introitus, mediolateral surgical incision called episiotomy may be given. Episiotomy is no longer recommended as a routine procedure and is performed only if the obstetrician feels its requirement.
- As the fetal head progressively distends the vaginal introitus, the obstetrician in order to facilitate the controlled birth of the head must place the fingers of one hand against the baby's head to keep it flexed and apply perineal support with the other hand. Increasing flexion of the fetal head would facilitate the delivery of the smallest diameter of fetal head. This can be achieved with help of Ritgen maneuver. In this maneuver, one of the obstetrician's gloved hand is used for exerting downwards and forward pressure on the chin through the perineum, just in front of the coccyx. The other hand exerts pressure superiorly against the occiput. This helps in providing controlled delivery of the head and favors extension at the time of actual delivery so that the head is delivered with its smallest diameter passing through the introitus and minimal injury accurs to the pelvic muscultature.
- Once the baby's head delivers, the woman must be encouraged not to push. The baby's mouth and nose must be suctioned.
- The obstetrician must then feel around the baby's neck in order to rule out the presence of cord around the fetal neck. If the cord is around the neck but is loose, it should be slipped over the baby's head. However, if the cord is tight around the neck, it should be doubly clamped and cut before proceeding with the delivery of fetal shoulders.
- *Delivery of the shoulders*: Following the delivery of fetal head, the fetal head falls posteriorly, while the face comes in contact with the maternal anus. As the restitution or external rotation of the fetal head occurs, the occiput turns towards one of the maternal thighs and the head assumes a transverse position. This movement implies that bisacromial diameter has rotated and has occupied the A-P diameter of the pelvis. Soon the anterior shoulder appears at the vaginal introitus. Following the delivery of the anterior shoulder, the posterior shoulder is born. The obstetrician must move the baby's head posteriorly to deliver the shoulder that is anterior.
- *Delivery of the rest of the body:* This is followed by the delivery of the rest of the body. The rest of the baby's body must be supported with one hand as it slides out of the vaginal introitus.
- *Clamping the cord*: The umbilical cord must be clamped and cut if not done earlier. Two clamps must be placed on the umbilical cord and cord must be cut in between them with help of scissors. Delayed clamping of the cord would help in transferring about 80 ml of blood from the placenta to the neonate which would help in supplying 50 mg of iron to the fetus. This strategy would help in preventing the development of anemia.
- The baby must be placed over the mother's abdomen and then handed over to the assisting nurse or the pediatrician.
- The baby's body must be thoroughly dried, the eyes be wiped and baby's breathing must be assessed.
- In order to minimize the chances of aspiration of amniotic fluid, soon after the delivery of the thorax, the face must be wiped and the mouth and fetal nostrils must be aspirated.
- The baby must be covered with a soft, dry cloth, and a blanket to ensure that the baby remains warm and no heat loss occurs.
- Following the delivery of baby, the placenta needs to be delivered. The obstetrician must look for signs of placental separation following the delivery of the baby.
- The third stage of labor must be actively managed (as described in chapter 10).

Complications

Important complications of pregnancy which must be looked for include the following:

Abnormal Fetal Presentations

- Breech presentation (chapter 2)
- Transverse lie (chapter 3)

Complications as a Result of Pregnancy

- Antepartum hemorrhage (chapter 4)
- Multifetal gestation (chapter 5)
- Rh negative isoimmunization (chapter 6)
- Previous LSCS (chapter 7)
- Gestational trophoblastic disease (chapter 8)
- Bad obstetric history (chapter 9)
- Postpartum hemorrhage (chapter 10)
- Intrauterine growth retardation (chapter 11)

Medical Disorders Related to Pregnancy

- Preeclampsia (chapter 12)
- Gestational diabetes (chapter 13)
- Anemia in pregnancy (chapter 14)
- Heart disease in pregnancy (chapter 15)

Important Questions and Answers

Q.1. In the above mentioned case study, there has been a decrease in S-F height by 1 cm over the past week. Should it be a cause of worry? Was the obstetrician correct in assuring the women that everything was fine?

Ans. A slight decrease in S-F height at 37 weeks of gestation is a normal phenomenon, which indicates that the fetal head is descending normally in the pelvis. This also helps in ruling out the cephalo-pelvic disproportion. The obstetrician was absolutely correct in assuring the women that every thing was fine.

Q.2. What is the significance of the fetal head which is two-fifths palpable above the pelvic brim?

Ans. The fact that the fetal head is two-fifths palpable above the pelvic brim implies that the fetal head has begun to engage in the pelvic brim.

Q.3. What should be the next line of management in the patient described at the beginning of this chapter?

Ans. An external cardiotocographic trace should be carried out in this patient. The patient must be reassured that she and her fetus are healthy, and she must be asked to attend the antenatal clinic again in a week's time.

Q.4. What symptoms or signs, which may indicate the presence of serious complications and must be discussed with patients?

Ans. The below described signs and symptoms may be indicators of a serious problem. If the patient experiences any of these complaints at any time she should be asked to immediately contact her obstetrician or visit the hospital:

1. Symptoms and signs like painless vaginal bleeding could be suggestive of placenta previa. On the other hands, symptoms like vaginal bleeding with persistent, severe abdominal pain could be suggestive of abruptio placenta (see chapter 4). Severe abruptio placenta may be also associated with reduced fetal movements and/or absent fetal heart sounds.
2. Symptoms and signs like persistent headache, visual disturbances (flashes of light), and sudden severe swelling of the hand, feet or face may suggest severe preeclampsia (see chapter 12)
3. Symptoms and signs including rupture of the membranes and regular uterine contractions before the expected date of delivery, suggest preterm labor.
4. Reduced fetal movements at any time.
5. Patient experiences rupture of membranes and finds the liquor to be stained greenish in color. This could be due to meconium stained liquor.

Q.5. What is symphysis-fundus growth curve?

Ans. The symphysis-fundus growth curve helps in comparing the S-F height with the period of gestation. The growth curve should ideally form part of the antenatal card (figure 1.33). In this figure there are three lines of which the middle one represents the 50th centile, the upper one 90th centile and the lower one 10th centile, respectively. If intrauterine growth

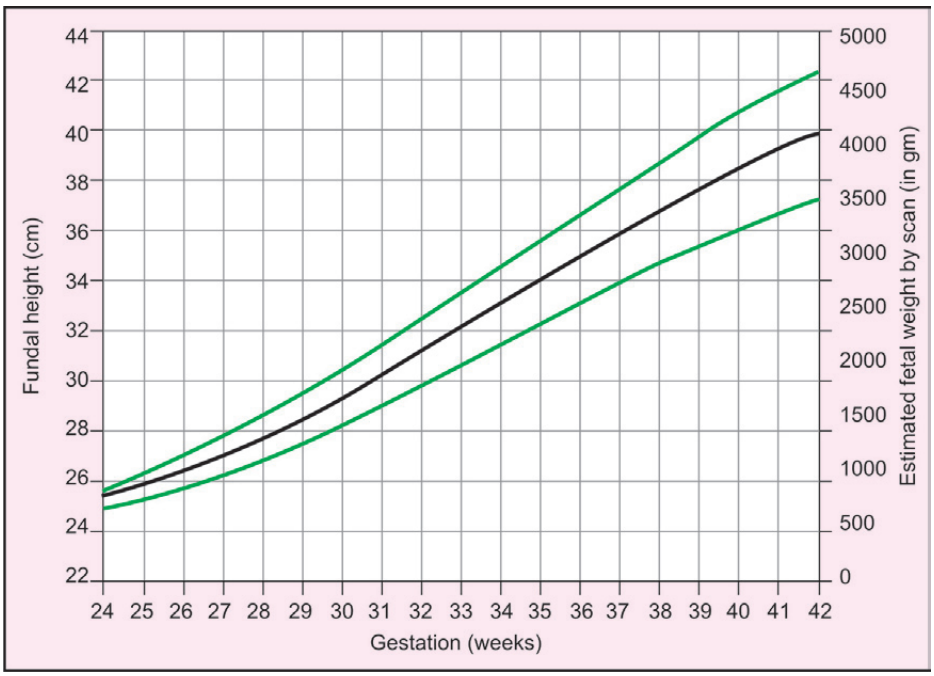


Fig. 1.33: Symphysis-fundus growth curves

is normal, the S-F height will fall between the 10th and 90th centiles. In a normal pregnancy, between 18 and 36 weeks of pregnancy, the S-F height normally increases at the rate of about 1 cm a week.

Q.6. When are fetal movements first felt?

Ans. Fetal movements felt for the first time during pregnancy are known as quickening. These movements are usually perceived by primigravida at about 20 weeks and at about 16 weeks in a multigravida. However, the exact time when the fetal movements are felt may very from woman to woman.

Q.7. What is the value of assessing fetal movements? Can fetal movements be used to determine the duration of pregnancy accurately?

Ans. Fetal movements is an indictor for fetal wellbeing. If the patient has reduced perception of the fetal movements, the obstetrician must confirm the fetal wellbeing using ultrasound examination or electronic fetal monitoring. Time of perception of fetal movements cannot be used for determining the period of gestation as the time of perception of fetal movements can greatly differ from patient to patient.

Q.8. How is the information recorded on the antenatal card?

Ans. In the front of the antenatal card, the patient's details including history, any significant findings on general physical, abdominal and vaginal examination, special investigations, LMP, EDD, and future plan of management needs to be mentioned. The back of the antenatal card is used to record the observations made at each antenatal visit throughout pregnancy. These include the following: Date of examination, blood pressure, presence of proteinuria or glycosuria on the urine examination with help of dipstick, fetal movements from 28 weeks onwards, fetal presenting part from 34 weeks onwards, hemoglobin concentration at 28 and 34 weeks and the symphysis-fundus height from 18 weeks onwards.

Q.9. What is interspinous diameter?

Ans. Interspinous diameter is the distance between the two ischial spines and represents the smallest diameter of the maternal pelvis. It corresponds to the trsansverse diameter of midpelvis and is also known as the plane of least pelvic dimensions.

Q.10. What is the importance of interspinous diameter?

Ans. Interspinous diameter is important because of the following reasons:

- Internal rotation occurs at this level.
- The obstetric axis of the pelvis changes its direction; it marks the beginning of the forward curve of pelvic axis.
- Most cases of obstructed labor or deep transverse arrest (DTA) occur at this level.
- Ischial spines correspond to the zero station of fetal presenting part.
- The head is considered engaged when the vault is felt at or below this level.
- It also corresponds to the origin of levator ani muscles and its ischiococcygeous part is attached to the ischial spines.
- Ischial spine can be considered as a landmark for giving pudental block.
- Forceps are applied only when the head is this level or lower.
- External os of the cervix is located at this level.
- The ring pessary should be applied above this level for the treatment of prolapse.
- The plane of obstetric outlet (plane of least pelvic dimensions) is at this level.

Bibliography

1. Api O, Balcin ME, Ugurel V, Api M, Turan C, Unal O. The effect of uterine fundal pressure on the duration of the second stage of labor: A randomized controlled trial. Acta Obstet Gynecol Scand. 2009;88(3):320-4.
2. ACOG. American College of Obstetricians and Gynecologists Practice Bulletin. Episiotomy. Clinical Management Guidelines for Obstetrician Gynecologists. No 71. American College of Obstetricians and Gynecologists: Washington, DC; April 2006.
3. ACOG. American College of Obstetricians and Gynecologists Practice Bulletin. Intrapartum Fetal Heart Rate Monitoring. Clinical Management Guidelines for Obstetricians Gynecologists. No 36. American College of Obstetricians and Gynecologists: Washington, DC; December 2005.
4. ACOG. American College of Obstetricians and Gynecologists Practice Bulletin. Dystocia and augmentation of labor. Clinical management guidelines for obstetricians gynecologists. No 49. American College of Obstetricians and Gynecologists: Washington, DC; December 2003.
5. ACOG. American College of Obstetricians and Gynecologists Practice Bulletin. Obstetric Analgesia and Anesthesia. Clinical Management Guidelines for Obstetricians Gynecologists. No 36. American College of Obstetricians and Gynecologist: Washington, DC; July 2002.
6. ACOG Practice Bulletin No. 80: Premature rupture of membranes. Clinical management guidelines for obstetrician gynecologists. Obstet Gynecol. 2007;109(4):1007-19.
7. Beckmann CR, Ling FW, Barzansky BM. Obstetrics and Gynecology. 4th ed. Philadelphia, Pa: Lippincott Williams and Wilkins; 2001.
8. Bloom SL, Casey BM, Schaffer JI, et al. A randomized trial of coached versus uncoached maternal pushing during the second stage of labor. Am J Obstet Gynecol. 2006;194(1):10-3.
9. Bofill JA, Vincent RD, Ross EL, et al. Nulliparous active labor, epidural analgesia and cesarean delivery for dystocia. Am J Obstet Gynecol. 1997;177(6):1465-70.
10. Caldwell WE, Moloy HC. Anatomical variations in the female pelvis and their effect in labor with a suggested classification. Am J Obstet Gynecol. 1933;26:479.

11. Christianson LM, Bovbjerg VE, McDavitt EC, et al. Risk factors for perineal injury during delivery. Am J Obstet Gynecol. 2003;189(1):255-60.
12. Creasy RK, Resnik R, Iams JD. Maternal Fetal Medicine. In: Principles and Practice. 5th ed. Philadelphia, Pa: WB Saunders; 2004.
13. Cunningham FG, Gant NF, Leveno KJ. Williams Obstetrics. 22nd ed. New York, NY: McGraw-Hill; 2005.
14. Friedman EA. Labor. In: Clinical evaluation and management. New York, NY: Appleton-Century-Crofts; 1967:34.
15. Gabbe SG, Niebyl JR, Simpson JL. Obstetrics Normal and Problem Pregnancies. 5th ed. New York: Churchill Livingstone; 2007.
16. Greenberg MB, Cheng YW, Hopkins LM, et al. Are there ethnic differences in the length of labor? Am J Obstet Gynecol. 2006; 195(3):743-8.
17. Hansen SL, Clark SL, Foster JC. Active pushing versus passive fetal descent in the second stage of labor: A randomized controlled trial. Obstet Gynecol. 2002;99(1):29-34.
18. Janni W, Schiessl B, Peschers U, et al. The prognostic impact of a prolonged second stage of labor on maternal and fetal outcome. Acta Obstet Gynecol Scand. 2002;81(3):214-21.
19. Kilpatrick SJ, Laros RK Jr. Characteristics of normal labor. Obstet Gynecol. 1989;74(1):857.
20. Kudish B, Blackwell S, Mcneeley SG, et al. Operative vaginal delivery and midline episiotomy: A bad combination for the perineum. Am J Obstet Gynecol. 2006;195(3):749-54.
21. Labor: clinical evaluation and management. New York (NY): Appleton Century Crofits; 1978
22. lbers LL, Schiff M, Gorwoda JG. The length of active labor in normal pregnancies. Obstet Gynecol. 1996;87(3):355-9.
23. McCandlish R, Bowler U, van Asten H, Berridge G, Winter C, Sames L, Garcia J, Renfrew M, Elbourne D. A randomised controlled trial of care of the perineum during the second stage of normal labour. British Journal of Obstetrics and Gynaecology. 1998;105:1262-72.
24. Menticoglou SM, Manning F, Harman C, et al. Perinatal outcome in relation to second stage duration. Am J Obstet Gynecol. 1995;173(3 Pt 1):906-12.
25. Norwitz ER, Robinson JN, Repke JT. Labor and delivery. In: Gabbe SG, Niebyl JR, Simpson JL, eds. Obstetrics: Normal and problem pregnancies. 3rd ed. New York: Churchill Livingstone; 2003.
26. O'Driscoll K, Meagher D. Introduction. In: O'Driscoll K, Meagher D, eds. Active Management of Labor. 2nd ed. Eastbourne, United Kingdom: Balliere Tindall; 1986.
27. Prendiville WJ, Elbourne D, McDonald S. Active versus expectant management in the third stage of labor. Cochrane Database Syst Rev. 2000;CD000007.
28. Rasmussen S, Bungum L, Hoie K. Maternal age and duration of labor. Acta Obstet Gynecol Scand. 1994;73(3):231-4.
29. Senécal J, Xiong X, Fraser WD. Effect of fetal position on second stage duration and labor outcome. Obstet Gynecol. 2005; 105(4):763-72.
30. Sheiner E, Levy A, Feinstein U, et al. Obstetric risk factors for failure to progress in the first versus the second stage of labor. J Matern Fetal Neonatal Med. 2002;11(6):409-13.
31. Sheiner E, Levy A, Feinstein U, et al. Risk factors and outcome of failure to progress during the first stage of labor: A population based study. Acta Obstet Gynecol Scand. 2002;81(3): 22-26.
32. Steer P, Flint C. ABC of labour care: Physiology and management of normal labor. BMJ 1999;318:793-96.

Chapter

2

Breech Presentation

Case Study

A 30-year-old primi patient with 39 completed weeks of gestation having breech presentation as diagnosed by ultrasound examination had presented for regular antenatal check-up. No other abnomality was detected on the ultrasound.

Introduction

Definition of Breech Presentation

The fetus lies longitudinally with the buttocks presenting in the lower pole of the uterus (figure 2.1).

Types of Breech Presentation

The different types of breech presentations are shown in figure 2.2 and are described below in details.

Frank breech

Most common type of breech presentation (50% to 70% cases). Buttocks present first with flexed hips and legs extended on the abdomen. This position is also known as the pike position.

Complete breech

Also known as the cannonball position, this type of presentation is present in 5% to 10% cases. In this, the buttocks

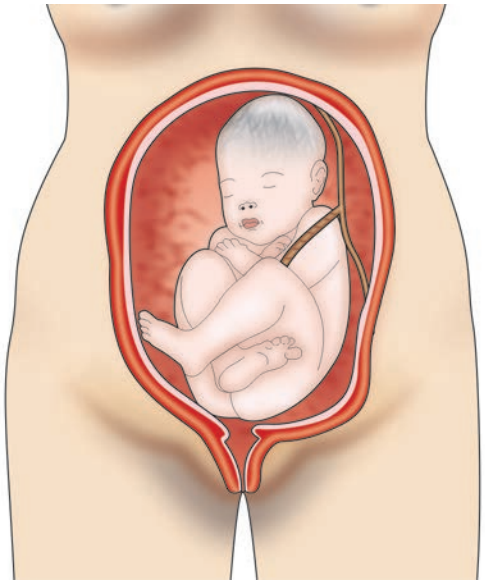


Fig. 2.1: Breech presentation

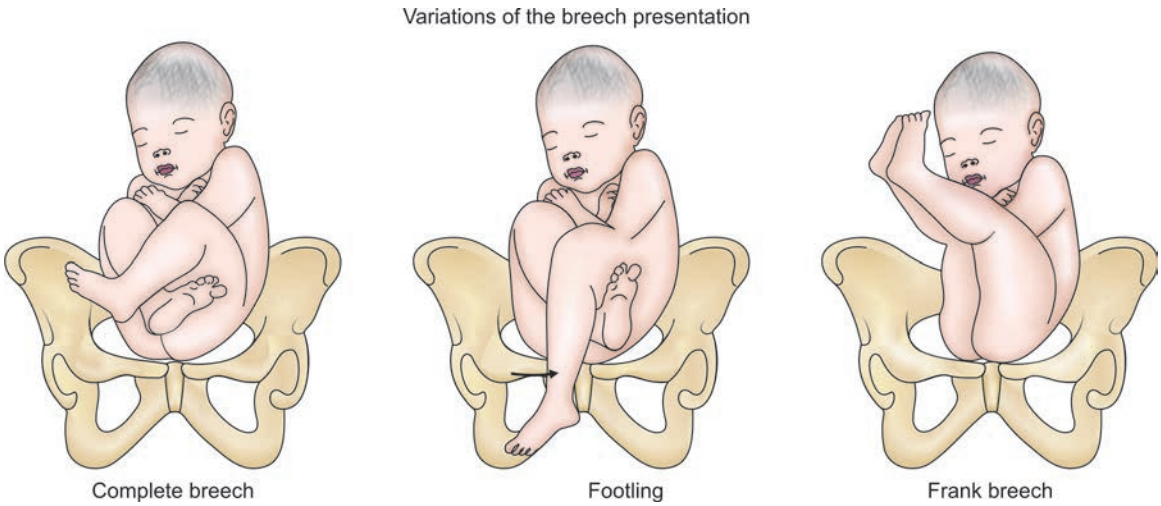


Fig. 2.2: Different types of breech presentation

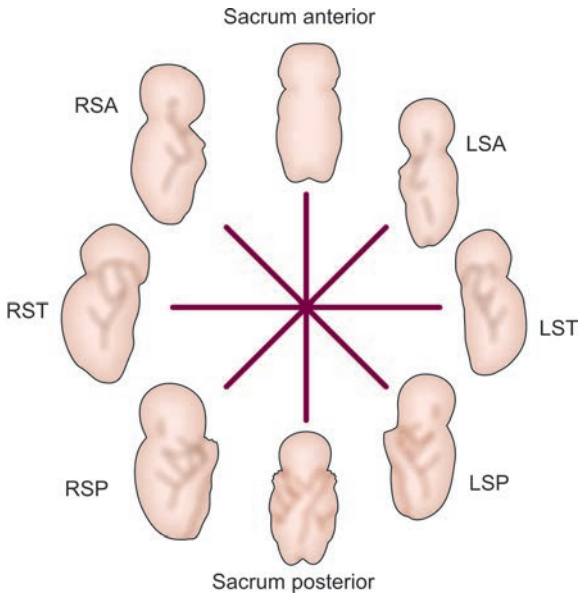


Fig. 2.3: Different positions of the breech

present first with flexed hips and flexed knees. Feet are not below the buttocks.

Footling breech

One or both feet present as both hips and knees are in extended position. As a result, feet are palpated at a level lower than the buttocks.

The denominator of breech presentation is considered to be the sacrum. Depending on the relationship of the sacrum with the sacroiliac joint, the following positions of the breech are possible (figure 2.3). These include the left sacroanterior position (LSA); right sacroanterior position (RSA); right sacroposterior position (RSP) and left sacroposterior (LSP) position. LSA position is the most common position.

History

RISK FACTORS

Maternal Factors

Maternal risk factors for breech presentation include factors such as cephalo-pelvic disproportion, contracted maternal pelvis; liquor abnormalities (polyhydraminos, oligohydramnios); uterine anomalies (bicornuate or septate uterus); space occupying lesions (e.g. fibroids in the lower uterine segment); placental abnormalities (placenta previa, cornuofundal attachment of placenta), multiparity (especially grand multiparas); cord abnormalities (very long or very short cord); previous history of breech delivery; presence of pelvic tumor.

Fetal Factors

Prematurity, fetal anomalies (e.g. neurological abnormalities, hydrocephalus, anencephaly and meningomyelocele), intrauterine fetal death, etc.

General Physical Examination

No specific finding is observed on GPE.

Specific Systemic Examination

ABDOMINAL EXAMINATION

Abdominal Palpation

Fetal lie is longitudinal with fetal head on one side and breech on the other side.

First Lepold maneuver/fundal grip

Smooth, hard, ballotable structure suggestive of fetal head.

Second Lepold maneuver/lateral grip

Firm, smooth board like fetal back on one side and knob like structures suggestive of fetal limbs on other side.

Lepold third maneuver

If the engagement has yet not occurred, the breech is movable above the pelvic brim.

Pelvic examination

Head is not felt in pelvis, instead an irregular, soft, non-ballotable structure suggestive of fetal buttocks and or feet may be felt.

Fetal heart auscultation

In case the engagement has not occurred, FHS is just heard above the umbilicus; if the engagement has occurred, the FSH is heard just below the umbilicus.

VAGINAL EXAMINATION

Soft, irregular, rounded mass may be felt; very thick meconium may be present after rupture of membranes (ROM). On vaginal examination, anus, sacrum, external genitalia and/or the foot of the baby can be palpated.

Management

Management comprising of investigations and definitive obstetric management is discussed next.

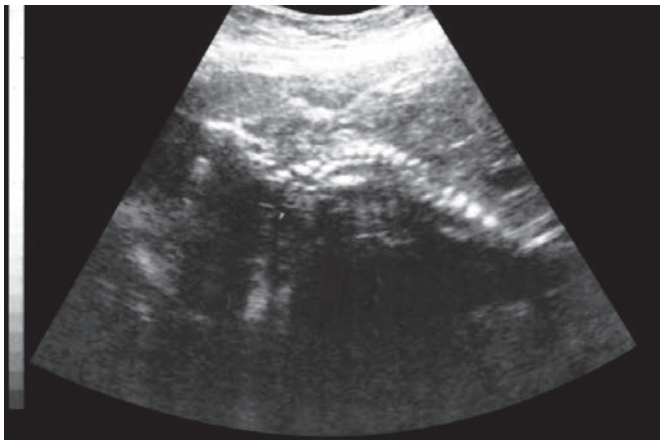


Fig. 2.4: Ultrasound examination showing breech gestation

Investigations

Ultrasound Examination

Ultrasound helps in confirming the type of breech presentation (figure 2.4). The other things which can be seen on the ultrasound include the following:

- Presence of uterine and/or fetal anomalies
- Extension of fetal head: "Star gazing sign" on ultrasound examination can be observed if the degree of extension of fetal head is more than 90°.
- Fetal maturity
- Placental location and grading
- Adequacy of liquor
- Ruling out multiple gestation

Treatment/Obstetric Management

MANAGEMENT DURING PREGNANCY

The management options for breech presentation include external cephalic version during pregnancy or delivery by cesarean section or a breech vaginal delivery at term (flow chart 2.1). Each of these management options would be described below in details.

External Cephalic Version (ECV)

Definition

External Cephalic Version is a procedure in which the clinician externally rotates the fetus from a breech presentation into a cephalic presentation. The use of external cephalic version helps in producing considerable cost savings in the management of the breech fetus at term by reducing the rate of cesarean section. The most common indications for cesarean section in obstetric practice include history of previous cesarean section and labor dystocia, followed by breech presentation. The procedure of ECV initially became popular in the 1960s and 1970s. However its use virtually disappeared following the reports of fetal deaths after the procedure. It was reintroduced in1980s and became increasingly popular in the 1990s, with increased advancement in the field of fetal monitoring. Routine use of external version has been observed to reduce the rate of cesarean delivery by about two thirds. Therefore this procedure must become a routine part of obstetric practice.

Some clinicians are against the use of ECV due to the assumption that an external version converts only those fetuses to vertex that would have converted spontaneously anyway. Review of literature shows that the efficacy of external cephalic version varies between 48% to 77%, with an average of 62%. Use of ECV is associated with minimal risks, including complications like umbilical cord entanglement, abruption placenta, preterm labor, premature rupture of the membranes (PROM), transient fetal heart changes and severe maternal discomfort.

Timing for ECV

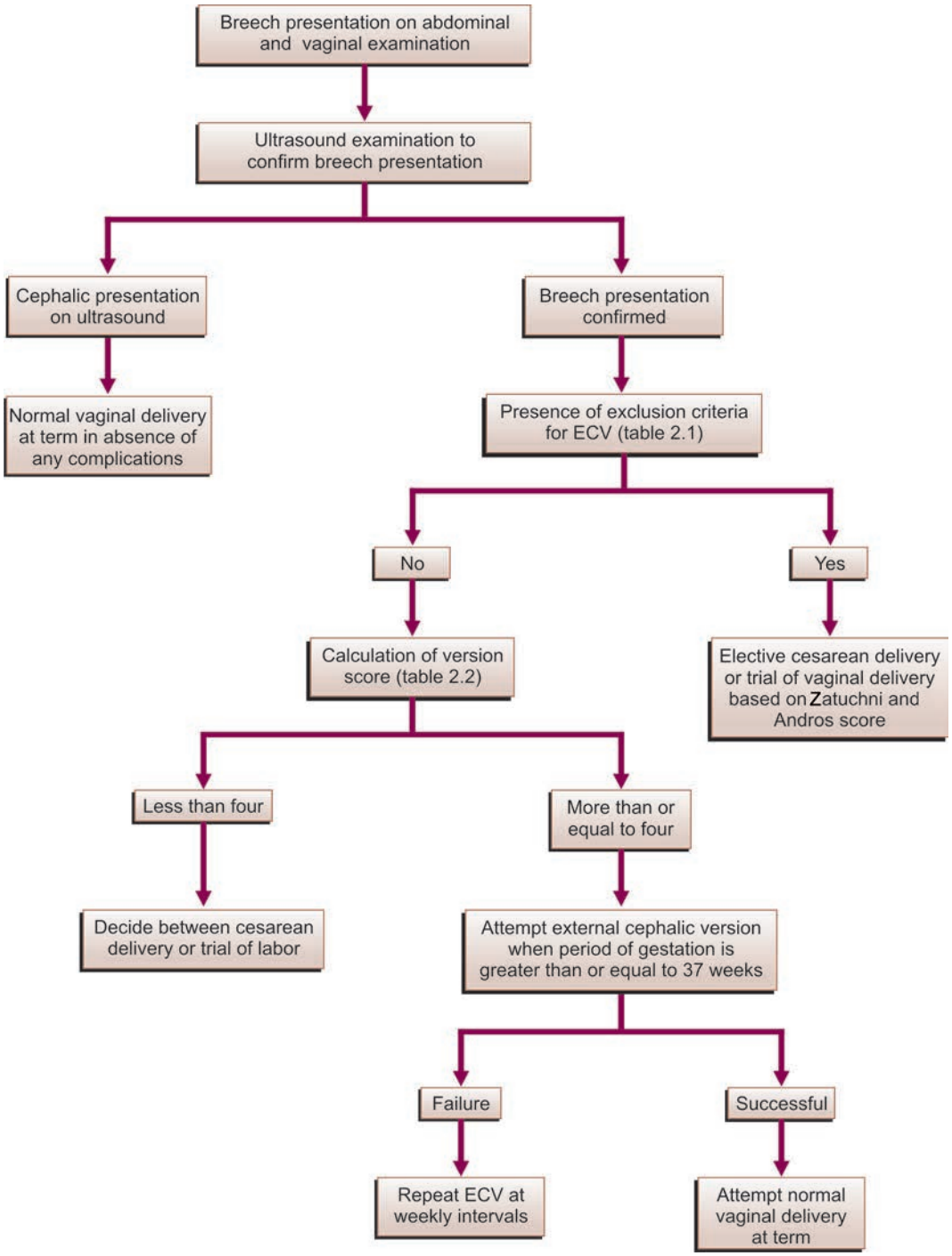
It is preferable to wait until term (37 completed weeks of gestation) before external version is attempted because of an increased success rate and avoidance of preterm delivery if complications arise. If external version is performed in preterm gestations, the success rate is believed to be 80%. However, small sized fetuses with preterm gestation may undergo spontaneous reversion back to breech presentation in about 16% cases. A small preterm fetus has more room to be turned and therefore, can revert on its own. When ECV is performed at term, though the success rate falls to 63%, the reversion rate improves to 6% to 7%. This is so the larger fetus has less freedom of movement and is therefore is less likely to revert back to breech presentation. The most important reason to wait until the fetus is at term is to avoid iatrogenic prematurity in case emergency delivery is required. This can happen if an attempt at external version results in complications like active labor, ruptured membranes, fetal compromise, etc. ECV should not be performed in the women having contraindications mentioned in table 2.1.

Prerequisites for ECV

Before the performance of ECV, the following prerequisites should be fulfilled:

- The place where ECV is being performed should have all facilities available for cesarean section or emergency breech vaginal delivery, in case it is required. There is

Flow chart 2.1: Management options for breech presentation



always a possibility for emergency cesarean section during the procedure in case there is a decline in fetal heart rate.

- Blood grouping and cross matching should be done in case an emergency cesarean section is required. In case the mother is Rh negative, administration of 50 µg of anti-D immunoglobulin is required after the procedure in order to prevent the risk of isoimmunization.
- Anesthetists must be informed well in advance.
- Maternal intravenous access must be established.
- The patient should have nothing by mouth for at least 8 hours prior to the procedure.

Table 2.1: Contraindications for ECV

Absolute contraindications	*Relative contraindications*
Multiple gestations with a breech presenting fetus	Amniotic fluid abnormalities (Polyhydramnios or oligohydramnios)
Herpes simplex virus infection	Evidence of uteroplacental insufficiency (IUGR, preeclampsia, etc)
Placenta previa	Uterine malformation and fetal anomalies
Non-reassuring fetal heart rate tracing	Maternal cardiac disease
Premature rupture of membranes	
Significant third trimester bleeding (placenta previa)	
Women with a uterine scar or abnormality	

- An ultrasound examination must be performed to confirm breech, check the rate of fetal growth, amniotic fluid volume and rule out anomalies associated with breech.
- A non-stress test or a biophysical profile must be performed prior to ECV to confirm fetal wellbeing.
- Though ECV can be performed by a clinician single handedly, an assistant is also required.
- Before performing an ECV, a written informed consent must be obtained from the mother.
- A tocolytic agent such as terbutaline in a dosage of 0.25 mg, may be administered subcutaneously. By producing uterine relaxation, administration of this drug is supposed to help increase the success rate of the procedure. The use of oral, parenteral or general anesthesia should be avoided due to an increased risk of complications. However ECV can be performed under epidural or spinal analgesia. The use of these analgesic procedures also helps in eliminating maternal pain that may cause bearing down and tensing of the abdominal muscles. The main disadvantage of these regional analgesic procedures is that the lack of maternal pain could potentially result in excessive force being applied to the fetus without the knowledge of the operator.
- Whether the process has been successful or has failed, a non-stress test and ultrasound examination must be performed after each attempt of ECV and after the end of the procedure in order to rule out fetal bradycardia and to confirm successful version.

Procedure

- The patient is placed in a supine or slight Trendelenburg position to facilitate disengagement/mobility of the breech.

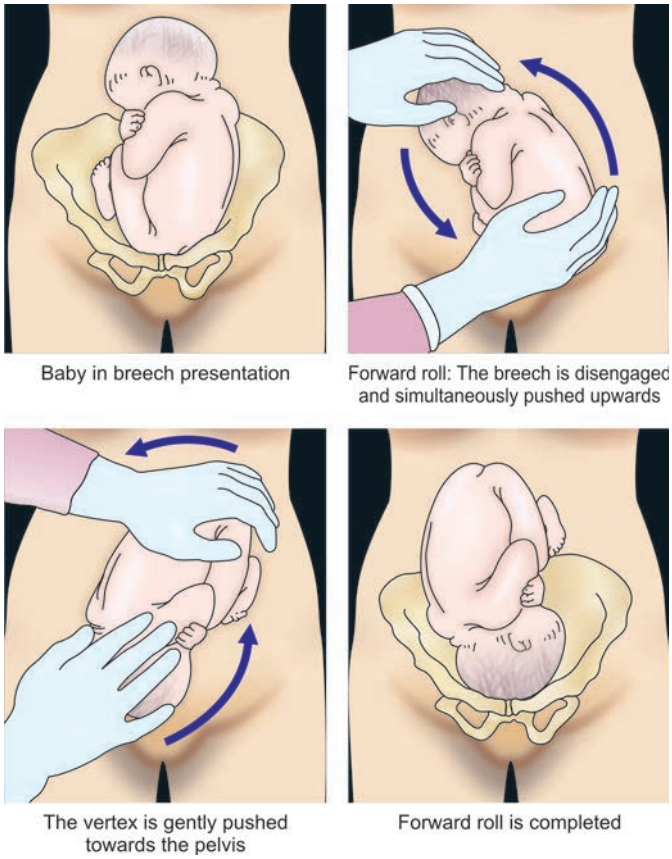
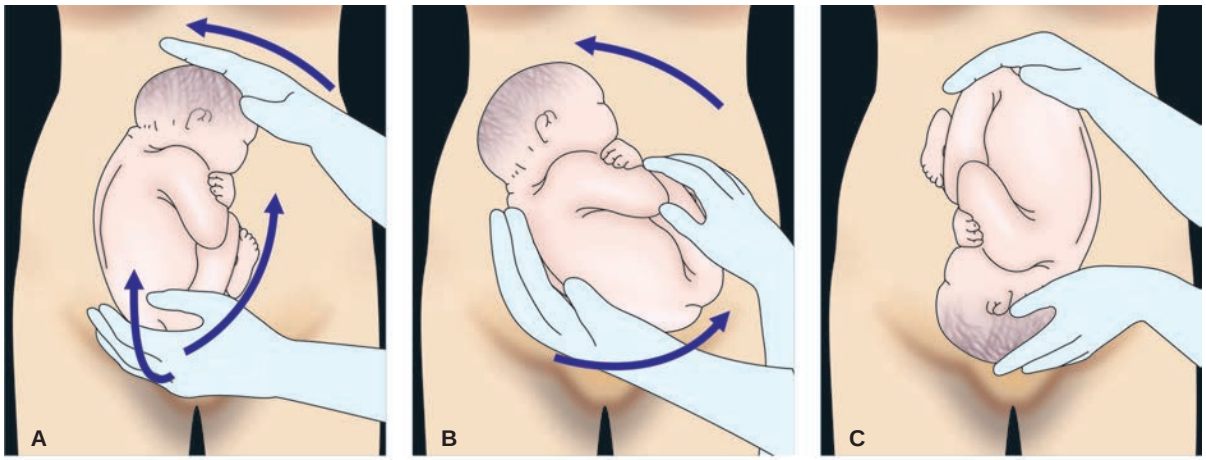


Fig. 2.5: ECV through forward roll

- Ultrasonic gel is applied liberally over the abdomen in order to decrease friction and to reduce the chances of an over-vigorous manipulation. External version can be performed by an clinician experienced in the procedure along with his/her assistant.
- Initially, the degree of engagement of the presenting part should be determined and gentle disengagement of the presenting part is performed if possible.
- While performing the ECV, the clinician helps in gently manipulating the fetal head toward the pelvis while the breech is brought up cephalad towards the fundus. Two types of manipulation of fetal head can be performed: A forward roll or a backward roll. The clinician must attempt a forward roll first and then a backward roll, if the initial attempt is unsuccessful. Though it does not matter in which direction the fetus is flipped, most physicians tend to start with a forward roll.
- The forward roll (figure 2.5) is usually helpful if the spine and head are on opposite sides of the maternal midline.
- If the spine and head of the fetus are on the same side of the maternal midline, then the back flip may be attempted (figures 2.6A to C). If the forward roll is unsuccessful, a



Disengaging the breech | Pushing the breech upwards and gently guiding the vertex towards the pelvis | Completing the back flip

Figs 2.6A to C: ECV through back flip

second attempt is usually made in the opposite direction. Use of an acoustic stimulator has been described by some researchers to help change the position of the fetal spine from midline to lateral, thereby improving the chances of success. However the advantages of the routine use of acoustic stimulation in the clinical practice has not yet been proven.

- While doing the ECV, the fetus should be moved gently rather than using forceful movements.
- If unsuccessful, the version can be reattempted at a later time. The procedure should only be performed in a facility equipped for emergency cesarean section.
- No consensus has been reached regarding how many external cephalic version attempts are appropriate at one particular time. At a particular time setting, multiple attempts can be made making sure that the procedure does not become uncomfortable for the patient. Also fetal heart rate needs to be assessed after each attempt at external cephalic version.
- If an attempt at ECV proves to be unsuccessful, the practitioner has either the option of sending the patient home and adopting an expectant management policy or proceeding with a cesarean delivery. Expectant management also involves repeat attempts of ECV at weekly intervals. With expectant management there is also a possibility that the fetus would undergo spontaneous reversion into cephalic position.

Complications of external cephalic version

Though external cephalic version is largely a safe procedure, it can have some complications, including the following:

- Premature onset of labor
- Premature rupture of the membranes
- A small amount of feto-maternal hemorrhage. This is especially dangerous in cases of Rh negative pregnancies as it can result in the development of Rh isoimmunization.
- Fetal distress leading to an emergency cesarean delivery.
- Failure of version: The baby might turn back to the breech position after the external cephalic version is done. ECV is associated with high rate of spontaneous reversion into breech presentation if performed before 36 weeks of gestation.
- Risk of cord entanglement: If fetal bradycardia is detected after a successful version, it is recommended that the infant be returned to its previous breech presentation with the hope of reducing the risk of a tangled cord.
- Transient reduction of the fetal heart rate, probably due to vagal response related to head compression with external cephalic version.

Indicators of successful ECV

Some of the indicators for successful ECV include the following:

- Multiparity: ECV is more likely to be successful in multiparous women.
- Nonfrank breech: ECV is more likely to be successful in nonfrank breech (complete breech) pregnancies in comparison to frank breech pregnancies. This is so as the splinting action of the spine in a frank breech gestation is likely to prevent movement of the fetus.
- Unengaged breech: Fetus in breech presentation which has engaged is less likely to undergo version in comparison to the unengaged fetus in breech presentation.
- Adequate liquor: Presence of reduced (oligohydramnios) or excessive liquor (hydramnios) is likely to interfere with successful version.

Table 2.2: The external version score

	0	*1*	*2*
Parity	0	1	≥2
Dilatation	≥3 cm	1 – 2 cm	0 cm
Estimated fetal weight	<2500 grams	2500–3500 grams	> 3500 grams
Placenta	Anterior	Posterior	Fundal/lateral
Station	≥ –1	– 2	≥ – 3

- Fetal acoustic stimulation and transabdominal amnioinfusion of saline: Role of fetal acoustic stimulation and transabdominal amnioinfusion of saline in improving the success rate of ECV has yet not been proven.

External version score

The external version score (table 2.2) helps in predicting the success rate of ECV. Five factors (parity, placental location, dilatation, station and estimated fetal weight) are used for calculating this score. A higher version score (greater than or equal to four) is associated with increased likelihood of successful breech version.

The type of breech (frank, complete or footling) is not a factor in determining eligibility for ECV. ECV has also been found to be safe in those who have a history of cesarean birth in the past and are the candidates for vaginal birth after cesarean delivery (VBAC). External version has been used successfully in VBAC candidates without any increase in the incidence of adverse effects including uterine rupture.

Areas of controversy regarding ECV

Presently it is yet not clear whether ECV should be performed on a woman in active labor or a woman with a previous history of uterine incisions. Though use of ECV is largely considered to be safe in women with a previous history of cesarean section, the present evidence is scant. Further studies are required to evaluate the safety and efficacy of ECV at the time of active labor and on women with a previous history of uterine incision. Also, it is yet not clear whether tocolysis should be used routinely or selectively at the time of ECV.

MANAGEMENT DURING LABOR

Mode of Delivery

There are two choices regarding mode of delivery for patients with breech presentation: Breech vaginal delivery (also known as trial of breech) or an elective cesarean section. There has been much controversy regarding choosing the best option for delivery. Parents must be informed about potential risks and benefits to the mother and neonate for both vaginal breech delivery and cesarean delivery. Presently the trend for term breech presentation is elective cesarean section. With increase in the rates of cesarean sections for breech presentation, vaginal breech deliveries are being performed at a much lower rate. The breech scoring system by Zatuchni and Andros (table 2.3) can be also used for deciding whether to perform a vaginal or an abdominal delivery. If the women has a score of 3 or less in this scoring system, it means that she should probably be delivered by a cesarean section, which would be associated with a lower degree of fetal morbidity and mortality in comparison to vaginal delivery. Higher scores, although not guarantying a safe vaginal delivery, suggest that a trial of labor with close monitoring can be considered.

Table 2.3: Zatuchni and Andros score

Parameter	*0 point*	*1 point*	*2 points*
Parity	Primigravida	Multigravida	
Gestational age	39 weeks or more	38 weeks	37 weeks
Estimated fetal weight	> 8 pounds (3690 grams)	7–8 pounds (3176–3690 grams)	<7 pounds (<3176 grams)
Previous breech > 2500 grams	None	One	Two or more
Cervical dilatation on admission by vaginal examination	2 cm or less	3 cm	4 cm or more
Station at the time of admission	–3 or higher	– 2	–1 or lower

Elective Cesarean Section

Vaginal breech deliveries had been routinely used in the past. The question regarding the use of vaginal route or abdominal route for delivery of the fetuses in breech presentation has been associated with much controversy. This controversy was particularly flared up after the declaration of the results of "the term breech trial" in 2000. The results of this trial showed that perinatal mortality and morbidity was significantly lower for women with breech presentation undergoing planned cesarean delivery in comparison to those having planned vaginal delivery. In breech presentation, sudden delivery of fetal head can cause excessive pressure on the aftercoming head of the breech resulting in a high risk for tentorial tears and intracranial hemorrhage in comparison to the fetuses in cephalic presentation. However, no significant difference in rates of maternal mortality or morbidity was observed between the

two methods in this "term breech trial". After the declaration of these results, it was proposed that all breech presentations should be delivered abdominally to reduce the rates of perinatal morbidity and mortality. In the United States, the standard recommendation is to deliver breech babies by cesarean section. Proponents of "elective cesarean section" support cesarean section because of the concern for birth asphyxia and possibility of an unexpected arrest of fetal parts at the time of vaginal delivery. Increased risk of medicolegal litigations is another factor associated with the rising incidence of elective breech cesarean deliveries. Thus, the management of term breech fetus has largely shifted from routine vaginal breech delivery to elective cesarean delivery for all. In the developing part of the world, it may sometimes not be possible to resort to cesarean delivery in every case of breech presentation. Vaginal breech delivery may become unavoidable in certain situations e.g. gravidas presenting in advanced labor with a term breech and imminent delivery or in case of a non-vertex second twin. Some of the absolute indications for cesarean section in cases of breech presentation are enumerated in table 2.4.

The proponents of the breech vaginal delivery argue that intrapartum, perinatal and neonatal risks associated with breech vaginal delivery have been overstated in several trials. The results of "the term breech trial" are now being considered to be deeply flawed. The study is thought to be suffering from selection bias as the women had not been allocated randomly to the different modes of delivery. There was lack of assurance that the clinician is trained in the skills of breech vaginal delivery, lack of comments regarding intrapartum management, etc. Furthermore, the trial may have included pregnancies which would not usually be considered for a trial of labor, e.g. footling breeches.

Also it has been argued that the same maneuvers are being used for the delivery of after coming head of the breech in cesarean delivery as in vaginal breech delivery, including the maneuvers like the Pinard's maneuver, maneuvers for delivering the shoulders and arms, the Mauriceau Smellie Veit maneuver, etc. Thus the risk rate for perinatal and neonatal injuries should be similar in both the cases.

Table 2.4: Indications for cesarean section

Cephalopelvic disproportion
Placenta previa
Estimated fetal weight > 4 kg
Hyperextension of fetal head
Footling breech (danger of entrapment of head in an incompletely dilated cervix)
Severe IUGR
Clinician not competent with the technique of breech vaginal delivery
A viable preterm fetus in active labor

A possibility of entrapment of head can still occur during cesarean delivery as the uterus contracts after delivery of the body up to the level of shoulders. The chances of head entrapment are higher with preterm breeches, especially when a low transverse uterine incision is used at the time of cesarean section. Due to this, some practitioners have routinely started performing low vertical uterine incisions for preterm breeches prior to 32 weeks' gestation to avoid head entrapment. Low vertical incisions may require extension up to the corpus, thereby mandating the requirement for cesarean delivery for all future deliveries.

Certain precautions which a clinician can take to prevent head entrapment include the following:

- At the time of cesarean delivery, the physician must try to keep the membranes intact as long as possible. He/she should move quickly once the breech has been extracted in order to deliver the after coming head before the uterus begins to contract. The clinician should make sure that not more than four minutes elapse from the time of uterine incision to the delivery of fetal head.
- The transverse uterine incision can be extended vertically upward (T-shaped incision) or laterally while curving upwards (J-shaped incision) if any difficulty occurs with delivery of the fetal head.
- A short acting dose of nitroglycerin can be used to relax the uterus and cervix in order to facilitate delivery.

Trial of Breech (Vaginal Breech Delivery)

The major difference between the breech vaginal delivery and normal vaginal delivery in cephalic presentation is based on the fact that in cephalic presentation, the head which is the largest and least compressible structure of the fetus is delivered first followed by the rest of the body. Once the head has delivered in cases of cephalic presentation, the rest of the body follows without much difficulty. On the other hand in breech presentation, the buttocks which are compressible structures are delivered first followed by the head. This can result in the entrapment of fetal head. The criteria for defining entrapment of fetal head are described in table 2.5. The maximum danger for entrapment of fetal head is case of footling presentation. In these cases the fetal leg and foot can deliver through partially dilated cervix followed by entrapment of fetal head. Also breech presentation is a slow dilator of cervix. Due to an irregular-fitting presenting fetal part, the risk of PROM and cord prolapse is increased. Therefore with breech vaginal delivery anytime during the course of vaginal

Table 2.5: Criteria for describing entrapment of fetal head

More than 90 seconds have elapsed between delivery of fetal head and the body
Need for additional or unusual maneuvers to effect the delivery of fetal head
In case of cesarean section, more than four minutes have elapsed from the time of uterine incision to the delivery of fetal head

Table 2.6: Criteria for deciding trial of breech

37 completed weeks of gestation
Frank or complete breech
Estimated fetal weight between 1.5–3.5 kg
Well-flexed fetal head
No feto-pelvic disproportion
No contraindication for labor or vaginal birth
No obstetric indication for cesarean section
No IUGR
Informed consent given by the patient

delivery, a situation may arise when the clinician might have to resort to cesarean section for fetal or maternal sake. Thus the vaginal breech birth should take place in a hospital with facilities for emergency cesarean section. Vaginal breech delivery may become unavoidable in situations like gravidas presenting in advanced labor with a term breech, delivery appearing imminent, a nonvertex second twin, etc. Criteria which need to be kept in mind before deciding trial of breech are described in table 2.6.

While in cephalic presentation, the head delivers gradually after undergoing molding, in breech presentation the fetal head delivers suddenly. As a result, sudden excessive pressure on the aftercoming head of the breech is associated with a high risk of tentorial tears and intracranial hemorrhage in comparison to the fetuses in cephalic presentation.

Mechanism of breech vaginal delivery

The breech most commonly presents in left sacroanterior position, which causes the bitrochanteric diameter of the buttocks (9.5 cm) to enter through the pelvic inlet in the right oblique diameter of the pelvic brim (figure 2.7A). Once the bitrochanteric diameter has passed through the oblique diameter of pelvis, engagement is said to occur (figure 2.7B). With full dilatation of the cervix, the buttocks descend deeply into the pelvis. The descent of remaining fetal parts is however slow.

When the buttocks reach the pelvic floor, the anterior hip which reaches the pelvic floor first, internally rotates through 45° so that the bitrochanteric diameter lies in the anteroposterior diameter of the pelvic outlet.

With continuing fetal descend, the anterior buttock appears at the vulva. With further uterine contractions the buttocks distend the vaginal outlet. There is delivery of anterior hip followed by that of posterior hip by lateral flexion. The anterior hip slips out under the pubic symphysis followed by the lower limbs and feet (figure 2.7C).

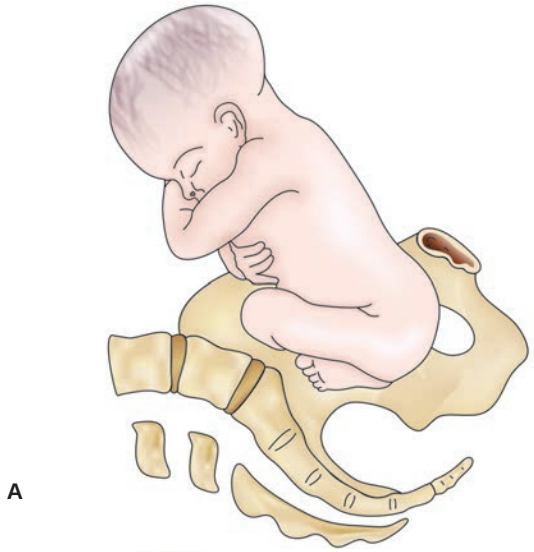
Following the delivery of buttocks and legs, sacrum rotates by 45° in the direction opposite to the internal rotation, resulting in the external rotation of the breech. This causes the back to turn anteriorly (figure 2.7D). With continuing descend, the bisacromial diameter (12 cm) of the shoulders engages in right oblique diameter of the pelvis and descent continues (figure 2.7E). On touching the pelvic floor, the anterior shoulders undergo internal rotation by 45° so that the bisacromial diameter lies in the anteroposterior diameter of the outlet. Simultaneously, the buttocks and sacrum externally rotate anteriorly through 45°.

As the anterior shoulder impinges under the pubic symphysis, the posterior shoulders and arm are born over the perineum followed by the delivery of anterior shoulder. Following the delivery, anterior shoulders undergo restitution through 45° and assume a right oblique position. At the same time the neck undergoes a torsion of 45°. As a result the engaging diameter of the head (suboccipitofrontal diameter, 10.5 cm) or suboccipitobregmatic diameter engages in the left oblique diameter of the pelvis (figure 2.7F). Descent into the pelvis occurs with flexion of the fetal head. The flexion of fetal head is often maintained by uterine contractions aided by suprapubic pressure applied by the delivery assistant at the time of delivery. When the head reaches the pelvic floor, it undergoes internal rotation by 45° so that the saggital sutures lie in the A-P diameter of the pelvis, with the occiput present anteriorly and brow in the hollow of the sacrum. As the nape of the neck impinges against the pubic symphysis, the chin, mouth, nose, forehead, bregma and occiput are born over the perineum by flexion.

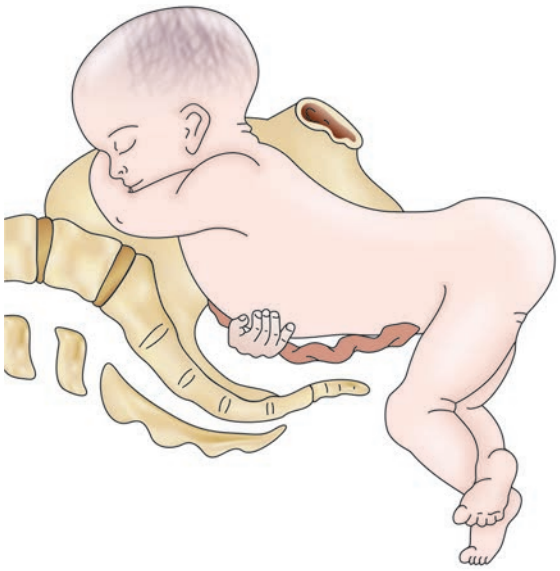
Types of breech vaginal delivery

Three types of vaginal breech deliveries are described:

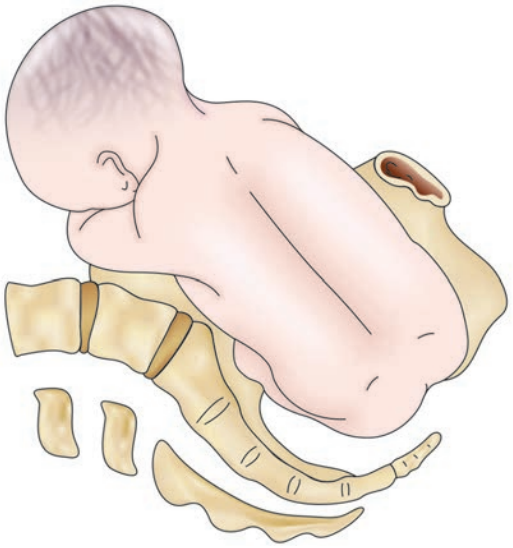
- *Spontaneous breech delivery*: No traction or manipulation of the infant by the clinician is done. The fetus delivers spontaneously on its own. This occurs predominantly in very preterm deliveries.
- *Assisted breech delivery*: This is the most common mode of vaginal breech delivery. In this method a "no-touch technique" is adopted in which the infant is allowed to spontaneously deliver up to the umbilicus, and then



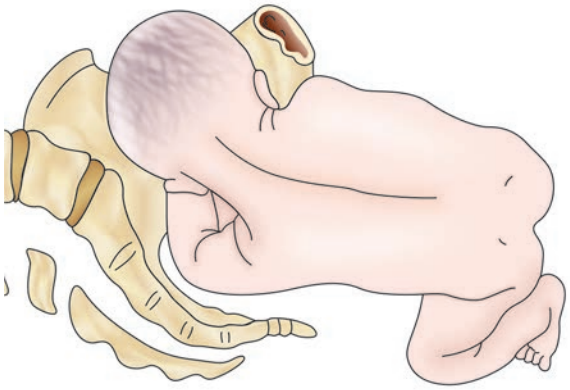
A



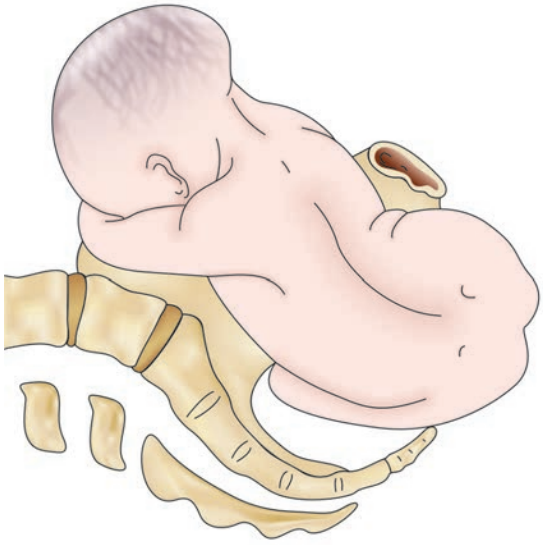
D



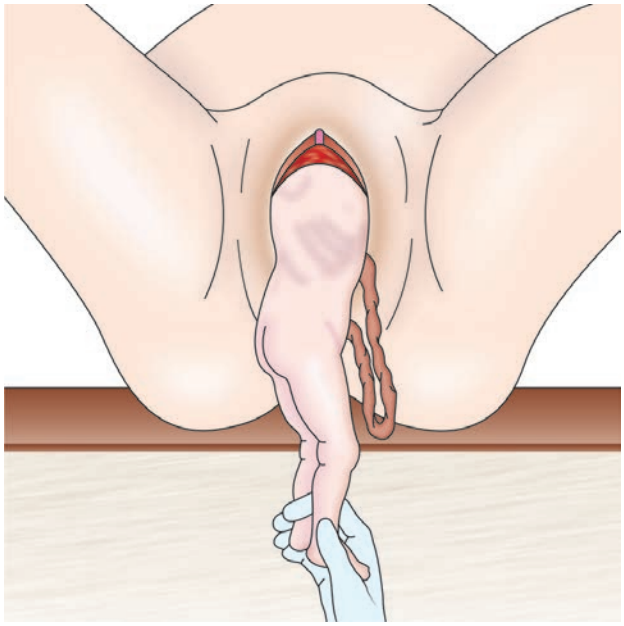
B



E



C



F

Figs 2.7A to F: Steps of breech vaginal delivery

certain maneuvers are initiated by the obstetrician to aid in the delivery of the remainder of the body, arms, and head.
- *Total breech extraction*: In this method, the fetal feet are grasped, and the entire fetus is extracted by the clinician. Total breech extraction should be used only for a nonce-phalic second twin (see chapter 5); it should not be used for singleton fetuses because the cervix may not be ade-quately dilated to allow passage of the fetal head.

Intrapartum care for patients undergoing breech vaginal delivery

- Informed consent must be taken from the patient after explaining that the trial of breech can fail in 20% cases, thereby requiring a cesarean section.
- At the time of labor, the risk factors for presence of breech presentation should be reviewed again (presence of pla-centa praevia, twins, etc) and a complete abdominal and vaginal examination needs to be carried out.
- Since both the mother and the fetus are at an increased risk during the course of breech vaginal delivery, increased maternal and fetal surveillance is required in patients undergoing breech vaginal delivery in comparison to those fetuses with cephalic presentation. Close monitor-ing of maternal vital conditions and uterine contractions and fetal heart rate needs to be done.
- Maternal intravenous line must be set up as the mother may require emergency induction of anesthesia at any time.
- Women should be advised to remain in bed to avoid the risk of PROM and risk of cord prolapse. The fetal mem-branes must be left intact as long as possible; they must not be ruptured artificially, but allowed to rupture on their own in order to prevent the hazard of overt cord prolapse. In case the bag of membranes ruptures spontaneously, a per vaginal examination must be performed immediately to rule out cord prolapse.
- Active management of labor preferably using a partogram needs to be done.
- Close surveillance of FHR can be done using internal and external cardiotocographic techniques. In case electronic fetal monitoring facilities are not available, the fetal heart rate must be monitored using intermittent auscultation every fifteen minutes during first stage of labor and after every contraction during second stage of labor.
- Following rupture of membranes, a vaginal examina-tion needs to be performed to rule out cord prolapse. It is advisable to do continuous fetal heart rate recording for five-ten minutes following rupture of membranes to rule out occult cord prolapse.
- Breech presentation should be confirmed by an ultrasound examination in the labor ward.
- Use of oxytocin induction and augmentation for breech presentation is controversial. Many clinicians fear that forceful uterine contractions induced by oxytocin could result in an incompletely dilated cervix and an entrapped head.
- An anesthesiologist and pediatrician should be present for all vaginal breech deliveries. A pediatrician is needed because of the higher prevalence of neonatal depression and the increased risk for unrecognized fetal anomalies. An anes-thesiologist may be needed if intrapartum complications develop and the patient requires general anesthesia.
- Labor must be preferably monitored using cardiotoco-graphic examination.
- Mother should be in dorsal lithotomy position for breech vaginal delivery.
- Lumbar epidural analgesia must be used to provide pain relief and to prevent voluntary bearing down efforts prior to complete dilatation of cervix. This would help to pre-vent the slipping of breech through a partially dilated cer-vix with the arrest of after coming head of the breech.
- Routine episiotomy for every breech vaginal delivery is not required. However if the clinician feels that the birth passage is too small, he/she must use their own discretion in giving an episotomy.
- In case of breech footling presentation, if the fetal feet prolapse through the vagina, treat expectantly as long as the fetal heart rate is stable to allow the cervix to com-pletely dilate around the breech.
- Delivery should be conducted in the operation theater by "assisted breech vaginal delivery" and an anesthetist stand-by.

Prerequisites for a vaginal delivery

Vaginal delivery should be undertaken if the conditions mentioned in tables 2.7 and 2.8 are fulfilled. Trial of vaginal breech delivery however continues to be offered to women who fulfill the criteria mentioned in tables below. These women should be explained about the benefits and risks of both breech vaginal delivery and cesarean section and allowed to choose between the two. The decision for breech vaginal delivery or cesarean section is made based on the

Table 2.7: Prerequisites for breech vaginal delivery

Facilities for cesarean section are available
Anesthetist, OT staff and pediatrician have been informed
Facilities are available for continuous monitoring of fetal heart rate
Adequate facilities for ultrasonography
Clinician and other health care staff, well versed in the technique of vaginal breech delivery and facilities for safe emergency cesarean delivery are available

Table 2.8: Indications for breech vaginal delivery

Estimated fetal weight from 2,000 to 4,000 g (4 lb, 6 oz to 8 lb, 13 oz)
Frank or complete breech presentation
Flexed fetal head, i.e., an extension angle of less than 90°
No major fetal anomalies or placenta previa on ultrasound
No obstetric contraindication for breech vaginal delivery (e.g. CPD, placenta previa, etc)
Delivery is imminent
Presence of severe fetal anomaly or fetal death
Mother's preference for vaginal birth

type of breech, degree of flexion of fetal head, fetal size, size of maternal pelvis etc.

Steps for breech vaginal delivery

- Once the buttocks have entered the vagina and the cervix is fully dilated, the woman must be advised to bear down with the contractions.
- Episiotomy may be performed, if the perineum appears very tight.
- A "no touch policy" by the clinician must be adopted until the buttocks and lower back deliver till the level of umbilicus. At this point the baby's shoulder blades can be seen.
- Sometimes the clinician may have to make use of maneuvers like Pinard maneuver and groin traction (will be described later), if the legs have not delivered spontaneously.
- The clinician should be extremely careful and gently hold the baby by wrapping it in a clean cloth in such a way that the baby's trunk is present anteriorly. The baby must be held by the hips and not by the flanks or abdomen as this may cause kidney or liver damage. At no point, must the clinician try to pull the baby out, rather the patient must be encouraged to push down.
- In order to avoid compression on the umbilical cord, it should be moved to one side, preferably in the sacral bay.
- The clinician must wait for the arms to deliver spontaneously. If arms are felt on chest, the clinician must allow the arms to disengage spontaneously one by one. Assistance should be provided only if necessary. After spontaneous delivery of the first arm, the buttocks must be lifted towards the mother's abdomen to enable the second arm to deliver spontaneously. If the arm does not spontaneously deliver, place one or two fingers in the elbow and bend the arm, bringing the hand down over the baby's face.
- If the arms still do not deliver, the clinician must reach into the vagina to determine their position. If they are flexed in front of the chest, gentle pressure must be applied to the crook of the elbow to straighten the arm and aid delivery. The same maneuver must be repeated with the other arm.
- The clinician needs to be aware that there are other maneuvers to deliver the arms and shoulders if needed, including Lovest's maneuver to deliver the anterior shoulder and delivery of the posterior shoulders in case the Lovset's maneuver fails.
- If arms are stretched above the head or folded around the neck, the clinician must use a maneuver called Lovset's maneuver (described later).
- Once the shoulders are delivered, the baby's body with the face down must be supported on the clinician's forearm. The clinician must be careful not to compress the umbilical cord between the infant's body and their arm.
- One of the following maneuvers can be used for delivery of after coming head of the fetus:

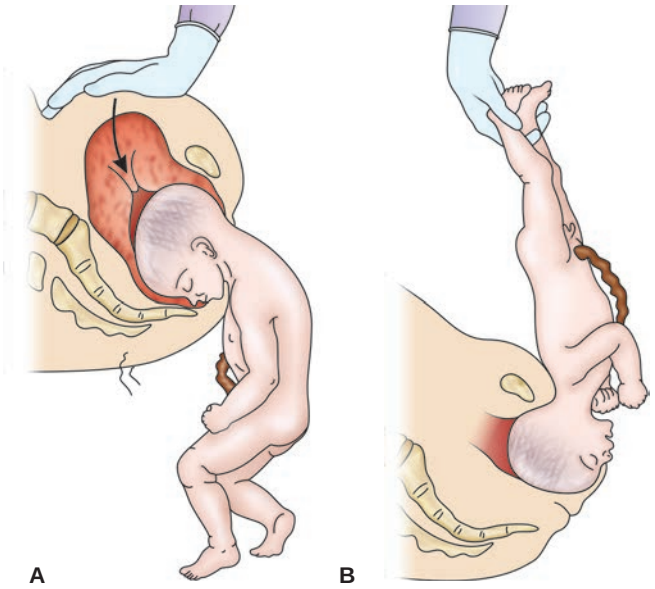
Burns Marshall technique

Following the delivery of shoulders and both the arms, the baby must be let to hang unsupported from the mother's vulva. This would help in encouraging flexion of fetal head (figure 2.8A). The nursing staff must be further advised to apply suprapubic pressure in downwards and backward direction, in order to encourage further flexion of the baby's head. As the nape of baby's neck appears, efforts must be made by the clinician to deliver the baby's head by grasping the fetal ankles with the finger of right hand between the two. Then the trunk is swung up forming a wide arc of the circle, while maintaining continuous traction when doing this (figure 2.8B). The left hand is used to provide pelvic support and to clear the perineum off successively from the baby's face and brow as the baby's head emerges out.

Mauriceau Smellie Veit maneuver

This is another commonly used maneuver for the delivery of after coming fetal head and is named after the three clinicians who had described the method of using this grip. This maneuver comprises of the following steps:

- The baby is placed face down with the length of its body over the supinated left forearm and hand of the clinician.
- The clinician must then place the first (index) and second finger (middle finger) of this hand on the baby's cheekbones and the thumb over the baby's chin. This helps in facilitating flexion of the fetal head. In the method originally described by Mauriceau, Smellie and viet, the index finger of the left hand was placed inside the baby's mouth. This is no longer advocated as placing a finger inside the infant's mouth is supposed to stimulate the vagal reflex. An assistant may provide suprapubic pressure to help the baby's head remain flexed.



Figs 2.8A and B: Burns Marshall technique

- The right hand of the clinician is used for grasping the baby's shoulders. The little finger and the ring finger of the clinician's right hand is placed over the baby's right shoulder, the index finger over the baby's left shoulder and the middle finger over the baby's suboccipital region (figure 2.9). With the fingers of right hand in this position, the baby's head is flexed towards the chest. At the same time left hand is used for applying downward pressure on the jaw to bring the baby's head down until the hairline is visible.
- Thereafter the baby's trunk is carried in upwards and forward direction towards the maternal abdomen, till the baby's mouth, nose and brow and lastly the vertex and occiput have been released.

Delivery of aftercoming head using forceps

Nowadays forceps are commonly used to deliver the after coming head of the breech. Use of forceps helps in better maintenance of flexion of fetal head and helps in transmitting the force to the fetal head rather than the neck. This helps in reducing the risk of fetal injuries. Prerequisites for application of forceps are enumerated in table 2.9. For delivery of fetal head using forceps, the following steps are required (figure 2.10):

- Ordinary forceps or Piper's forceps (specially designed forceps with absent pelvic curve) can be used.
- While the clinician is applying forceps, the baby's body must be wrapped in a cloth or towel and held on one side by the assistant.

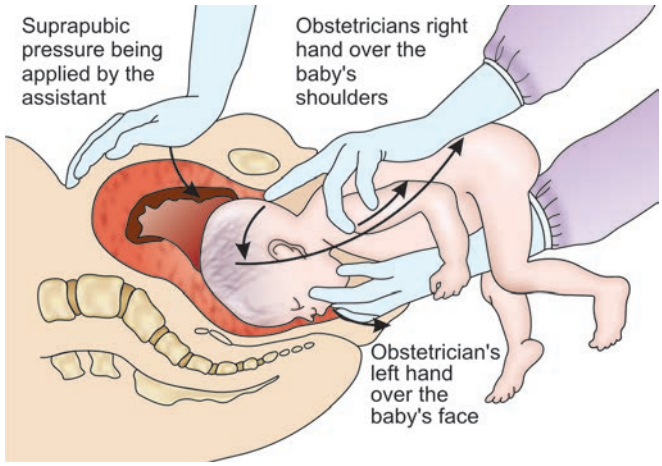


Fig. 2.9: Mauriceau Smellie Veit maneuver

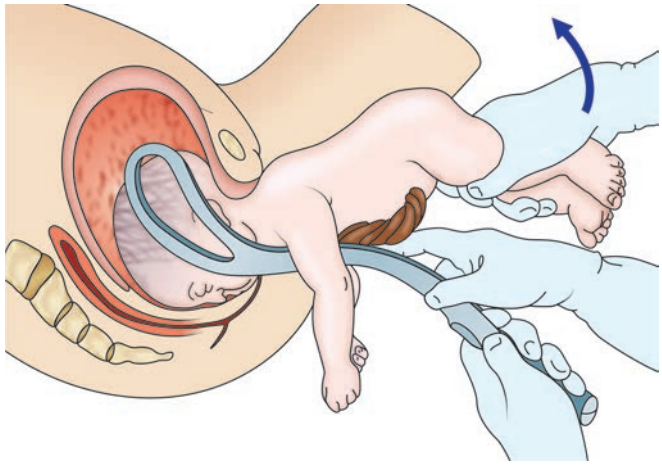


Fig. 2.10: Delivery of aftercoming head of the breech using forceps

Table 2.9: Prerequisites for application of forceps

Written or verbal consent to be taken from the patient
Bladder should be catheterized
Cervix should be fully dilated
Head should be in the pelvic cavity
No cephalopelvic disproportion

- Left blade of the forceps is applied first followed by the right blade and the handles are locked.
- The forceps are used for both flexing and delivering the baby's head.
- The head must be delivered slowly over one minute in order to avoid sudden compression or decompression of fetal head, which may be a cause for intracranial hemorrhage.

Lovset's maneuver

If the baby's arms are stretched above the head or folded behind the neck (nuchal displacement), the maneuver called Lovset's maneuver is used for delivery of fetal arms. This maneuver is based on the principle that due to the curved shape of the birth canal when the anterior shoulder is above the pubis symphysis, the posterior shoulder would be below the level of pubic symphysis. The maneuver should be initiated only when the fetal scapula becomes visible underneath the pubic arch and includes the following steps (figure 2.11):

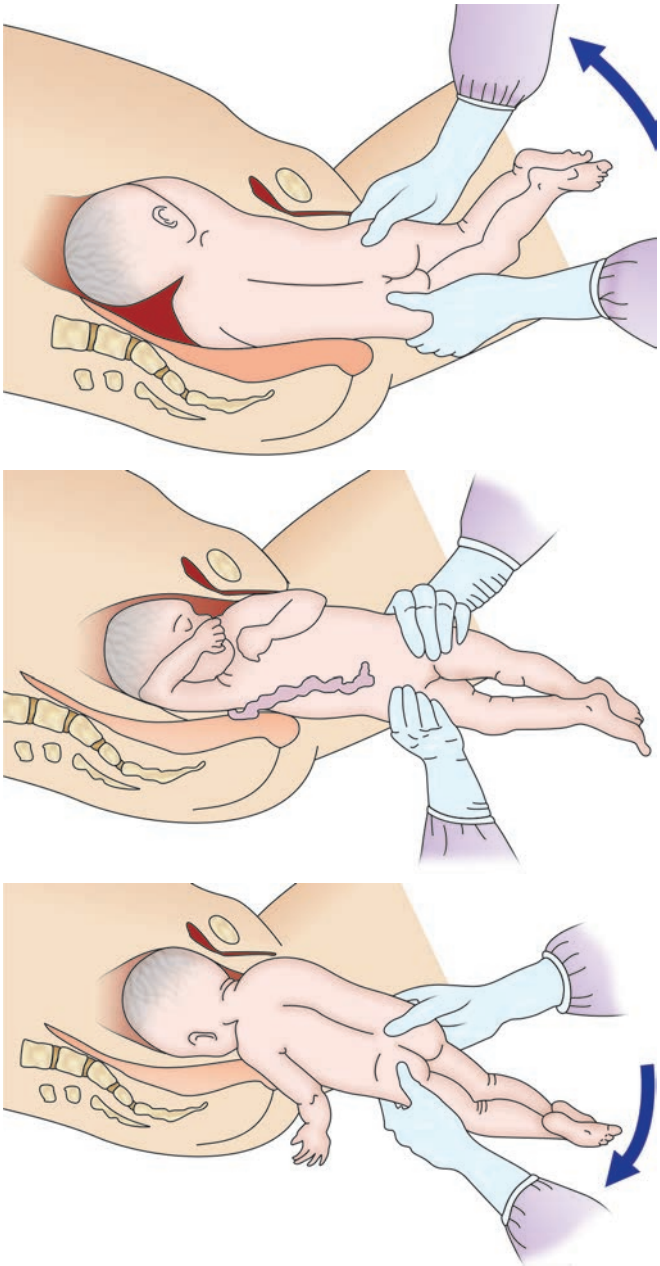


Fig. 2.11: Lovset's maneuver

- First the baby is lifted slightly to cause lateral flexion of the trunk.
- Then the baby which is held by pelvi-femoral grip is turned by half a circle, keeping the back uppermost. Simultaneously downward traction is applied, so that the arm that was initially posterior and below the level of pubic symphysis now becomes anterior and can be delivered under the pubic arch.
- Delivery of the arm can be assisted by placing one or two fingers on the upper part of the arm. Then the arm is gradually drawn down over the chest as the elbow is flexed, with the hand sweeping over the face.
- In order to deliver the second arm, the baby is again turned by 180° in the reverse direction, keeping the back uppermost and applying downward traction and then delivering the second arm in the same way under the pubic arch as the first arm was delivered.

Delivery of the posterior shoulder

If the clinician is unable to turn the baby's body to deliver the arm that is anterior first, through Loveset's maneuver, then the clinician can deliver the shoulder that is posterior, first (figure 2.12). Delivery of the posterior shoulder involves the following steps:

- The clinician must hold and lift the baby up by the ankles. At the same time the baby's chest must be moved towards the woman's inner thighs. The clinician must then hook the baby shoulder with fingers of his/her hand. This would help in delivering the shoulder that is posterior, followed by the delivery of arm and hand.

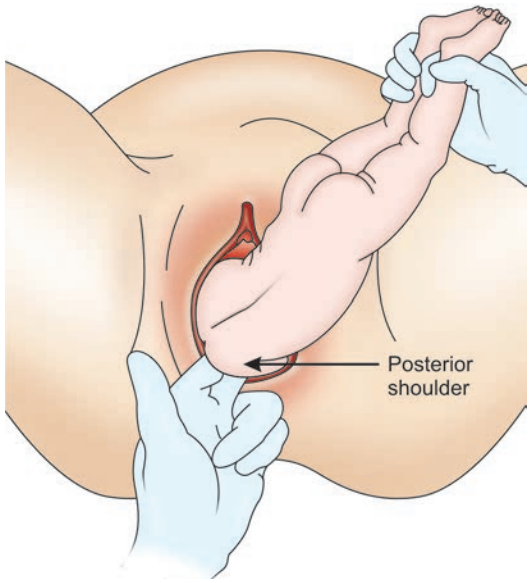


Fig. 2.12: Delivery of the shoulder that is posterior

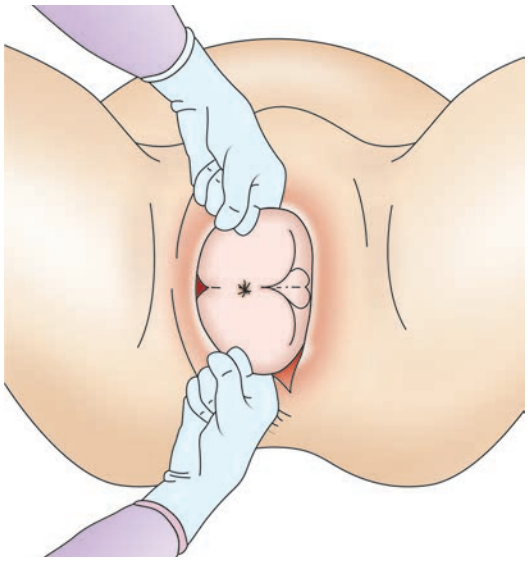


Fig. 2.13: Application of groin traction

- Then the baby's back should be lowered down, still holding it by ankles. This helps in the delivery of anterior shoulder followed by the arm and hand.

Groin traction

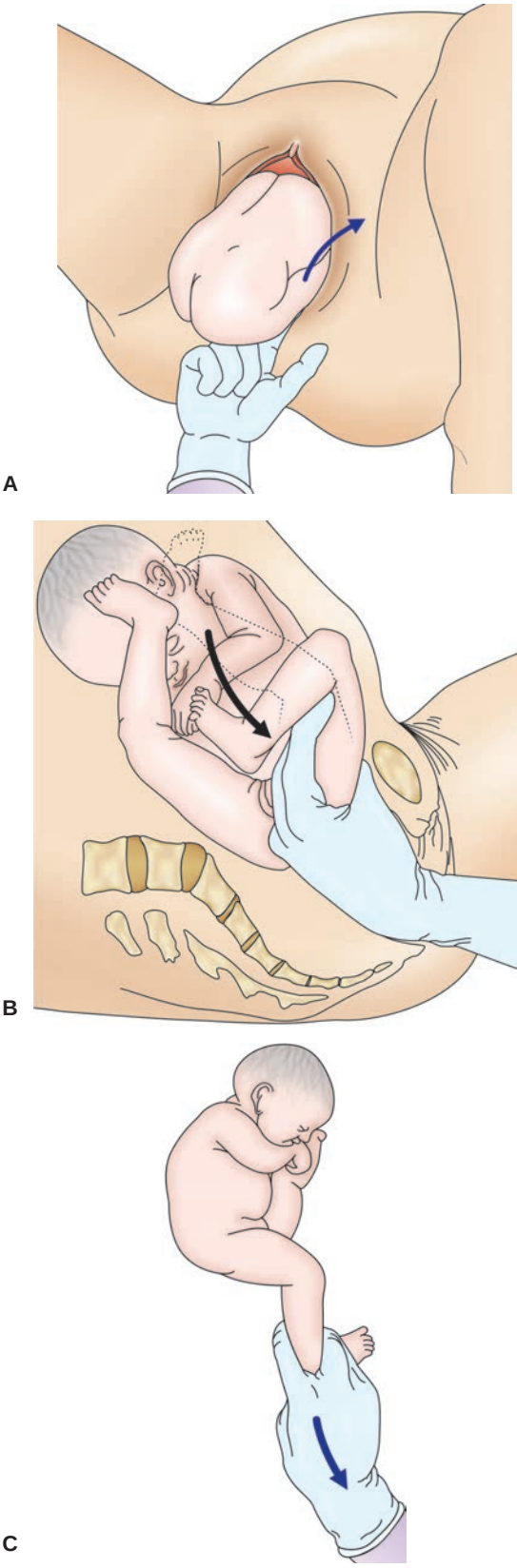
If the buttocks and hip do not deliver by themselves, the clinician can make use of simple maneuvers including groin traction or Pinard's maneuver to deliver the legs. Groin traction could be of two types: Single or double groin traction. In single groin traction, the index figure of one hand is hooked in the groin fold and traction is exerted towards the fetal trunk rather than towards the fetal femur, in accordance with the uterine contractions. In double groin traction, the index fingers of both the hands are hooked in the groin folds and then traction is applied (figure 2.13).

Pinard's maneuver

In this maneuver pressure is exerted against the inner aspect of the knee (popliteal fossa), with help of the middle and index fingers of the clinician (figure 2.14A). As the pressure is applied, the knee gets flexed and abducted. This causes the lower leg to move downwards, which is then swept medially and gently pulled out of the vagina (figures 2.14B and C).

Post-Delivery Care

- The baby's mouth and nose must be suctioned
- The cord must be clamped and cut.
- Active management of the third stage of labor needs to be done.
- The cervix and vagina must be carefully examined for presence of any tears and the episiotomy must be repaired.



Figs 2.14A to C: Pinard's maneuver

Complications

FETAL COMPLICATIONS

Low APGAR Scores

Low APGAR scores, especially at 1 minute are more common with vaginal breech deliveries and could be related to birth asphyxia. Increased risk of birth asphyxia in cases of breech vaginal delivery could be due to the following causes:

- Cord compression
- Cord prolapse
- Premature attempts by the baby to breathe while the head is still inside the uterine cavity
- Delay in the delivery of the head often due to head entrapment

Fetal Head Entrapment

Fetal head entrapment may result from an incompletely dilated cervix and head that lacks time to mold to the maternal pelvis. This occurs in 0% to 8.5% of vaginal breech deliveries. This percentage is higher with preterm fetuses (<32 wk), when the head is larger in comparison to the rest of the body. Dührssen incisions i.e., 1-3 cm deep cervical incisions made through several portions of the cervical canal to facilitate delivery of the fetal head) may be necessary to relieve cervical entrapment (figure 2.15). However, severe hemorrhage and extension can occur into the lower segment of the uterus. Therefore the operator must be equipped to deal with this complication.

Preterm Birth

Preterm birth (< 28 weeks) commonly occurs.

Neonatal Trauma

Neonatal trauma including brachial plexus injuries, hematomas, fractures, viscereal injuries, etc can occur in about 25% of cases. Risks of fetal injuries may be reduced by avoiding rapid extraction of the infant during delivery of the body. Cervical spine injury is predominantly observed when the fetus has a hyperextended head prior to delivery. Successive compression and decompression of unmolded after coming head of the breech and increased risk of head entrapment can result in intracranial hemorrhage and tentorial tears.

Cord Prolapse

Cord prolapse is a condition associated with abnormal decent of the umbilical cord before the descent of the fetal presenting part (figure 2.16). The cord could be lying by the side of the fetal presenting part or it could have slipped down below the present part. In extreme cases the cord could be lying totally outside the vagina. Cord prolapse occurs in 7.5% of all breeches (table 2.10). This incidence varies with the type of breech: 0 to 2% with frank breech, 5% with complete breech and 10 to 15% with footling breech. Cord prolapse occurs twice as often in multiparas (6%) than in primigravidas (3%). Management for cord prolapse is described in flow chart 2.2.

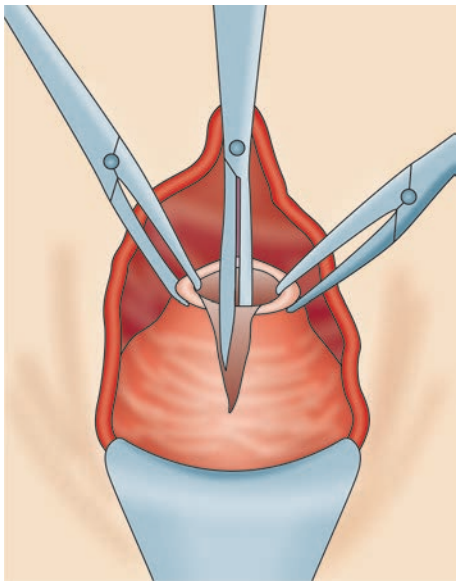


Fig. 2.15: Dührssen incision

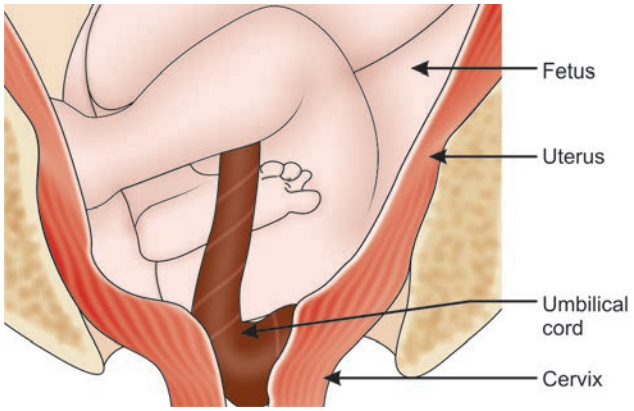
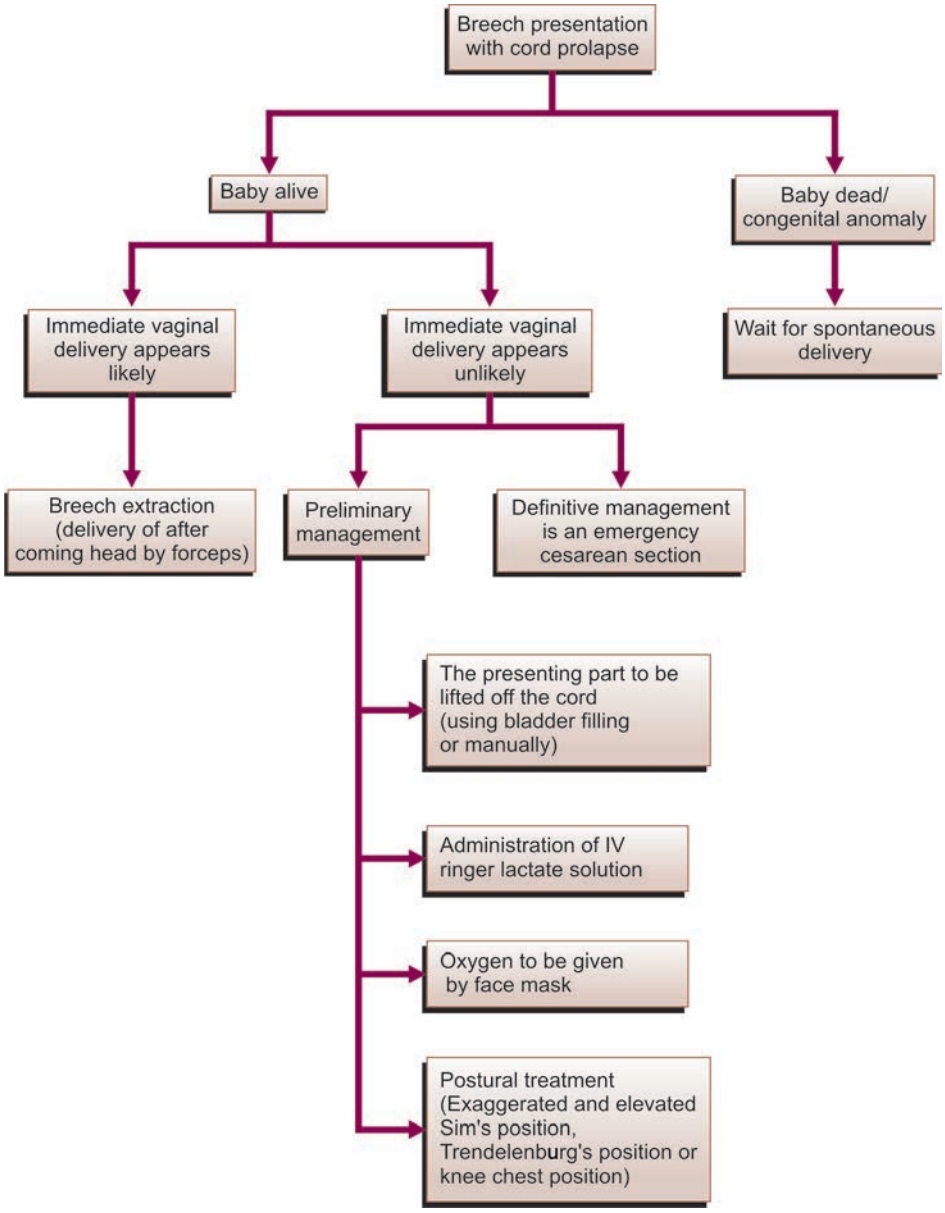


Fig. 2.16: Cord prolapse

Table 2.10: Incidence of cord prolapse with breech presentation

Type of breech presentation	*Incidence of cord prolapse*
Frank breech	0.5%
Complete breech	5%
Footling breech	15%

Flow chart 2.2: Management of cord prolapse



MATERNAL COMPLICATIONS

- Increased rate of maternal morbidity and mortality due to increased incidence of operative delivery.
- Traumatic injuries to the genital tract.

Important Questions and Answers

Q.1. What information should be given to woman in the above mentioned case study regarding mode of delivery?

Ans. The woman should be informed about both the maternal and fetal benefits and risks of planned cesarean section versus planned vaginal delivery for breech presentation at term. This risk needs to be explained for both current and future pregnancies. Woman should be informed that planned cesarean section for breech presentation is associated with slight increase in rates of maternal complications in comparison with planned vaginal birth. On the other hand, breech vaginal delivery is associated with increased rates of perinatal and neonatal mortality and morbidity in comparison with abdominal deliveries.

Q.2. What would be the best option for mode of delivery in the case presented in the beginning of the chapter? Would the management have been any different if the patient had been multiparous instead of being primiparous?

Ans. A cesarean section was performed in the above case. This mode of delivery for breech presentation was decided after explaining both the patient and her partner about the maternal and fetal risks associated with both the modes of delivery. In this case the couple was not willing to take any chance of risk to the baby. Therefore they opted for a cesarean delivery. Zatuchni and Andros score in this case was less than three, therefore the clinician was also in the favor of performing a cesarean section.

It is commonly believed that primigravidas with breech presentation should have a cesarean delivery, although there is insufficient evidence to support this view. The risk for cord prolapse is higher in multiparous women compared with primiparous women. This may increase the requirement for caserean section in case of multiparous breech pregnancies. Breech vaginal delivery could be performed in this case of breech presentation if Zatuchni and Andros score calculated in this case would have been more than three.

Q.3. What is the place of labor induction in case of breech vaginal delivery? Where should vaginal breech birth take place?

Ans. There is no place for induction or augmentation of delivery in case of breech prsentation. Vaginal delivery should take place in settings with facilities for emergency cesarean section. Emergency cesarean section may be required in the event of poor progress in the second stage of labor. Facilities for general anesthesia must be available in the event, intrauterine manipulation for performance of various maneuvers is required.

Q.4. If the second stage of labor is delayed in case of breech vaginal delivery, what should be the next step?

Ans. Cesarean section should be considered if there is delay in the descent of the breech at any stage in the second stage of labor as failure of the presenting part to descend may be a sign of relative fetopelvic disproportion.

Q.5. Should routine episiotomy be performed?

Ans. There is no requirement for a routine episiotomy; episiotomy should be performed only when the perineum appears too tight and a surgical cut is required to facilitate delivery.

Q.6. How should preterm babies in breech presentation be delivered?

Ans. Although most clinicians prefer to use cesarean section for the uncomplicated preterm breech deliveries, presently there is insufficient evidence available to justify this policy. The available evidence indicates that routine cesarean section for the delivery of preterm breech presentation is not required. The mode of delivery of the preterm breech presentation should be discussed on an individual basis with a woman and her partner. The parents should be informed about the perinatal risks associated with breech vaginal delivery. The main problem encountered during preterm breech delivery is entrapment of head due to the delivery of the trunk through an incompletely dilated cervix. Since the same maneuvers, which are used for delivery of fetal head during breech delivery are used for delivery of fetal head during the cesarean section for breech presentation, there appears to an equal chance of fetal head entrapment with both the modes of delivery.

Q.7. What is breech extraction? Should breech extraction be performed routinely?

Ans. Breech extraction involves immediate extraction of the fetus by the clinician using the vaginal route. There is no place for routine use of total breech extraction in modern obstetrics except in cases of noncephalic second twin. The procedure is performed as follows:

- The procedure is performed under general anesthesia. The cervix must be fully dilated and feto-pelvic disproportion must have been ruled out.
- The bladder must be catheterized.
- After taking complete aseptic precautions and wearing disinfected gloves, clinician inserts a hand into the uterine cavity to grasp the baby's foot. The foot can also be brought down using Pinard's maneuver, especially in cases of frank breech.
- For extracting the breech successfully, it is important that the clinician makes no attempt to pull but applies steady, gentle traction in downward direction, until the lower parts of the scapula become visible below the pubic arch.
- No attempt should be made at the delivery of shoulders and arm until axilla become visible. The same maneuvers as described previously must be used for the delivery of shoulders, arms and head.

Bibliography

1. Coco AS, Silverman SD. External Cephalic Version. Am Fam Physician. 1998;58(3):731-8, 742-4.
2. Cruikshank DP. Breech presentation. Clin Obstet Gynecol. 1986;29:255-63.
3. Hannah ME, Hannah WJ, Hewson SA, Hodnett ED, Saigal S, Willan AR, et al. Planned cesarean section versus planned vaginal birth for breech presentation at term: A randomised multicentre trial. Lancet. 2000;356:1375–83.
4. Royal College of Clinicians and Gynaecologists (RCOG). External cephalic version and reducing the incidence of breech presentation. London (UK): Royal College of Clinicians and Gynaecologists; 2006 Dec. 8 p. (Green-top guideline; no. 20a).
5. Royal College of Clinicians and Gynaecologists (RCOG). The management of breech presentation. London (UK): Royal College of Clinicians and Gynaecologists; 2006 Dec. 13 p. (Green-top guideline; no. 20b).

Chapter

3

Transverse Lie

Case Study

A 28-year-old primi patient with 36 completed weeks of gestation having fetus with shoulder presentation (diagnosed by ultrasound examination at previous antenatal visit) presented for a routine antenatal check-up.

Introduction

Definition

Transvere lie is an abnormal fetal presentation in which the fetus lies transversely with the shoulders presenting in the lower pole of the uterus (figures 3.1A and B). In this presentation, long axis of the fetus is perpendicular to the maternal spine. As a result, the presenting part becomes the fetal shoulder. The denominator is the fetal back. Depending on whether the position of the fetal back is anterior, posterior, superior or inferior (figure 3.2), the following positions are possible:

Dorso-anterior

The commonest position where the fetal back is anterior.

Dorso-posterior

Fetal back is posterior.

Dorso-superior

Fetal back is directed superiorly.

Dorso-inferior

Fetal back is directed inferiorly.

Depending on the position of the fetal head, the fetal position can be described as right or left.

History

RISK FACTORS

The various maternal and fetal risk factors mentioned below need to be elicited in the history.

Maternal Factors

Cephalo-pelvic disproportion, contracted maternal pelvis; liquor abnormalities (polyhydraminos, oligohydramnios); uterine anomalies (bicornuate, septate); space occupying

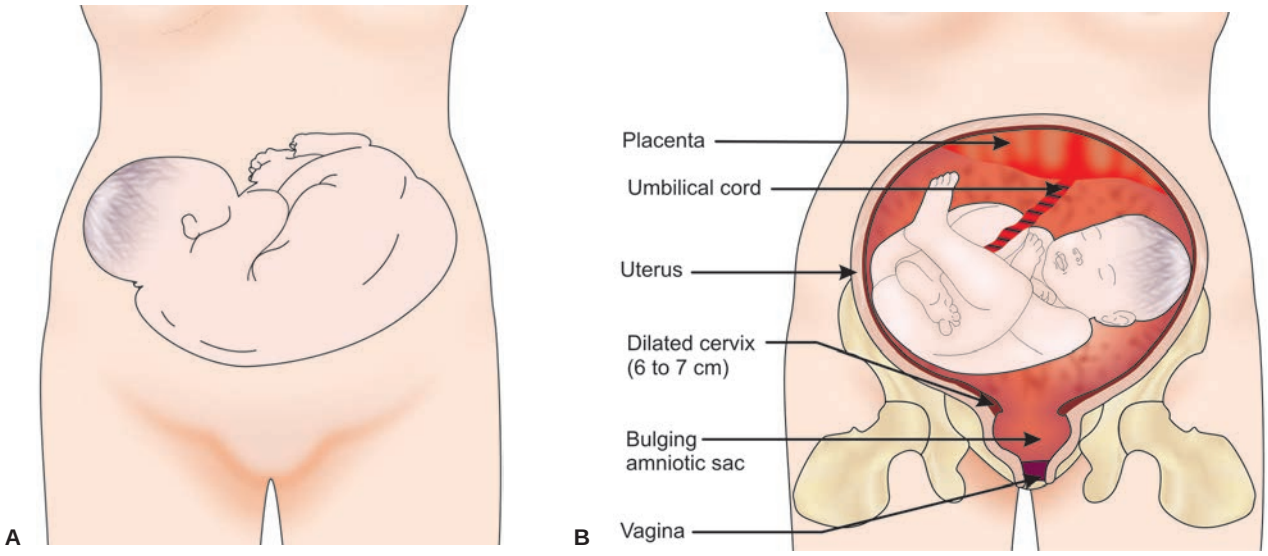


Fig. 3.1: Fetus in transverse lie

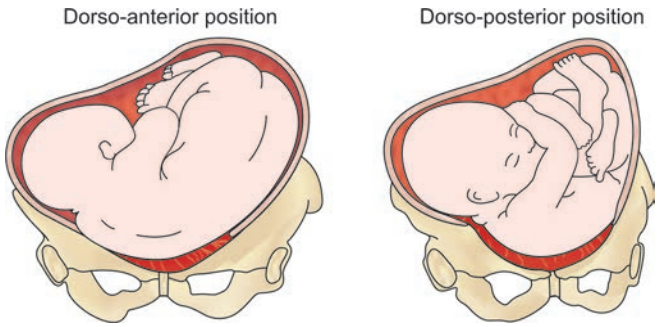


Fig. 3.2: Different positions of transverse lie

lesions (e.g. fibroids in the lower uterine segment); placental abnormalities (placenta praevia, cornuofundal attachment of placenta), multiparity (especially grand multiparas); presence of pelvic tumor.

Fetal Factors

Prematurity, twins, hydramnios, intrauterine fetal death, fetal anomalies, etc.

General Physical Examination

No specific finding was observed on GPE.

Specific Systemic Examination

ABDOMINAL PALPATION

On abdominal palpation, the following findings can be elicited:

- Fetal lie is in the horizontal plane with fetal head on one side of the midline and podalic pole on the other.
- The abdomen often appears barrel shaped and is asymmetrical.
- Funda height is less than the period of amenorrhea.

First Lepold maneuver/fundal grip

No fetal pole (either breech or cephalic) is palpable on the fundal grip.

Second Lepold maneuver/lateral grip

Soft, broad, smooth irregular part suggestive of fetal breech is present on one side of the midline, while a smooth hard globular part suggestive of the fetal head is present on the other side of the midline. The fetal head is usually placed at a level lower than the rest of the body and is usually confined to one iliac fossa. In case of dorso-anterior position, back may be felt anteriorly in the midline on the lateral grip. In case of dorso-posterior position, small irregular knob like structures suggestive of the fetal limbs are felt anteriorly in the midline while performing lateral grip.

Lepold third maneuver

Pelvic grip appears to be empty during the time of pregnancy. It may be occupied by the shoulder at the time of labor.

Fetal heart auscultation

Fetal heart rate is easily heard much below the umbilicus in dorso-anterior position. On the other hand in dorso-posterior position, the fetal heart may be located at a much higher level and is often above the umbilicus.

VAGINAL EXAMINATION

On vaginal examination during the antenatal period, the pelvis appears to be empty. Even if something is felt on vaginal examination, no definite fetal part may be identified.

At the time of labor, on vaginal examination, fetal shoulder including scapula, clavicle, humerus and grid iron feel of fetal ribs can be palpated (figures 3.3 and 3.4). Due to ill-fitting fetal part, an elongated bag of membranes may be felt on vaginal examination. If the membranes have ruptured, the fetal shoulder can be identified by feeling the acromion process, the scapula, clavicle, axilla, ribs and intercostal spaces. Ribs and intercostal spaces upon palpation give feeling of grid iron. If the arm prolapse has occurred, the fetal arm might be observed lying outside the vagina.

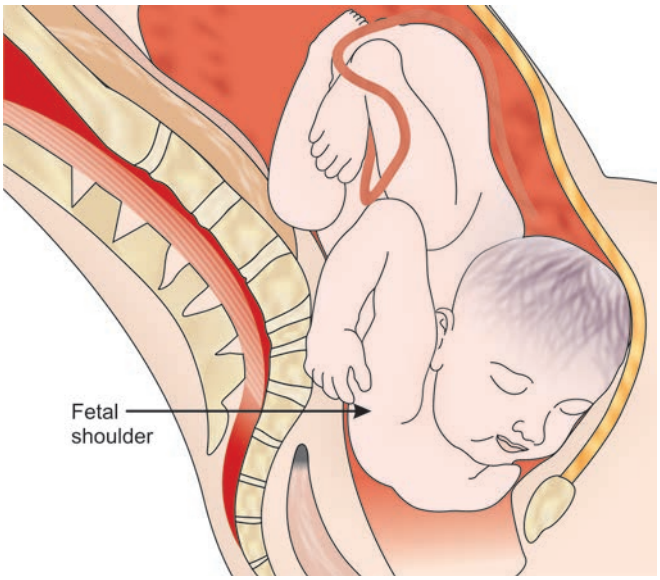


Fig. 3.3: Fetal shoulder presentation

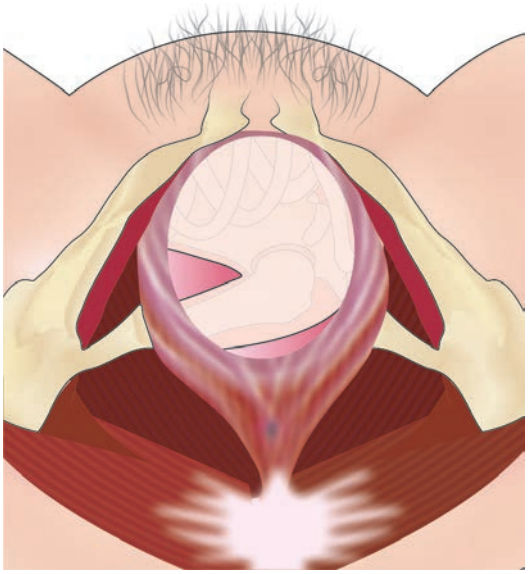


Fig. 3.4: Fetal shoulder as identified on vaginal examination

Management

Management comprising of investigations and definitive obstetric management is discussed below.

Investigations

Ultrasound Examination

Ultrasound helps in confirming the transverse lie. The other things which can be observed on the ultrasound include the following:

- Presence of uterine and/or fetal anomalies
- Fetal maturity
- Placental location and grading
- Adequacy of liquor
- Ruling out multiple gestation.

Treatment/Obstetric Management

There is no mechanism of labor for a fetus in transverse lie, which remains uncorrected until term. A cesarean section is required to deliver the baby with shoulder presentation.

MANAGEMENT DURING PREGNANCY

The management options for transverse lie include external cephalic version during pregnancy or delivery by cesarean section (elective or an emergency). At some centers, stabilizing induction is used for converting transverse to cephalic presentation at the time of labor. Flow chart 3.1 illustrates the algorithm for management of fetus in transverse lie. If the version is unsuccessful, the only option for delivering the fetus in transverse lie is performing a cesarean delivery.

Each of these management options would be described below in details.

External Cephalic Version (ECV)

Definition

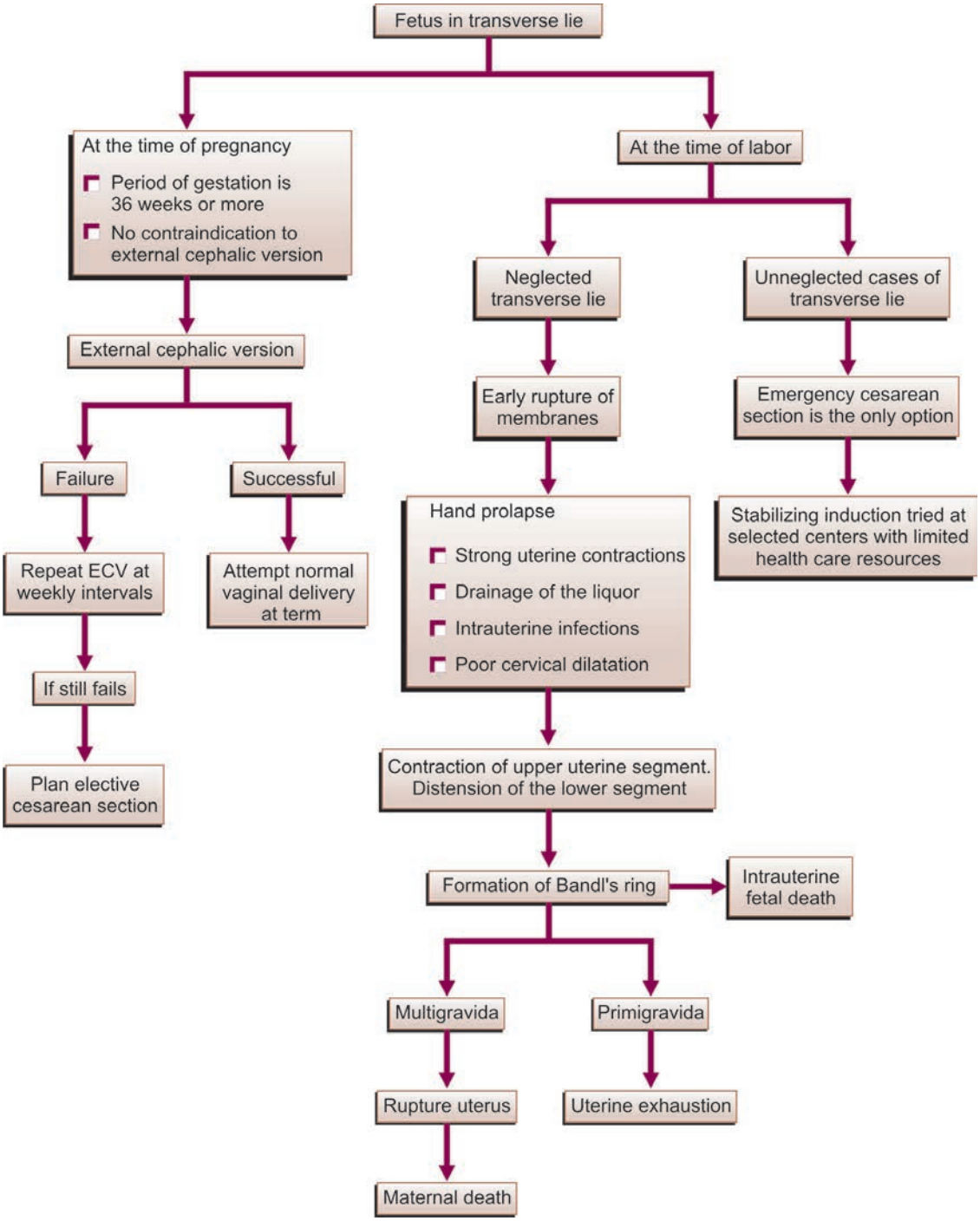
External Cephalic Version is a procedure in which the clinician externally rotates the fetus from a transverse lie into a cephalic presentation. The use of external cephalic version helps in producing considerable cost savings in the management of the fetus in tranverse lie by reducing the rate of cesarean section.

Prerequisites for ECV

Before the performance of ECV, the following prerequisites should be fulfilled:

- The place where ECV is being performed should have all facilities available for cesarean section. There is always a possibility for emergency cesarean section during the procedure, in case there is a decline in fetal heart rate.
- Blood grouping and cross matching should be done in case an emergency cesarean section is required. In case the mother is Rh negative, administration of anti-D immunoglobulin is required after the procedure in order to prevent the risk of isoimmunization.
- The patient should have nothing by mouth for at least 8 hours prior to the procedure.
- An ultrasound examination must be performed to confirm the shoulder presentation, check the rate of fetal growth, amniotic fluid volume and rule out presence of any associated anomalies.
- A non-stress test or a biophysical profile must be performed prior to ECV to confirm fetal wellbeing.
- Though ECV can be performed by a clinician single handedly, an assistant is usually required.
- Before performing an ECV, a written informed consent must be obtained from the mother.
- A tocolytic agent such as terbutaline in a dosage of 0.25 mg, may be administered subcutaneously. By producing uterine relaxation, administration of this drug is supposed to help increase the success rate of the procedure. The use of oral, parenteral or general anesthesia should be avoided due to an increased risk of complications.
- Whether the process has been successful or has failed, a non-stress test and ultrasound examination must be performed after each attempt of ECV and after the end of the procedure in order to rule out fetal bradycardia and

Flow chart 3.1: Algorithm for management of a fetus in transverse lie



to confirm successful version. Some contraindications for the procedure are described in table 3.1.

Procedure

- The patient is placed in a supine or slight Trendelenburg position.
- Ultrasonic gel is applied liberally over the abdomen in order to decrease friction and to reduce the chances of an overvigorous manipulation. External version can be performed by a clinician who is experienced in the procedure along with his/her assistant.
- Initially, the clinician grasps the fetus from its two poles.

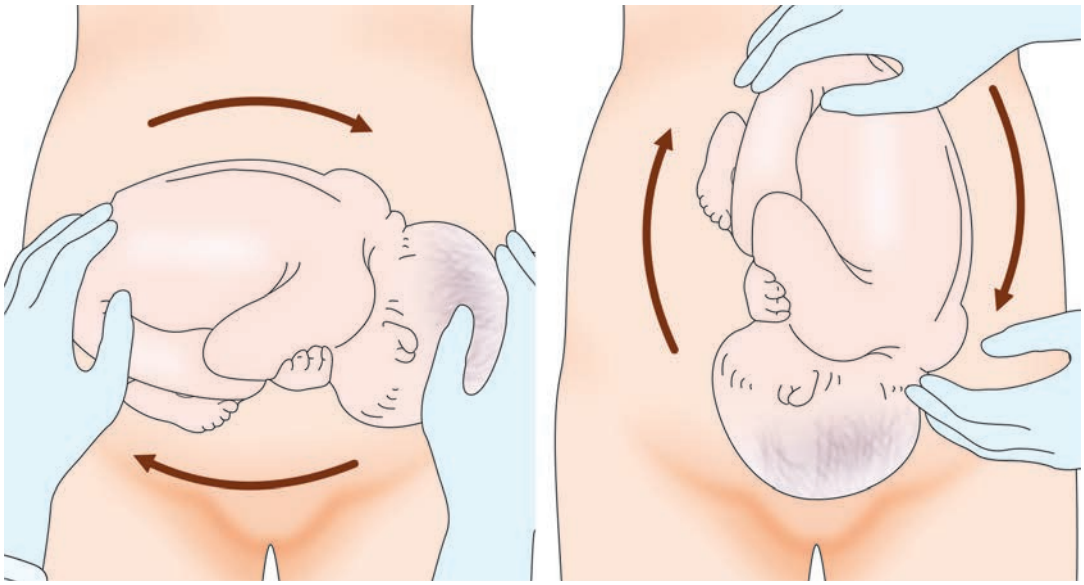


Fig. 3.5: Procedure for external cephalic version

Table 3.1: Contraindications for ECV

Absolute contraindications	*Relative contraindications*
Multiple gestation with a fetus presenting as a transverse lie	Uterine malformation
Herpes simplex virus infection	Evidence of uteroplacental insufficiency (IUGR, preeclampsia, etc)
Placenta previa	Fetal anomaly
Non-reassuring fetal heart rate tracing	Maternal cardiac disease
Premature rupture of membranes	
Significant third-trimester bleeding (placenta previa, etc)	

Table 3.2: Complications of external cephalic version

Premature onset of labor, premature rupture of the membranes.
Feto-maternal hemorrhage (danger of development of Rh isoimmunization in Rh negative pregnancies).
Fetal distress (e.g. cord entanglement resulting in fetal bradycardia).
Transient reduction of the fetal heart rate.
Failure of version: Spontaneous reversion into transverse presentation.

- While performing the ECV, the clinician helps in gently manipulating the fetal head toward the pelvis while the podalic pole is brought up cephalad towards the fundus (figure 3.5).
- While doing the ECV, the fetus should be moved gently rather than using forceful movements.
- If unsuccessful, the version can be reattempted at a later time. The procedure should only be performed in a facility equipped for emergency cesarean section.
- No consensus has been reached regarding how many ECV attempts are appropriate at one particular time. At a particular time setting, multiple attempts can be made ensuring that the procedure does not become uncomfortable for the patient. Also fetal heart rate needs to be assessed after each attempt at ECV.
- If an attempt at ECV proves to be unsuccessful, the practitioner has either the option of sending the patient home after fixing the date for elective cesarean delivery or proceeding with a cesarean delivery.

Complications of external cephalic version

Though external cephalic version is largely a safe procedure, it can have some complications, some of which are mentioned in table 3.2.

MANAGEMENT DURING LABOR

There is hardly any scope for external cephalic version in labor as fetal manipulation at this time is likely to rupture the membranes and cause drainage of amniotic fluid, increasing the further risk for development of complications. Therefore if the maternal and fetal condition are stable, the best option would be to perform a cesarean section. However at some health care centers with limited resources, clinicians opt for a stabilizing induction in which ECV is used for converting transverse lie into a cephalic presentation and ensuring that

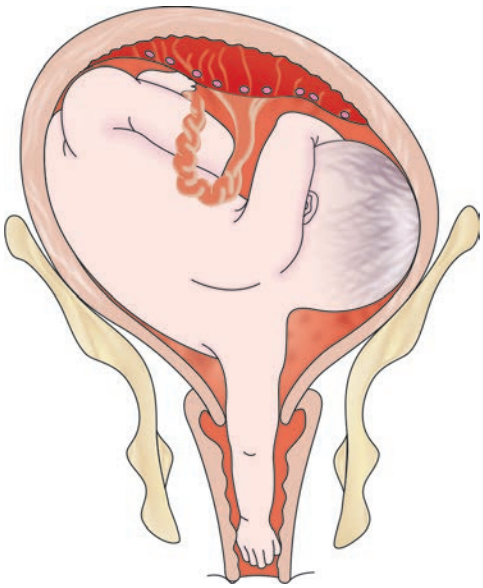


Fig. 3.6: Arm prolapse

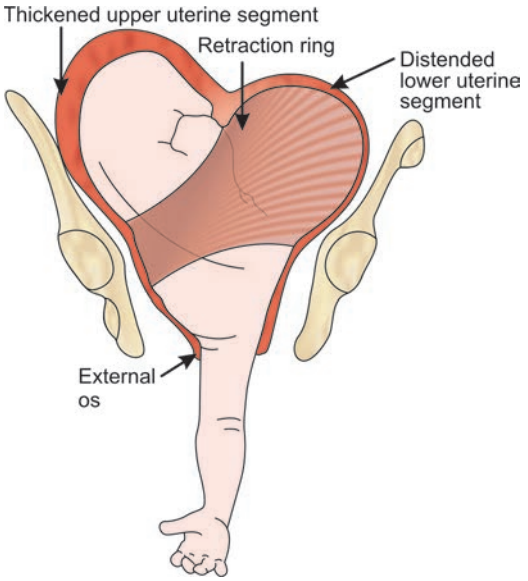


Fig. 3.7: Formation of retraction ring

the fetus remains in that position by starting an oxytocin drip immediately following the procedure of version. The labor is closely monitored and an ARM is done when the head is engaged. Labor follows in normal fashion and is usually followed by a normal vaginal delivery in cephalic presentation.

Complications

Maternal Complications

Arm prolapse

Due to the ill-fitting fetal part, the sudden rupture of membranes can result in the escape of large amount of liquor and the prolapse of fetal arm (figure 3.6). Prolapse of fetal arm is often accompanied by a loop of cord. The consequences of a neglected arm prolapse is shown in flow chart 3.2.

Obstructed labor

If the transverse lie with or without a prolapsed arm is left neglected, a series of complications including obstructed labor can occur (flow chart 3.2). In primi gravidas as a result of obstructed labor, features of maternal exhaustion and sepsis are apparent. However the uterus becomes inert. On the other hand, in multigravidae, the uterus responds vigorously in face of obstruction. In order to push out the fetus, the upper uterine segment thickens whereas the lower uterine segment distends. A retraction ring forms at the junction of upper and lower uterine segments (figure 3.7).

If the uterine obstruction is not immediately relieved, the intensity of uterine contractions increases. As the frequency of uterine contraction increases, there is a progressive reduction in the relaxation phase. This results in setting up a phase of tonic contractions. Retraction of upper uterine segment continues, this causes the lower uterine segment to elongate, become progressively thinner in order to accommodate the fetus which is being pushed down from the upper segment. This results in formation of a circular groove between the upper and lower uterine segment. This is known as the pathological retraction ring or Bandl's ring. As the degree of obstruction increases, the retraction ring becomes more prominent. Eventually, there is rupture of uterus as the lower

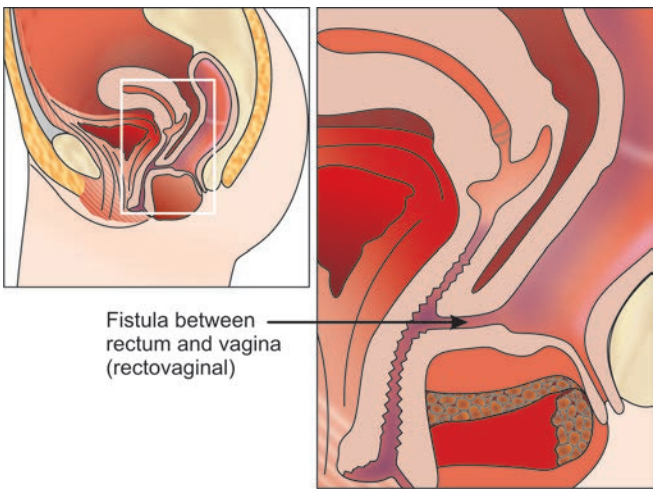
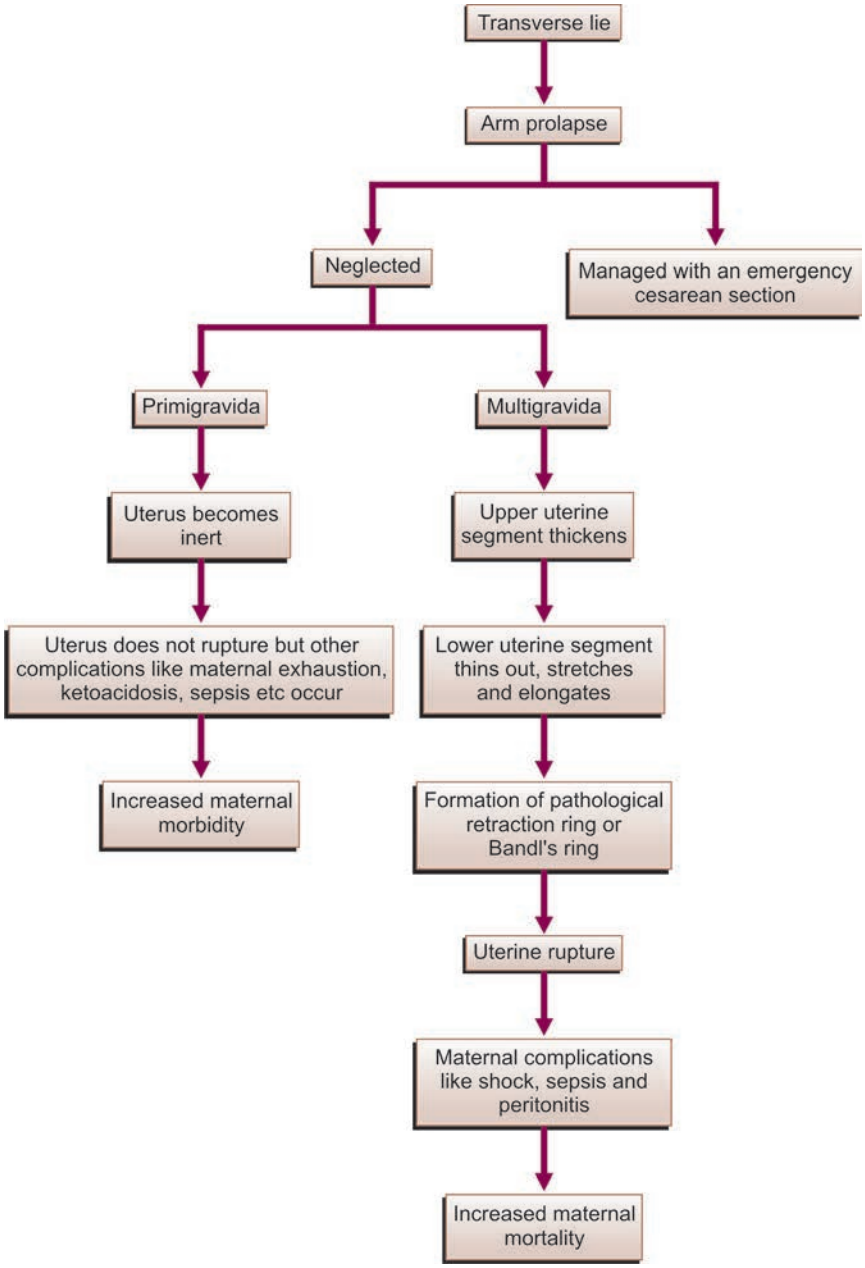


Fig. 3.8: Genitourinary fistula

Flow chart 3.2: Consequences of a neglected arm prolapse



segment gives way due to marked thinning of the uterine wall. There is an increased incidence of dehydration, ketoacidosis, septicemia, rupture uterus, postpartum hemorrhage, shock, peritonitis, injury to the genital tract, etc. All these factors result in increased rate of both maternal and fetal morbidity and mortality.

Long term complications

Long term maternal complications include development of genitourinary fistulas (figure 3.8), secondary amenorrhea (related to Sheehans syndrome associated with PPH), hysterectomy etc.

Fetal Complications

Fetal asphyxia

Tonic uterine contractions can interfere with uteroplacental circulation resulting in fetal distress. Other fetal complications may include preterm birth, premature rupture of membranes, intrauterine fetal death and increased fetal mortality.

Important Questions and Answers

Q.1. What is the next step of management in the above described case study?

Ans. Patient was called for ECV. After failure at multiple attempts of ECV, she was posted for an elective cesarean section.

Q.2. Is there any scope for internal version for management of transverse lie in modern obstetrics?

Ans. There is no scope for internal version in management of transverse lie and obstructed labor in modern obstetrics.

Q.3. A 27-year-old primigravida with preterm gestation (28 weeks) presented with an intrauterine death (IUD) with transverse lie having uterine contractions. What would be further management in this case?

Ans. Firstly, the clinician needs to ensure that the patient is in a stable condition. After taking the patients history and doing a general physical examination, an abdominal and vaginal examination must be performed. The fetal heart was absent on auscultation. On performing the vaginal examination, the cervix was found to be almost fully dilated and fully effaced except for a cervical rim remaining. The transverse fetal presentation and absent fetal heart were confirmed by performing an ultrasound examination. Since the baby was small in size and dead and cervix fully dilated, the best option would be to take the patient to the operation theater and perform internal version under general anesthesia. However if the obstetrician is not conversant with the technique of internal version, the best option would be to perform a cesarean section.

Bibliography

1. Carrascosa-Romero MC, Ruiz-Cano R, Abad-Ortiz L, Calatayud-Pérez V, Martínez-Gutiérrez A, Tebar-Gil R. Intrauterine spinal cord injury resulting from a transverse lie. Magnetic resonance imaging. Rev Neurol. 2002;35(4):398-9.
2. Chauhan AR, Singhal TT, Raut VS. Is internal podalic version a lost art? Optimum mode of delivery in transverse lie. J Postgrad Med. 2001;47(1):15-8.
3. Cruikshank DP, White CA. Obstetric malpresentations: Twenty years' experience. Am J Obstet Gynecol. 1973;116(8): 1097-104.
4. Gemer O, Segal S. Incidence and contribution of predisposing factors to transverse lie presentation. Int J Gynaecol Obstet. 1994;44:219-21.
5. Gemer O, Kopmar A, Sassoon E, Segal S. Neglected transverse lie with uterine rupture. Arch Gynecol Obstet. 1993;252: 159-60.
6. Nassar N, Roberts CL, Cameron CA, Olive EC. Diagnostic accuracy of clinical examination for detection of noncephalic presentation in late pregnancy: Cross sectional analytic study. BMJ. 2006; 333(7568):578-80.
7. Nicholson JM. Noncephalic presentation in late pregnancy. BMJ. 2006;333(7568):562-3.
8. Phelan JP, Boucher M, Mueller E, McCart D, Horenstein J & Clark SL. The nonlaboring transverse lie. A management dilemma. J Reprod Med. 1986;31(3):184-6.

Section 2

Complications of Pregnancy

- Antepartum Hemorrhage
- Twin Pregnancy
- Rh Negative Pregnancy
- Previous Cesarean Section
- Hydatidiform Mole
- Bad Obstetric History
- Postpartum Hemorrhage
- Intrauterine Growth Restriction

Chapter

4 Antepartum Hemorrhage

Hemorrhage has been identified as one of the most important causes of maternal death worldwide. Maternal bleeding in the antepartum period, before the birth of the child, can be considered as one of the most disastrous obstetric emergency which is encountered in clinical practice. This condition can cause a pregnant patient to become exsanguinated and bleed to death within a matter of minutes, thereby resulting in the death of her baby as well. Therefore all clinicians need to be well versed with the causes and the management of bleeding taking place during the antenatal period, which is also known as antepartum hemorrhage or APH.

Antepartum hemorrhage can be defined as hemorrhage from the genital tract occurring after the 28th week of pregnancy, but before the delivery of baby. It does not include the bleeding which occurs after the delivery of the baby; this bleeding which occurs in the postpartum period after the birth of the baby is known as postpartum hemorrhage. The 28 weeks interval is arbitrarily taken as a limit while defining APH because the fetus is supposed to have attained viability by that time.

Causes of APH

The various causes of APH are illustrated in flow chart 4.1. The antepartum bleeding could be due to placental or extraplacental causes. Besides this, some cases of APH could be due to unexplained causes and are also termed as indeterminate APH. The placental causes of bleeding are termed as true APH and can be due to placenta previa or placental abruption. Extraplacental cause of bleeding is also termed as false APH and includes bleeding related to the presence of cervical polyps, carcinoma cervix, cervical polyps, cervical varicosities, etc. Placental causes of bleeding are the most common cause of APH, accounting for nearly 70% to 75% cases; whereas the extraplacental causes account for 5% cases and unexplained causes for the remaining 20% to 25%.

Part 1: Placenta Previa

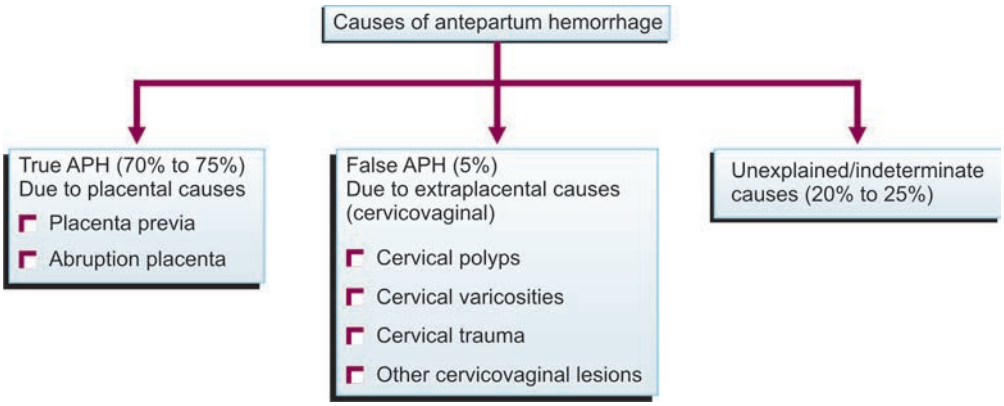
Case Study

A 32-year-old G2 P1 L1 lady with 33 weeks gestation, presented with painless bleeding per vaginum since last two hours. This was the first time during the pregnancy that she has experienced this bleeding. According to her, the bleeding was severe and she gave a history of soaking nearly 5–6 pads in last two hours. Her pulse rate is 90 beats/minute and her BP is 110/70 mm Hg.

Introduction

Placenta previa is one of the important placental causes of APH and can be defined as abnormal implantation of the

Flow chart 4.1: Causes of APH



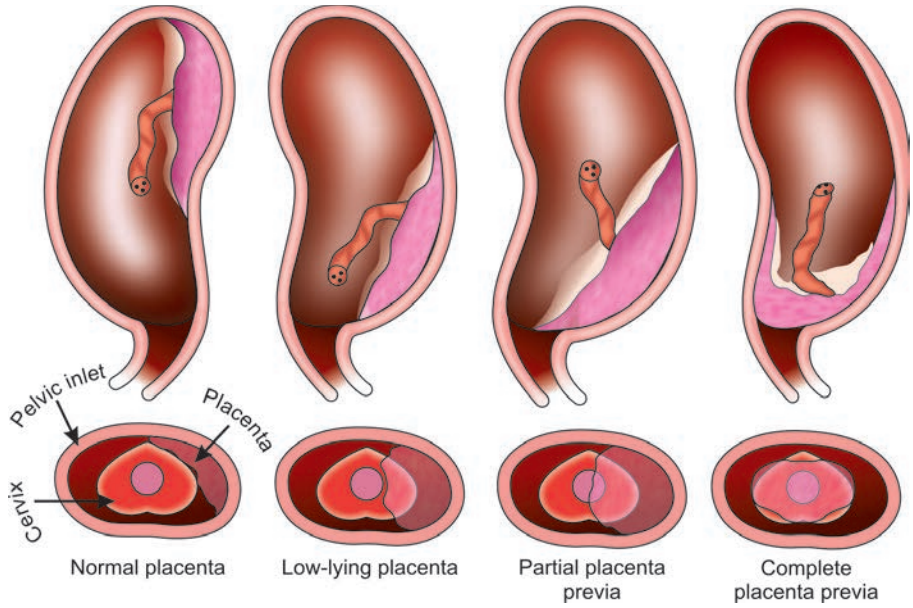


Fig. 4.1: Relationship of various degrees of placenta previa with the cervix

placenta in the lower uterine segment. Depending on the location of placenta in the relation of cervical os, there can be four degrees of placenta previa, which are described in the figure 4.1. The cause of bleeding is related to mechanical separation of the placenta from the site of implantation. This usually occurs at the time of formation of the lower uterine segment, during third trimester, or during effacement and dilatation of the cervix at the time of labor. As the lower uterine segment progressively enlarges in the later months of pregnancy, the placenta gets sheared off from the walls of the uterine segment. This causes opening up of uteroplacental sinuses which can initiate an episode of bleeding. Since the growth of the lower uterine segment is a physiological process, the episode of bleeding becomes inevitable in cases of placenta previa. The episode of bleeding is also triggered off, if placenta is separated from the lower uterine segment due to traumatic acts like vaginal examination, sexual intercourse, etc.

Degrees of Placenta Previa

There are four specific types of placenta previa:

Type 4 placenta previa

This is also known as total or central placenta previa (figure 4.2). In total placenta previa, the placenta completely covers the cervix.

Type 3 placenta previa

This is also known as partial placenta previa (figure 4.3). In partial placenta previa, the placenta partly covers the cervical os.

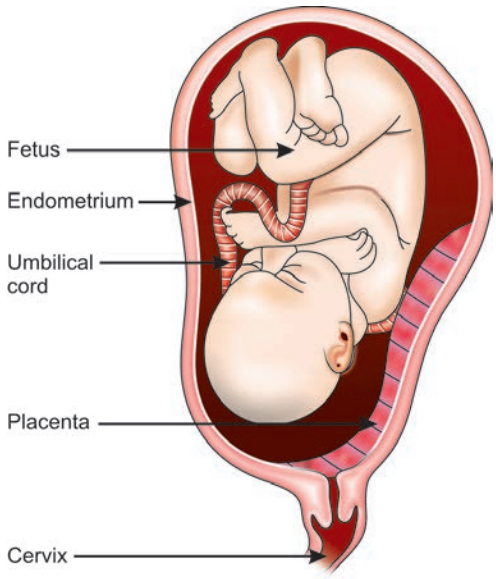


Fig. 4.2: Total placenta previa

Type 2 placenta previa

This is also known as marginal placenta previa (figure 4.4). In marginal placenta previa, the placenta does not in any way cover the cervical os, but it approaches the edge of the cervix.

Type 1 placenta previa

This is also known as low lying placenta (figure 4.5): Low lying placenta is a term used to describe a placenta which is implanted in the lower uterine segment, but isn't quite close enough to the cervix to qualify as marginal placenta previa. Though the placenta does lie in close proximity to the internal

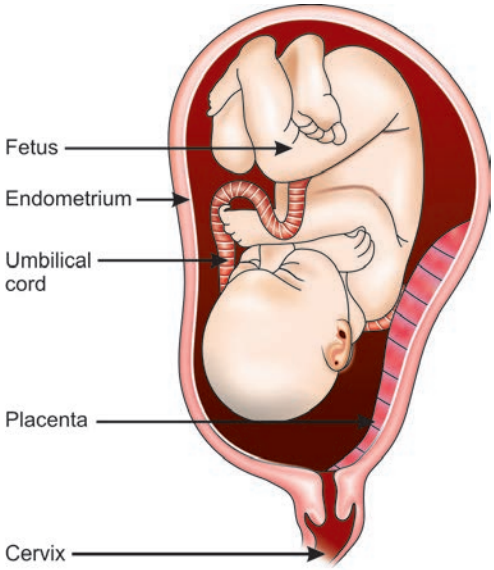


Fig. 4.3: Partial placenta previa

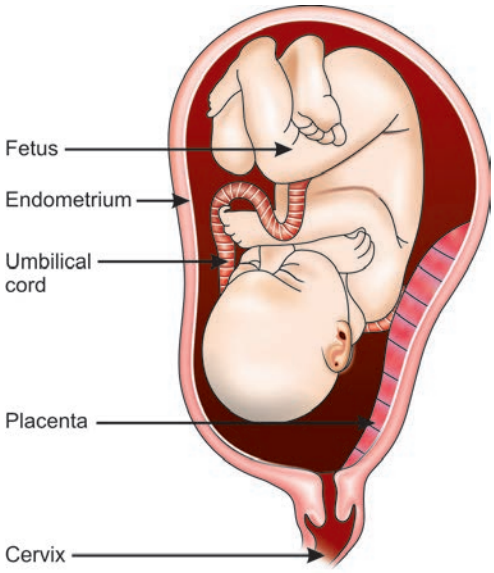


Fig. 4.4: Marginal placenta previa

os, the placental margin does not approach the cervical edge in any way.

Dangerous Placenta Previa

Marginal placenta previa when implanted over the posterior uterine wall is termed as dangerous placenta previa. This is so, as the placental thickness (about 2.5 cm) overlying the sacral promontory greatly diminishes the anterior posterior diameter of the pelvic inlet, thereby preventing the engagement of fetal presenting part. Since the engagement of the presenting part does not take place, effective compression of the separated placenta cannot take place and the vaginal

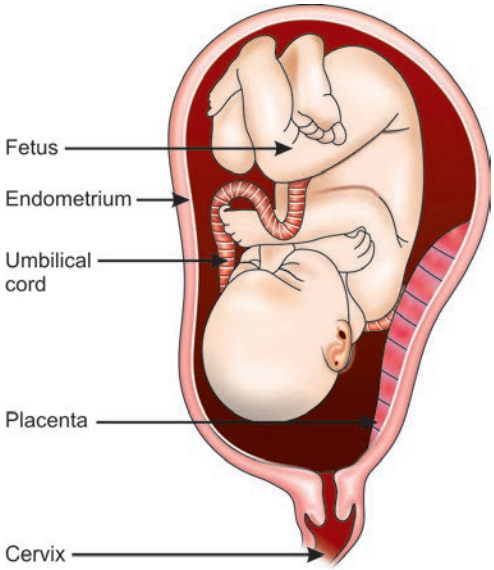


Fig. 4.5: Low lying placenta previa

bleeding continues to occur. In fact if the vaginal bleeding is allowed to occur, fetal distress may develop soon.

History

CLINICAL FEATURES

- Such patient presents with bleeding after 28 weeks of gestation, which is suggestive of antepartum hemorrhage.

It is important to elicit the characteristics of bleeding in order to arrive at a diagnosis. As previously described, true APH occurs due to two causes: Placenta previa and Placental abruption. History is one of the most important parameter for differentiating between these two most important causes for bleeding, late in pregnancy. While placenta previa will be discussed in this part, placental abruption would be discussed in part 2 of this chapter.

- *Type of bleeding:* Placenta previa is typically associated with sudden, painless, apparently causeless, recurrent and profuse bleeding, which is bright red in color.
- *Amount of bleeding:* The amount of bleeding in cases of placenta previa may range from light to heavy. It may stop, but it nearly always recurs days or weeks later. Some women who have placenta previa may also experience uterine contractions with bleeding, especially if they are in labor. The patient may also give a history of experiencing small "warning hemorrhages" before the actual episode of bleeding. The occurrence of these warning hemorrhages must be viewed with greatest suspicion and caution and appropriate steps must be taken to exclude placenta previa.

It is also important to take the history regarding the amount of blood loss. Most of the times, it is difficult to rely upon the patient's own estimation regarding the amount of bleeding. An important parameter to help decide the severity of hemorrhage is to ask the patient regarding the number of pads she had to use during the episode of bleeding. A history of passage of clot is also indicative of severe hemorrhage. Presence of blood at the sides of patient's legs, at the time of examination often extending up to the heels is also indicative of severe hemorrhage.

- *Timing of bleeding:* Bleeding usually occurs late in the third trimester. The earlier in pregnancy, the bleeding occurs, more likely it is to be due to severe degree of placenta previa.

RISK FACTORS

Some risk factors which are associated with an increased incidence of placenta previa and need to be elicited in the history include the following:

- Multiparity
- Often the woman gives history of previous cesarean section or some other uterine surgery in the past (e.g. D&C, myomectomy, etc). It is important to elicit the history of previous uterine surgery as presence of a uterine scar along with placenta previa may be often associated with placenta accreta, increta or percreta.
- History of placenta previa in the previous pregnancy
- Age of 35 years or more
- History of smoking
- History of multiple gestation: Multifetal gestation is usually associated with a large placenta which commonly encroaches upon the lower uterine segment.
- Fetal malpresentation
- Fetal congenital anomaly

General Physical Examination

The patient's physical condition is proportional to the amount of blood loss.

Anemia or shock: Repeated bleeding can result in anemia, whereas heavy bleeding may cause shock.

Profuse hemorrhage can result in hypotension and/or tachycardia.

Specific Systemic Examination

ABDOMINAL EXAMINATION

- Uterus is soft, relaxed and non tender.
- Uterine contractions may be palpated.
- Size of the uterus is proportional to the period of gestation.
- The fetal presenting part may be high and cannot be pressed into the pelvic inlet due to the presence of placenta.
- Abnormal fetal presentation (e.g. breech presentation, transverse lie, etc)
- Fetal heart rate is usually within normal limits. Fetal heart tones may be rarely absent in cases of APH due to placenta previa as a result of maternal shock. Slowing of fetal heart rate can sometimes result in cases of dangerous placenta previa (described previously).

Stallworthy's sign

In cases of placenta previa, when the head is pushed into the pelvis, there is slowing of fetal heart rate. This usually occurs due to compression of placenta and cord, especially in cases where marginal degree of placenta previa is located posteriorly (dangerous placenta previa).

VAGINAL EXAMINATION

Vaginal examination must never be performed in suspected cases of placenta previa. Instead, an initial inspection must only be performed. On inspection, the following points must be noted:

- To see if bleeding is occurring or not.
- In case the bleeding is occurring, to note the amount and color of the bleeding.

A per speculum inspection using a Cusco's speculum can be performed once the patient has become stable. Performance of per speculum examination helps in ruling out the local causes (e.g. cervical erosions, polyps, etc) of bleeding per vaginum. Nowadays the diagnosis of placenta previa can be confirmed on ultrasound examination. Thus, there is no need to perform a vaginal examination in suspected cases of placenta previa. In case, facilities for ultrasound examination are not available and a vaginal examination is required, it must be performed in the operating room under double set-up conditions (i.e., arrangements for an emergency cesarean delivery are in place). An emergency cesarean section may be required in case the vaginal examination provokes an episode of bleeding. The vaginal examination must be performed just prior to the delivery and the following steps must be taken:

- An intravenous drip should be started.
- Arrangements for blood transfusion must be in place at time of examination.
- The patient should be put under general anesthesia.

At the time of vaginal examination, firstly the index finger must be gently introduced inside. The vaginal fornices must be palpated for presence of any bogginess between the fetal presenting part and the finger. If the fetal presenting part can be palpated through the fornix, the finger can be introduced

with some confidence into the cervical canal. If the placental edge is felt at any point, the examination must be stopped and finger must be withdrawn. If no placental edge is palpable, the entire lower segment can be gradually explored.

RECTAL EXAMINATION

A rectal examination is more dangerous than a vaginal examination and must never be performed in cases of suspected placenta previa. On vaginal examination it may be sometimes possible to feel the placenta, before it is seriously disturbed. However, on rectal examination, the gloved finger is covered by rectal wall, vaginal wall and the intervening fascia before it can feel the placenta. Thus on rectal examination, it virtually appears to be impossible to detect the placenta before it has separated and has provoked serious bleeding.

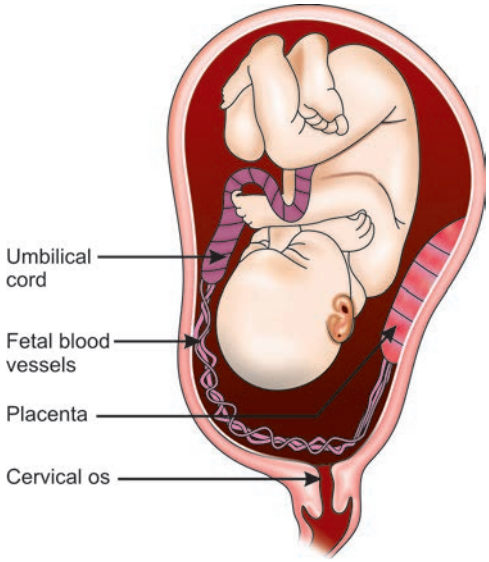


Fig. 4.6: Vasa previa

Differential Diagnosis

Various causes for antepartum vaginal bleeding are listed in flow chart 4.1. In the above mentioned case where the patient presents with the history of bleeding after 28 weeks of gestation, the most important task of the obstetrician is to determine whether the bleeding is due to placental abruption or placenta previa. Another important but rare cause of hemorrhage, where bleeding is of fetal origin rather than from the mother is vasa previa.

Vasa Previa

Vasa previa is an uncommon obstetrical complication which may be associated with a high risk of fetal demise if it is not recognized before rupture of membranes. In vasa previa, umbilical vessels traverse the membranes in the lower uterine segment in front of the fetal presenting part (figure 4.6). Neither the umbilical cord nor the placenta supports the vessels. Due to the absence of Wharton's jelly, the vessels may be easily lacerated at the time the membranes rupture. Also during uterine contractions, fetal vessels can get compressed resulting in fetal hypoxia and death. Some risk factors for vasa previa include bilobed and succenturiate placentas, low lying placentas, multiple pregnancies, marginal insertion of the cord, velamentous insertion of the cord, etc. When the diagnosis of vasa previa has been made, the patient must be posted for an elective cesarean section at 37 to 38 weeks of gestation or when fetal lung maturation has been confirmed. Patient with vasa previa presents with painless vaginal bleeding at the time of spontaneous rupture of membranes or amniotomy. Since the bleeding occurs from fetal vessels, fetal shock or demise can occur rapidly. When the membranes rupture, a small amount of continuous bright red bleeding occurs. The blood is from the fetal circulation and therefore, the fetus can bleed to death. If the cervix is almost fully dilated, the fetus can be delivered vaginally. If cervix is not completely dilated, an emergency cesarean section must be done to save the fetus. The presence of fetal blood can be confirmed by performing the Apt test. In this test, one drop of blood is added to 9 drops of 1% sodium hydroxide in a glass test tube. The color of the test tube must be checked after one minute. If the blood is of fetal origin, the mixture remains pink. However, if the blood is of maternal origin, the mixture turns brown in color.

Antepartum Hemorrhage due to Placental Abruption

This is explained in detail in part 2 of this chapter.

Extraplacental Causes of APH

Extraplacental causes of hemorrhage, including the presence of cervical polyps, erosion, varicosities or carcinoma are usually rare and can be ruled out on the per speculum examination.

Management

Management comprising of investigations and definitive obstetric management is discussed below.

Investigations

ABO/Rh Compatibility

At least four units of blood need to be crossmatched and arranged. At any time, if severe hemorrhage occurs, the patient may require a blood transfusion.

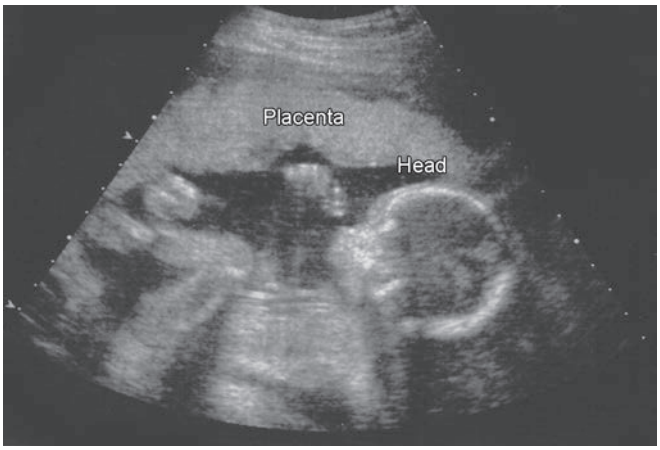


Fig. 4.7: Placental localization on transabdominal imaging

Imaging Studies

The main way of confirming the diagnosis of placenta previa is by imaging studies, especially ultrasonography. Placenta previa is diagnosed through ultrasound, either during a routine prenatal appointment or following an episode of vaginal bleeding. Ultrasound examination can be of two types: Transabdominal and Transvaginal ultrasound.

Transabdominal ultrasonography

Transabdominal ultrasound (TAS) helps in determining the placental position (figure 4.7), fetal maturity, fetal wellbeing, fetal presentation and presence of congenital anomalies. Some of the disadvantages of transabdominal ultrasound include, poor visualization of the posterior placenta and influence of many factors on the accuracy of ultrasound examination. Some of the factors which can interfere with the visualization of the lower segment include patient obesity, underfilled or overfilled bladder and skills of the operator. Nevertheless, TAS is a simple, precise and safe method of visualizing the placenta, having an accuracy rate of 93% to 98%. Transvaginal ultrasound, however, is more accurate than transabdominal ultrasound in the diagnosis of placenta previa.

Transvaginal ultrasonography

According to SOGC, Transvaginal sonography (TVS), if available, must be used to confirm the placental location at any time in pregnancy when the placenta is thought to be low lying. TVS is considered to be significantly more accurate than transabdominal sonography and its safety is well established. On TVS examination, the actual distance from the placental edge to the margin of internal cervical os must be determined in millimeters. A placental edge exactly reaching the internal os is described as 0 mm. When the placental edge reaches or overlaps the internal os on TVS between 18 and 24 weeks' gestation, a follow up examination in the third trimester is recommended to reconfirm the placental position. Overlap of more than 15 mm is associated with an increased likelihood of placenta previa at term. Placental overlap of 20 mm or more on TVS at any time in the third trimester is highly predictive of the need for cesarean section. The os-placental edge distance on TVS after 35 weeks' gestation is valuable in planning route of delivery. When the placental edge lies > 20 mm away from the internal cervical os, women can be offered a trial of vaginal delivery. However, if the placental edge lies less than 20 mm from the cervical os, a cesarean section is usually required, although vaginal delivery may sometimes be possible depending on the clinical circumstances. Diagnosis by TVS is more accurate than by TAS and its safety has been established. The angle between the transvaginal probe and the cervical canal is such that the probe does not enter the cervical canal and therefore the placenta remains undisturbed. Some clinicians advocate that the probe must not be inserted more than 3 cm for visualization of the placenta.

Transvaginal examination need not be performed in all the women. A reasonable antenatal imaging policy would be to perform a transvaginal ultrasound scan on all women in whom a low lying placenta is suspected from their transabdominal anomaly scan (at approximately 20–24 weeks). In case of low lying placenta at 20–24 weeks of gestation, a repeat ultrasound examination needs to be done in third trimester to re-confirm the placental position. Due to the growth of lower uterine segment in the third trimester, placental migration is likely to occur. Placental migration however is unlikely if the placenta is posterior or if there has been a previous cesarean section. Thus, the clinician needs to remain more vigilant in these cases.

In the case of asymptomatic women in whom the placental edge has only reached or just overlapped the cervical os at the second trimester scan, a repeat scan should be performed at 36 weeks. However, the individuals in whom a major placenta previa is suspected at the time of initial scan at 20–24 weeks, further clarification of the diagnosis is required earlier in gestation and therefore a repeat ultrasound scan should be conducted at around 32 weeks.

Magnetic resonance imaging (MRI)

Magnetic resonance imaging has been reported as a safe technique in the diagnosis of placenta previa when the images obtained by ultrasound (both TAS and TVS) have been unsatisfactory. MRI has the advantage of being possible without a full bladder and is not dependent on operator skills. It is also particularly useful in imaging posterior placentas. Since MRI

is able to give information regarding myometrial invasion, it has been suggested as a safe and alternate method for determining the presence of placenta accreta. However, future large scale trials for determining the efficacy and safety of the use of MRI during pregnancy need to be performed in future.

Doppler ultrasound

Antenatal imaging by color flow Doppler ultrasonography is especially useful in women with placenta previa who are at an increased risk of placenta accreta. Women with placenta previa with a previous history of uterine scar are at an increased risk of having a morbidly adherent placenta, especially when there has been a short cesarean to conception interval. Doppler ultrasound examination should be preferably done in such individuals.

Rx *Treatment/Obstetric Management*

PREVENTION

Antenatal Period

There is no treatment to change the position of the placenta. However steps can be taken to reduce the development of hemorrhage and other related complications. Important measures, which can be taken in the antenatal period to reduce the complications resulting due to placenta previa include the following:

- *Early hospital admission of woman at risk*: The women at high risk of developing APH should be admitted to the hospital early in third trimester. These particularly include those patients who have had previous histories of antepartum hemorrhages; those with high parity; those over the age of 35 years, etc.
- *Prevention of anemia*: It is an obvious fact that greater the degree of anemia, the lower would be the woman's ability to withstand hemorrhage. Therefore, prevention and treatment of anemia in the antenatal period helps in reducing the complications related to APH.
- *Prevention of placental abruption:* Preventive steps like early detection of preeclampsia; avoidance of trauma and avoidance of sudden uterine decompression, all of which can be associated with an increased risk of placental abruption, help in reducing the development of APH in relation to placental abruption.

Intrapartum Period

As previously described, cervical digital and rectal digital examination must never be performed in suspected cases of placenta previa, unless the woman is in the operation theater, with all the preparations in place for an emergency cesarean delivery. Even the gentlest of cervical examination can sometimes precipitate torrential vaginal bleeding, thereby necessitating an emergency cesarean delivery.

Also, once placenta previa is diagnosed, additional ultrasound examinations must be performed as the placental migration may often take place during the third trimester.

DEFINITIVE MANAGEMENT/TREATMENT

In order to decide the final treatment plan for patients with placenta previa, each of the factors described in table 4.1 need to be taken into consideration.

Evaluation of the amount of bleeding is an important step in the management of patients with placenta previa. There are no medicines to stop the bleeding but in many cases it stops on its own. Depending on the amount the bleeding present at the time of examination, the management options in a patient with placenta previa are shown in flow chart 4.2.

Management of Patients with Severe Bleeding

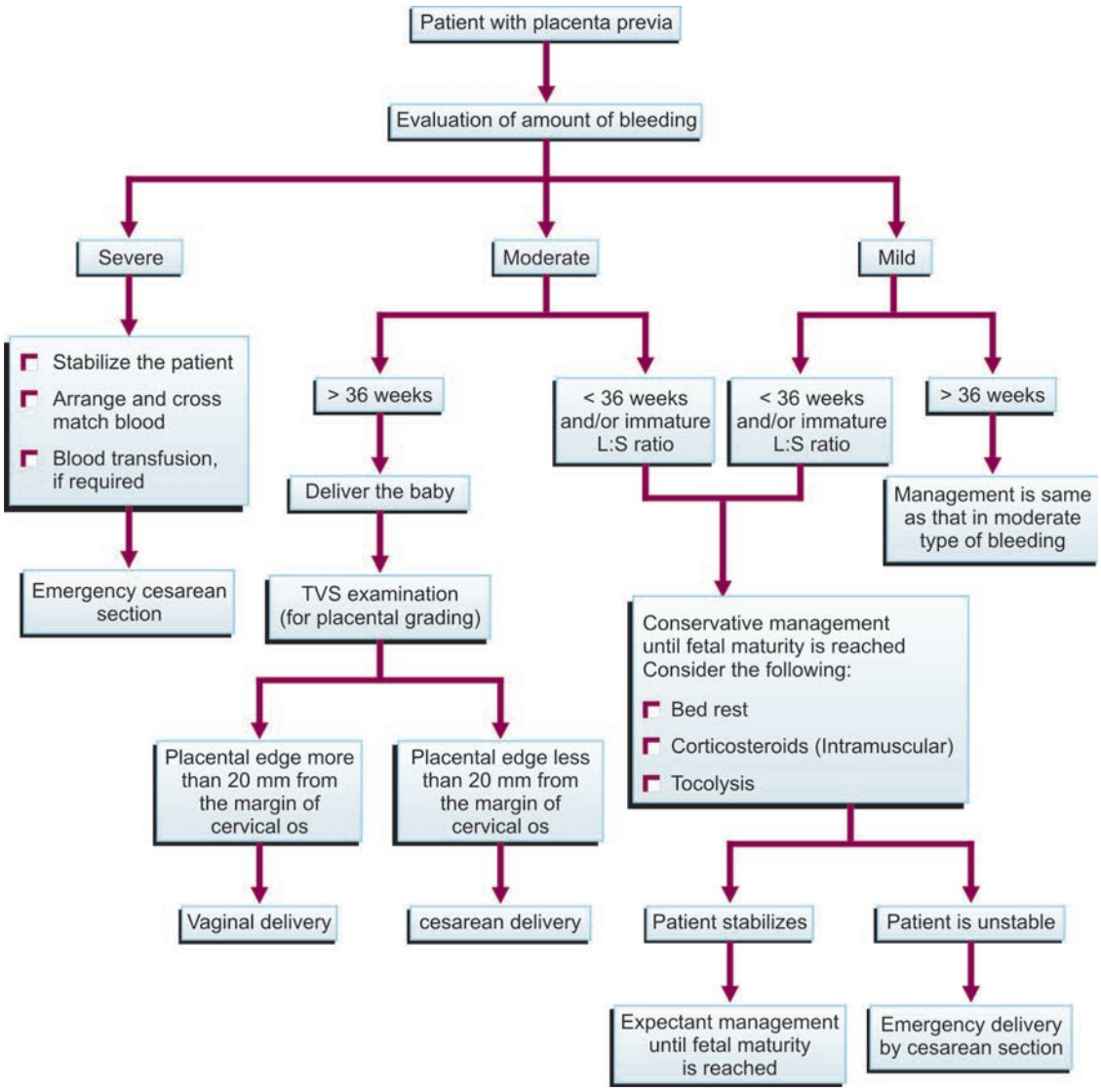
Patients with severe bleeding need to be carefully monitored in the hospital. These women must be transferred to tertiary care units as soon as possible. In cases of severe bleeding, the most important step in management is to stabilize the patient; arrange and crossmatch at least four units of blood and start blood transfusion if required. All efforts must be made to shift her to the operating theater as soon as possible for an emergency cesarean delivery. The following steps need to be taken:

- One or two large bore IV cannula need to be inserted and IV fluids like ringer lactate must be started.
- Monitoring of pulse, blood pressure and amount of vaginal bleeding to be done at every half hourly intervals.
- Input-output charting at hourly intervals.
- If the bleeding is severe, a blood transfusion may be required in order to replace lost blood.
- Once the patient has stabilized, the blood sample should be taken and sent for complete blood count, blood grouping and crossmatching. At least four units of blood need to be arranged.

Table 4.1: Factors to be considered before deciding the final treatment plan for patients with placenta previa

Amount of vaginal bleeding
Whether bleeding has stopped or is continuing
The gestational age
Fetal condition
Maternal health
Position of the placenta and baby

Flow chart 4.2: Management plan in a patient with placenta previa



- Sedative analgesics like pethidine can be administered.
- Severe bleeding is usually due to a major degree of placenta previa. The definitive treatment in these cases would be delivery by cesarean section.

Management of Patients with Moderate Bleeding

- The initial five steps as mentioned in patients with severe bleeding must be applied at the same time using clinical discretion.
- The timing for delivery in these patients must be based upon the period of gestation as follows:

Period of gestation ≥ 36 weeks

If the period of gestation is 36 weeks or more, the women must be delivered by performing a cesarean section.

Period of gestation is between 32–36 weeks

If the period of gestation is between 32–36 weeks, assessment of fetal lung maturity needs to be done using the L: S ratio. The L: S ratio of ≥ 2 indicates fetal lung maturity, implying that the fetus can be delivered in these cases.

If L: S ratio is < 2, the fetal lungs have yet not attained maturity. Intramuscular corticosteroid injection must be given to the mother. Until the complete dose of corticosteroids has been administered, the delivery should be preferably delayed. During this waiting period, the patient must be kept under intensive monitoring. Tocolytic agents can be used to prevent uterine activity. If the patient remains stable for next 24–48 hours, she becomes a candidate for expectant management. If the patient does not remain stable for the next 24–48 hours, she must be delivered by a cesarean section.

Management of Patients with Mild Bleeding

Similar to the patients with moderate bleeding, in the patients with mild bleeding the management is based on period of gestation and fetal pulmonary maturity. If the period of gestation is less than 36 weeks or the fetal lungs are immature (i.e. L:S ratio is less than 2), the woman becomes a candidate for expectant management. If the fetus has attained maturity, the women can be delivered. The mode of delivery depends upon the grade of placenta previa.

Expectant Management

The expectant management was introduced by Macafee and Johnson and is often also known as Macafee and Johnson's regime. The aim of expectant management is to delay pregnancy until the time fetal maturity is reached.

Prerequisites for expectant management

The prerequisites for expectant management are as follows:

- Stable maternal health (Hb>10%).
- Period of gestation is less than 37 completed weeks.
- Fetal wellbeing is assured on ultrasound examination.
- No active bleeding is present.
- Facilities for emergency cesarean section are there, in case it is required.

Steps to be taken

The expectant management includes the following steps:

- If there is little or minimal bleeding, the woman is advised to limit her physical activity and to take bed rest. Bed rest helps in reducing pressure on the cervix, which may help in stopping preterm contractions or vaginal bleeding. Bed rest also helps in increasing blood flow to the placenta, thereby stimulating fetal growth.
- The women must be asked to avoid sexual intercourse, which can trigger vaginal bleeding by initiating contractions or causing direct trauma.
- The woman is also advised not to engage in any type of physical exercise as far as possible.
- The woman should be prescribed iron tablets throughout pregnancy in order to keep the blood hemoglobin levels under control.
- In case preterm delivery is anticipated, the mother must be administered corticosteroids intramuscularly.
- Placenta previa is likely to result in feto-maternal hemorrhage. Therefore, all Rh negative women with placenta previa who bleed must be offered anti-D immunoglobulin injections in order to prevent the risk of Rh-isoimmunization.
- Thromboprophylaxis may be offered to women who are offered prolonged bed rest in order to reduce the risk of thromboembolism.
- The use of prophylactic techniques like cervical cerclage to help reduce the bleeding and prolong the duration of pregnancy and tocolysis to reduce the uterine activity are not backed up by sufficient evidence to recommend their routine use.

Hospitalization vs. Outpatient Management in Placenta Previa

The expectant management plan can be carried out at home or in the hospital. The indications for hospitalization are described in table 4.2. The major concern in caring for an asymptomatic woman with placenta previa major is that she might suddenly start bleeding heavily at any time, requiring urgent delivery. For this reason, hospitalization is recommended by RCOG during the latter part of the third trimester (commencing from 32–34 weeks) in women with major degrees of placenta previa, who previously had been stable. Hospitalization is also advised as soon as heavy bleeding occurs at any period of gestation, irrespective of the degree of placenta. For heavy bleeding, bed rest in the hospital may be required, irrespective of the period of gestation. If the patient experiences reduced fetal movements, she must be admitted in the hospital for fetal monitoring and assessment.

If bleeding stops and the fetus has not attained maturity, hospital discharge and outpatient management may be allowed. Some criteria for outpatient management of women with placenta previa are described in table 4.3. It should be made clear to all women, who are being managed at home that they must attend hospital immediately if they experience any bleeding, any contractions or any pain. They must be advised to report to the hospital even if they experience vague suprapubic aches, similar to that experienced at the time of periods. The women who are being managed at home should have support of a partner or a carer who would bring her to the hospital in case of emergency. The woman's residence must not be too far away from the hospital and she should have facilities of communicating with the hospital through a telephone.

Table 4.2: Indications for hospitalization in women with placenta previa

Hospitalization at 32–34 weeks is required for women with major degrees of placenta previa, who had been previously stable
Severe bleeding irrespective of the period of gestation
Patient perceives reduced fetal movements

Table 4.3: Criteria for outpatient management of women with placenta previa

Woman is in stable condition (Hb>10 gm% and hematocrit > 33%)
Patient has been observed in the hospital setting for a period of 72 hours during which the maternal and fetal conditions, both were stable.
Non-stress test was reactive at the time of discharge
No active bleeding
Patient willing to take bed rest at home
Fetus has not attained maturity
Close proximity with the hospital and facilities for transportation to the hospital available, 24 hours all seven days of the week
The constant presence of a companion
Telephone communication with the hospital
Patient is willing to come for weekly check-ups until the time of delivery.

4

Mode of Delivery

Cesarean delivery is necessary for most cases of placenta previa, especially the major degree placenta previa including type II (posterior); type III and type IV. Severe blood loss may require a blood transfusion. Prior to delivery, the obstetrician needs to have detailed antenatal discussions with the woman and her partner, regarding the need for cesarean delivery, possibility of hemorrhage, possible blood transfusion and requirement for major surgical interventions, such as hysterectomy.

The os-placental edge distance on TVS after 35 weeks' gestation is valuable in planning route of delivery. If at the time of TVS performed at 35 to 36 weeks of gestation, the placental edge is more than 20 mm away from the cervical os, there are high chances for a vaginal delivery. Thus when the placental edge lies greater than 20 mm away from the internal cervical os, women can be offered a trial of labor with expectation of high success rates. However, if the placental edge lies between 20 to 0 mm away from the os, or there is any degree of cervical overlap, the woman must be delivered by performing a cesarean section. Regional anesthesia may be employed for cesarean section in the presence of placenta previa. Delivery of the women with placenta previa must be conducted by the most experienced obstetrician and anesthetist on duty; preferably a consultant obstetrician and anesthetist should be present within the delivery suite. A junior doctor under training should not be left unsupervised while caring for the women with placenta previa.

Indications for Emergency Delivery

Indications for immediate delivery by an emergency cesarean section irrespective of the period of gestation or degree of placenta previa are listed in table 4.4.

Table 4.4: Indications for an emergency cesarean section

Bleeding is heavy
Bleeding is uncontrolled
Major degree placenta previa (type II posterior, type III and type IV)
Fetal distress
Obstetric factors like CPD, fetal malpresentation, etc.

Table 4.5: Steps to be taken to control bleeding at the time of cesarean section

Use of uterotonic agents to reduce the blood loss
CHO sutures
B-lynch sutures
Bilateral uterine artery or internal iliac artery ligation
Intrauterine packing
Hydrostatic balloon catheterization
Aortic compression
Pelvic artery embolization

Some of the steps that can be taken at the time of cesarean section to reduce the chances of bleeding are described in table 4.5. Detailed description of all these techniques has been done in chapter 10**.** If all conservative measures methods mentioned in the table 4.5 fail and the patient continues to bleed, the obstetrician may have no other alternative left, but to resort to cesarean hysterectomy in order to save the mother's life.

Complications

MATERNAL

Bleeding

One of the biggest concerns with placenta previa is the risk of severe vaginal bleeding (hemorrhage) during labor, delivery or the first few hours after delivery. The bleeding can be heavy enough to cause maternal shock or even death.

Placenta Accreta, Increta, Percreta

Pathological adherence of the placenta is termed as placenta accreta. While the term "accreta" refers to abnormal attachment of the placenta to the uterine surface, the terms "increta" and "perceta" refer to much deeper invasion of the placental villi into the uterine musculature (figure 4.8). Abnormally adherent placenta can result in severe bleeding and, may often require cesarean hysterectomy. In placenta increta, the invasion by the placental villi is limited to approximately half the myometrial thickness. On the other hand, in cases of

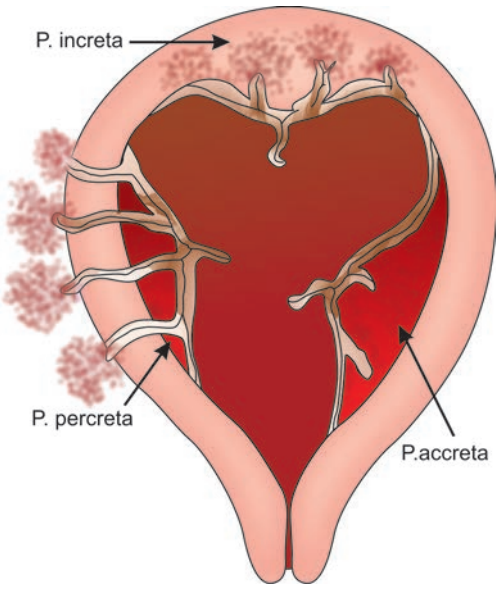


Fig. 4.8: Abnormally adherent placenta

placenta percreta there is through and through invasion of the uterine wall.

Previous history of a lower segment cesarean section is typically associated with an increased risk for placenta previa in the future pregnancies. Though the exact mechanism behind the association of placenta previa with previous scar is poorly understood, it may be due to reduced differential growth of the lower segment resulting in reduced upward shift in placental position with increasing gestation. Presence of placenta previa in association with the previous history of lower uterine scar is typically associated with adherent placentas. Color flow Doppler serves as a useful investigation in making a prenatal diagnosis of placenta accreta. The most commonly used therapeutic option for management of cases with placenta previa comprises of conservative management of placenta accreta with preservation of the uterus. Besides conservative management, varied other therapeutic options are used including prophylactic or therapeutic uterine artery embolization and internal iliac artery ligation at the same time as initial surgery and intramuscular methotrexate injections following the delivery of the baby. Hysterectomy may sometimes be required in cases with conservative management as a result of delayed hemorrhage.

When placenta accreta is anticipated, consultant anesthetic and consultant obstetrician need to discuss the plan of delivery. The consent for cesarean hysterectomy must be taken well in advance. Delivery should involve specialized multidisciplinary personnel and should occur in settings with facilities for high-volume blood transfusion.

Anemia and Infection

Excessive blood loss can result in anemia and increased susceptibility to infections.

FETAL

Premature Birth

Severe bleeding may force the obstetrician to proceed with an emergency preterm cesarean delivery.

Fetal Death or Fetal Distress

Though chances of fetal distress and fetal death are much less in cases with placenta previa in comparison to that in cases with placental abruption, severe maternal bleeding in cases with placenta previa is sometimes also responsible for producing fetal distress.

Important Questions and Answers

Q.1. What is the likely diagnosis in the above case? Why does this patient need to be assessed urgently?

Ans. Since the bleeding in this patient has occurred after 28 weeks of gestation, the most probable diagnosis of antepartum hemorrhage can be made. Most common causes for APH include placenta previa and placental abruption. In this case, the history of painless, causeless bleeding points in the direction of placenta previa. However the diagnosis needs to be confirmed by ultrasound examination. This patient needs to be urgently managed because antepartum hemorrhage due to any cause must always be regarded as an emergency, until the exact cause for the bleeding has been found. After the ultrasound examination, correct management can be given.

Q.2. What is the first step in the management of a patient with an antepartum hemorrhage?

Ans. The first step in the management of such a patient is to stabilize the patient. The clinical condition of the patient must be assessed. The priority should be towards the resuscitation of the patient with emphasis on maintenance of ABC (airway, breathing and circulation). Since the patient is likely to be hypovolemic, two wide bore cannulae must be inserted and IV fluids be started. The patient's blood must be sent for blood grouping and typing, hematocrit and coagulation profile. At least four units of blood need to be arranged as urgent transfusion may be required at any time.

Q.3. What is the next step in the management of a patient with an antepartum hemorrhage?

Ans. After the maternal condition has stabilized, the fetal condition must be assessed. Arrangements for an urgent ultra-

sound must be made in order to confirm the fetal wellbeing and presentation and placental localization.

Q.4. What should be done once the condition of the patient and her fetus has been assessed and the patient resuscitated, if necessary?

Ans. The cause of the antepartum hemorrhage must be investigated. Further management needs to decided based on the exact diagnosis.

Q.5. How does one clinically determine the severity of the condition?

Ans. The following parameters help in deciding the severity of hemorrhage:

- Taking the history regarding the number of sanitary pads soaked with blood. The amount of blood present on the sanitary pad needs to be visually assessed by the clinician. The patient should be advised to save all blood pads and show them to the clinician.
- Presence of blood along the side of patient's thighs and legs, running up to the heels is suggestive of excessive bleeding.
- Passage of blood clots is usually indicative of severe hemorrhage.

Q.6. Can engagement of the head occur if placenta previa is present?

Ans. No. Presence of a major degree placenta previa is usually associated with a free floating head in case of cephalic presentation. If two fifths or less of the fetal head can be palpated above the pelvic brim, the possibility of placenta previa can be nearly excluded**.**

Q.7. What do you understand by a "warning bleed"?

Ans. This bleeding refers to small episodes of hemorrhage which occur prior to the episode of the major hemorrhage in cases with placenta previa. The bleeding occurs at about 34 weeks of gestation or earlier when the lower uterine segment begins to form.

Q.8. How do you go about doing a double setup vaginal examination in an operation theater?

Ans. Double setup examination is rarely done nowadays for the danger of provoking torrential hemorrhage. The double setup examination is done while all the preparations for an emergency cesarean section are in place, in case it is required. The double setup vaginal examination involves the following steps:

- The obstetrician must scrub up and put on double pair of gloves. If on vaginal examination placenta is felt, the first pair of gloves would be discarded so that the obstetrician can immediately proceed for an emergency cesarean section.
- The OT nurse must be scrubbed up with her trolley ready.
- The patient must be preferably under GA or epidural anesthesia. In case an emergency cesarean section is required, the anesthetist must be ready to extend the anesthesia.
- A careful digital examination is done by the clinician.
  - Firstly the index finger must be gently introduced inside the vagina. The vaginal fornices must be palpated for presence of any bogginess between the fetal presenting part and the finger.
  - If the fetal presenting part can be palpated through the fornix, the finger can be introduced with some confidence into the cervical canal and a careful examination is done through the cervix.
  - If the placental edge is felt at any point, the examination must be stopped and finger must be withdrawn. In these cases, an emergency cesarean section needs to be performed. If no placental edge is palpable, the entire lower segment can be gradually explored. In these cases, the membranes can be ruptured with the aim of allowing a vaginal delivery.

Q.9. Why have patients with a placenta previa an increased risk of postpartum hemorrhage?

Ans. In cases of placenta previa, the placenta is implanted in the lower segment which, normally does not have the same ability as the upper segment to contract and retract after delivery. Due to this, the chances of bleeding following the delivery of the baby are increased. Therefore, measures must be taken in advance to prevent the occurrence of postpartum hemorrhage.

Part 2: Placental Abruption

Case Study

A G4 P3 L2 patient, who is 32 weeks' pregnant, presents with a history of severe vaginal bleeding and abdominal pain. The blood contains dark colored clots. Since the hemorrhage, the patient has also been complaining of reduced fetal movements. The patient's blood pressure is 80/60 mm Hg and the pulse rate 120 beats per minute.

Introduction

Definition

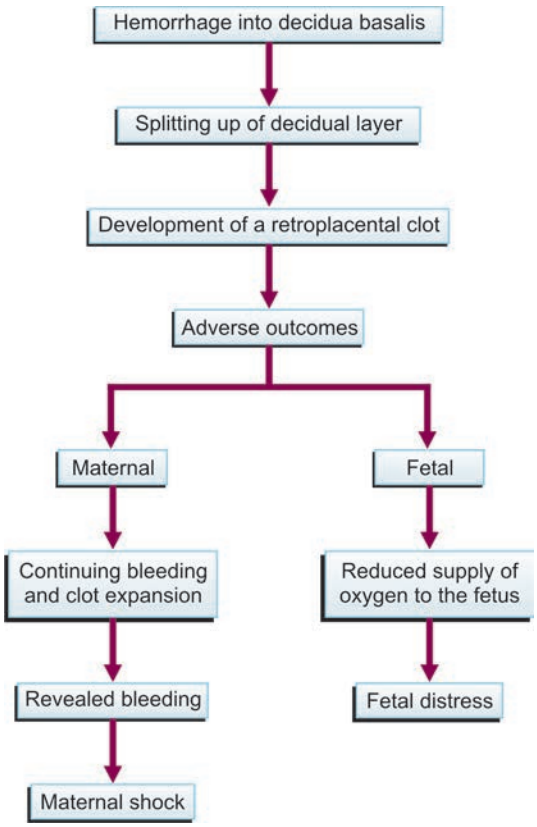
Placental abruption can be defined as abnormal, pathological separation of the normally situated placenta from its uterine attachment. As result, bleeding occurs from the opened sinuses present in the uterine myometrium. "Abruptio placentae" is a latin word meaning, "rending asunder of placenta", which denotes a sudden accident. Thus placental abruption

Table 4.6: Clinical classification of placental abruption

Parameter	*Grade 0*	*Grade 1*	*Grade 2*	*Grade 3*
External bleeding	Absent	Slight	Mild to moderate	Moderate to severe
Uterine tenderness	Absent	Uterus irritable, uterine tenderness may or may not be present	Uterine tenderness is usually present	Tonic uterine contractions and marked uterine tenderness.
Abdominal pain	Absent	Abdominal pain may or may not be present	Abdominal pain is usually present	Severe degree of abdominal pain may be present
FHS	Present, good	Present, good	Fetal distress	Fetal death
Maternal shock	Absent	Absent	Generally absent	Present
Perinatal outcome	Good	Good	May be poor	Extremely poor
Complications	Absent	Rare	May be present	Complication like DIC and oliguria are commonly present
Volume of retroplacental clot		Less than 200 ml	150–500 ml	More than 500 ml

is also known as accidental hemorrhage. Pathophysiology of bleeding related to placental abruption is shown in the flow chart 4.3. Separation of the normally situated placenta results in hemorrhage into the decidua basalis. A retroplacental clot develops between the placenta and the deciduas basalis, which interferes with the supply of oxygen to the fetus. As a result fetal distress can develop.

Flow chart 4.3: Pathophysiology of placental abruption



Clinical Classification of Placental Abruption

Clinical classification of placental abruption based on degree of disease severity is shown in table 4.6.

Depending on the severity of clinical features, the placental abruption could be of the following types:

Grade 0

No obvious clinical features are present. Diagnosis is made after the inspection of placenta following the delivery of the baby. Sometimes placental abruption is not diagnosed until after delivery, when an area of clotted blood may be found behind the placenta.

Grade 1 (mild)

There may be slight external bleeding. Uterus may be irritable; uterine tenderness and abdominal pain may or may not be present. FHS is good and shock is absent (no signs of low blood pressure in the mother). The perinatal outcome is usually favorable and volume of retroplacental clot is usually less than 200 ml.

Grade 2 (moderate)

In this type of placental abruption, the external bleeding is mild to moderate in amount. The uterus is tender and the abdominal pain is often present. Maternal shock is absent; the patient may have tachycardia but does not have signs of hypovolemia. Fetal heart sounds may be present or absent and often there are signs of fetal distress. The perinatal outcome may or may not be favorable and fetal death often occurs. The volume of retroplacental clot may vary from 150–500 ml.

Grade 3 (severe)

This type of placental abruption is associated with moderate to severe amount of revealed bleeding or concealed (hidden)

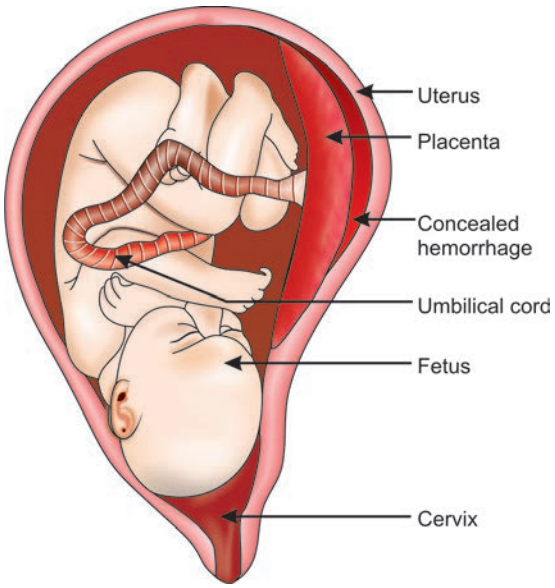


Fig. 4.9: Concealed type of placental abruption

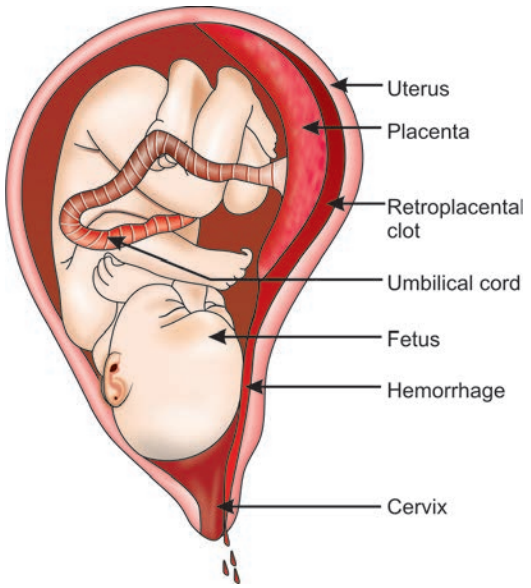


Fig. 4.10: Revealed type of placental abruption

bleeding. In this condition, more than half of the placenta separates and the volume of retroplacental clot is often more than 500 ml. Retroplacental clot volume more than 2.5 liters is usually sufficient to cause fetal death. Tonic uterine contractions (called tetany), abdominal pain and marked uterine tenderness may be present. The abdominal pain is very severe. On examination, the uterus is tender and rigid; it may be impossible to feel the fetus. Maternal shock is pronounced and the blood pressure may become extremely low. Fetal death commonly occurs. Complications related to severe disease like coagulation failure or anuria may be present.

Types of Placental Abruption

Based on the type of clinical presentation, there can be three types of placental abruption:

Concealed type (figure 4.9)

In this type of placental abruption, no actual bleeding is visible. The blood collects between the fetal membranes and decidua in form of the retroplacental clot. Though this type of placental abruption is usually rarer than the revealed type, it carries a higher risk of maternal and fetal hazards because of the possibility of consumptive coagulopathy, which can result in the development of disseminated intravascular coagulation (DIC).

Revealed type (figure 4.10)

In this type of placental abruption, following the placental separation, the blood does not collect between the fetal membranes and decidua but moves out of the cervical canal and is visible externally. This type of placental abruption is commoner than the concealed variety.

Mixed type

This is the most common type of placental abruption and is associated with both revealed and concealed hemorrhage.

History

CLINICAL PRESENTATION

The clinical features depend upon the degree of placental separation and the speed at which the separation occurs and whether it remains concealed or revealed. Signs and symptoms of placental abruption include:

Vaginal Bleeding

The most common symptom of placental abruption is dark red vaginal bleeding with pain, usually occurring after 28 weeks of gestation. It also can occur during labor. The amount of vaginal bleeding can vary greatly. Bleeding in placental abruption is mainly of maternal origin. The amount of bleeding may not be proportional to the amount of placental separation as in many cases the bleeding may be concealed.

Abdominal Pain

Abdominal and back pain often begins suddenly. Uterine tenderness may be present. There may be tonic uterine contractions in which there are rapid uterine contractions,

coming one after another, without any intervening period of relaxation.

Some women may experience slightly different symptoms including, faintness and collapse, nausea, thirst, reduced fetal movements, etc

RISK FACTORS

The specific cause of placental abruption is often unknown. Some of the commonly associated risk factors which need to be elicited at the time of history include the following:

Trauma or injury to the abdomen

Injury resulting due to a vehicle accident or fall is a common cause for placental abruption. Rarely, placental abruption may be caused by an unusually short umbilical cord or sudden uterine decompression (as in cases of polyhydramnios) which may cause sudden placental detachment.

Increased age and parity

Increased maternal age (>40 years) and parity (>4) are commonly associated with an increased risk of placental abruption.

Previous history of placental abruption

If the woman has a history of experiencing placental abruption in past, she is at a high risk of experiencing the same condition during her present pregnancy as well.

High blood pressure associated with preeclampsia and chronic hypertension

High blood pressure increases the risk of placental abruption. The Magpie trial has demonstrated that use of magnesium sulfate in women with severe preeclampsia is associated with reduced incidence of placental abruption.

Blood clotting disorders

Blood clotting disorders e.g. thrombophilias (both inherited and acquired) may also act as risk factors.

Multifetal gestation

Carrying multiple fetuses including twins, triplets, etc increases the woman's risk of developing placental abruption.

Hydramnios

The women with polyhydramnios are associated with an increased risk of placental abruption. Sudden uterine decompression resulting in escape of large quantities of amniotic fluid can act as a predisposing factor for the development of placental detachment.

Substance abuse especially cocaine abuse

Placental abruption is more common in women who smoke; drink alcohol, or abuse drugs like cocaine or methamphetamine during pregnancy.

Preterm rupture of membranes

Presence of uterine leiomyomas

Presence of uterine leiomyomas especially at the site of placental implantation is supposed to be associated with an increased incidence of placental abruption.

General Physical Examination

Most important sign of placental abruption are vaginal bleeding and abdominal and back pain.

The patient may be in shock (tachycardia and low blood pressure).

There may be signs and symptons suggestive of preeclampsia (increased blood pressure, proteinuria, etc.)

Often the patient's clinical condition is disproportionate to the amount of blood loss, especially in cases of concealed hemorrhage.

Specific Systemic Examination

ABDOMINAL EXAMINATION

- Uterine hypertonicity and frequent uterine contractions are commonly present. It may be difficult to feel the fetal parts due to presence of uterine hypertonicity. Uterine rigidity may become apparent on abdominal palpation.
- Absent or slow fetal heart sounds: Severe degree of placental abruption may be associated with fetal bradycardia and other fetal heart rate abnormalities. In extreme cases, fetal demise may even be detected at the time of examination.

VAGINAL EXAMINATION

Though presence of placental abruption is not a contraindication for vaginal examination, vaginal examination should ideally not be performed in patients with history of APH due to the risk of placenta previa. If the cause of APH turns out to be placenta previa rather than placental abruption, performance of a vaginal examination can provoke an episode of torrential bleeding. In case vaginal examination needs to be done, a double setup examination must be performed as has been previously described in this chapter. In patients with placental abruption, an artificial rupture of membranes may result in the release of blood stained amniotic fluid.

Differential Diagnosis

Placenta Previa

The differential diagnosis includes various causes for antepartum vaginal bleeding, which are listed in flow chart 4.1. In this particular case though the history points towards the diagnosis of placental abruption, the differential diagnosis is however not that simple. This is so as labor accompanying placenta previa can cause pain suggestive of placental abruption. On the other hand, placental abruption may mimic normal labor. Thus the main responsibility of the obstetrician in this case is to rule out the presence of placenta previa and to confirm the diagnosis of placental abruption. The differences between clinical presentation of placenta previa and placental abruption are enumerated in table 4.7.

Bloody Show

Slight vaginal bleeding, also known as bloody show is common during active labor. Cervical effacement and dilatation is often associated with tearing of small blood vessels resulting in the development of blood stained discharge. Small amount of dark colored bleeding associated with placental abruption may at times be confused with bloody show. Bloody show usually occurs in presence of active labor and is not associated with uterine tenderness and rigidity. Also, show has a mucoid character in which the mucus is mixed with blood.

Management

Management comprising of investigations and definitive obstetric management is discussed below.

Investigations

The diagnosis of placental abruption is usually made on history and clinical examination. Ultrasound examination must be performed in order to confirm the diagnosis.

Ultrasound Examination

USG examination helps in showing the following details:

Table 4.7: Difference between placenta previa and placental abruption

Parameter	*Placenta previa*	*Placental abruption*
	Characteristics of bleeding	
Nature of bleeding	Painless, causeless, recurrent episodes of bleeding	Bleeding is associated with abdominal pain and is usually related to some cause such as trauma or preeclampsia
Color of blood	Blood is bright red in color	Blood is dark colored
Amount of blood loss	Profuse, may be preceded by small amounts of warning hemorrhages	Blood loss may vary from slight in amount to large. In cases of concealed hemorrhages, the blood loss may be disproportionately low in relation to the woman's general physical condition (pallor, shock, etc)
	Abdominal examination	
Fundal height	Fundal height is proportionate to the period of gestation	Uterus may be disproportionately enlarged in cases of concealed hemorrhage
Feel of the uterus	Uterus is soft and relaxed	Uterus is usually tense, tender and rigid
Fetal presentation	Fetal malpresentation is commonly present	Fetal malpresentation is not related to the etiology of placental abruption
Engagement of fetal presenting part	The fetal presenting part remains high up; the engagement of the presenting part does not take place.	The fetal presenting part commonly gets engaged.
FHS	FHS is usually present and is within the normal limits	Fetal bradycardia related to fetal distress may commonly be present
	Investigations	
Ultrasound examination	Placenta is present in the lower uterine segment	Normal placental location
Coagulation profile	Usually not affected	May be altered in severe cases of placental abruption associated with DIC

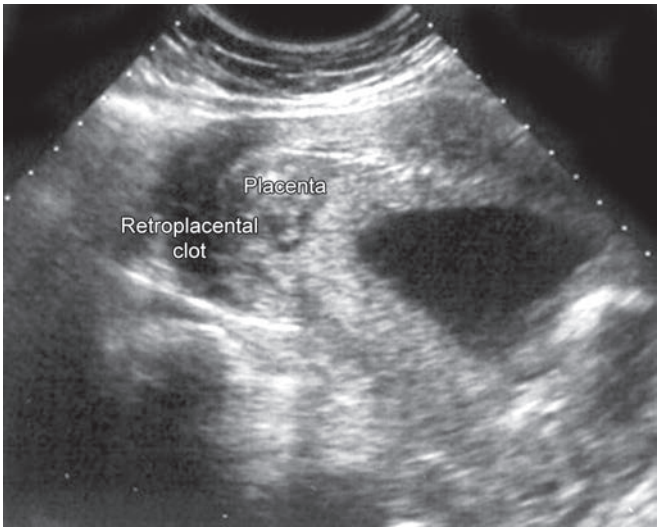


Fig. 4.11: Ultrasound examination in case of placental abruption showing presence of a retroplacental clot

- Ultrasound examination may help in showing the location of the placenta and thus would help in making or ruling out the diagnosis of placenta previa because many at times it may become clinically become impossible to differentiate between placenta previa and placental abruption.
- Ultrasound examination also helps in visualization of retroplacental clot (figure 4.11), thereby confirming the diagnosis of placental abruption.
- Ultrasound also helps in checking the fetal viability and presentation.

Ultrasound examination is especially important in cases of placental abruption as it may become extremely difficult to palpate the fetal parts due to uterine hypertonicity. Also it is important to record the fetal heart rate as the fetus is quite likely to be at jeopardy in the severe cases of placental abruption.

Rx *Treatment/Obstetric Management*

PREVENTION

Though once placental detachment has occurred, presently there is no treatment to replace the placenta back to its original position, some of the following steps can be taken to help reduce its occurrence:

- Early detection and treatment of preeclampsia
- Avoidance of smoking, drinking alcohol or using illicit drugs during pregnancy.
- Avoidance of trauma
- Avoidance of sudden uterine decompression
- The obstetrician need to remain more vigilant during the antenatal period in the cases associated with high risk factors for development of placental abruption.

DEFINITIVE TREATMENT

The treatment plan for the patient with placental abruption is shown in flow chart 4.4.

The management plan depends on grade of placental abruption (extent and severity of the disease process) and fetal maturity. Other factors which need to be considered before deciding the specific treatment for placental abruption include the maternal condition, amount of maternal bleeding and fetal condition.

Mild Placental Abruption

In cases with mild abruption, where fetal maturity has yet not been attained, expectant management can be undertaken until the fetus attains maturity. If at any time severe bleeding occurs; fetal distress appears or maternal condition worsens, an emergency cesarean delivery may be required.

Moderate Placental Abruption

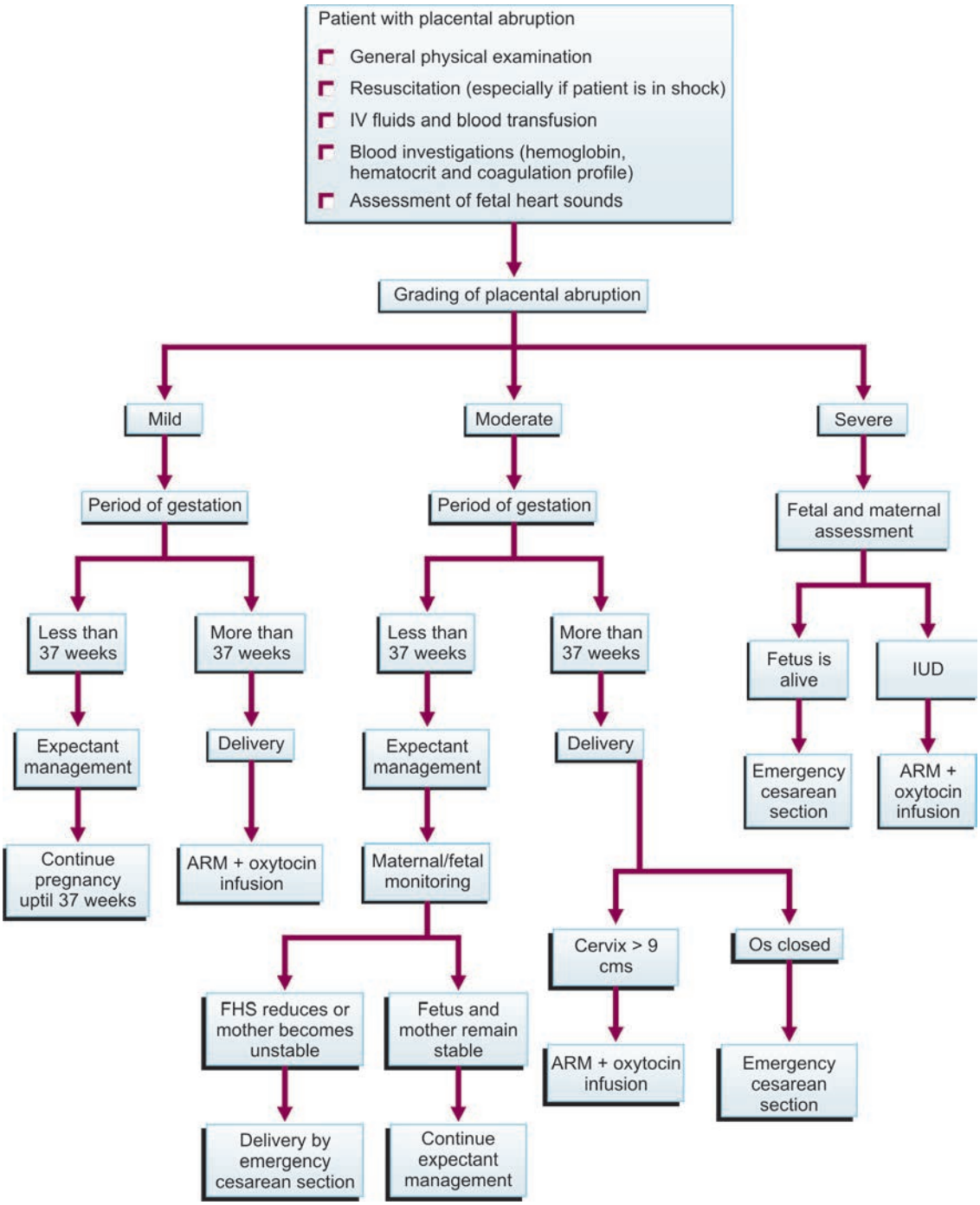
A moderate case of placental abruption requires hospitalization and constant fetal monitoring. The expectant management can be continued if the mother remains stable. In case the maternal condition deteriorates or fetal distress develops, an emergency cesarean delivery may be required. If the uterus remains soft, the pregnancy must be terminated by induction of labor by ARM and oxytocin infusion. Amniotomy helps in the escape of fluid, which might help in reducing the amount of bleeding from the implantation site. It also helps in reducing the entry of thromboplastin into the maternal circulation, thereby preventing the development of DIC. If during labor, the FHR becomes nonreassuring or if the uterus becomes hypertonic, an emergency cesarean section is usually required.

Severe Placental Abruption

If the women presents with severe placental abruption, the following steps need to be urgently undertaken:

- The patient requires urgent admission to the hospital.
- Insertion of a central venous pressure line, IV line and a urinary catheter.
- Blood needs to be sent for ABO and Rh typing, cross-matching and CBC. At least four units of blood needs to be arranged.
- Blood transfusion must be started if signs of shock are present.

Flow chart 4.4 : Treatment plan for the patient with abruption placenta



- Once the patient has stabilized the following investigations need to be sent: Clotting time, fibrinogen levels, prothrombin time, activated partial thromboplastin time and platelet count
- Analgesia can be administered.
- Intravenous fluids and blood should be administered in such a way as to a maintain hematocrit at 30% and a urine output of at least 30ml/hour.
- Inspection of vaginal pads and monitoring of vitals (pulse, blood pressure, etc) at every 15–30 minutes intervals depending upon the severity of bleeding.
- Blood coagulation profile (fibrinogen, fibrin degradation products, APTT, prothrombin time, platelet count etc) needs to be done at every two hourly intervals.
- The placental position must be localized using an ultrasound scan.

- After the patient has stabilized, the cervix must be inspected with the help of a speculum in order to rule out the local causes of bleeding.
- The fetal heart sounds must be monitored continuously with external cardiotocography.
- Intramuscular corticosteroids need to be administered to the mother in case of fetal prematurity.
- As the chances of the baby being distressed at birth are high, pediatrician and neonatologist need to be informed for resuscitation of the baby, immediately after the delivery.
- Definitive treatment in these cases is the delivery of the baby.

In case of severe abruption, delivery should be performed by the fastest possible route. Cesarean delivery needs to be performed for most cases with severe placental abruption. Severe blood loss may require a blood transfusion. If the baby is alive, a cesarean section is often the best mode of delivery especially when the cervical os is closed. In conditions where the baby has already died in the womb, urgent delivery is still warranted keeping in view the development of possible maternal complications particularly DIC. In cases of intrauterine death, delivery by vaginal route appears to be the best option as the complications of serious coagulation defects are less dangerous than with LSCS. In patients with fetal death and unripe cervix, misoprostol 400 µgms intravaginally or high dose oxytocin (50–100 mIU/minute) may be required in order to accelerate vaginal delivery. In the past, it was believed that the specific time interval between obtaining a vaginal delivery and intrauterine death must be 4–6 hours. However, nowadays this interval can be easily extended up to 24 hours. Patients with fibrinogen concentration of less than 100 mg/dl may benefit from administration of 10–20 units of cryoprecipitate. In case of patients with abruption and fetal demise, the following steps need to be undertaken:

- Infusion of packed red blood cells.
- Administration of blood and crystalloids to maintain a hematocrit of 30% and a urine output of 30 ml/hour.
- Sonography to confirm fetal death and fetal malpresentation.
- Obtaining a DIC profile.
- Heparin is not to be administered.

Expectant Management for Mild Placental Abruption

A mild abruption may resolve and the patient can often be closely observed on an outpatient basis for the remainder of pregnancy. With expectant management, some small abruption will stop bleeding on their own. The patient may be discharged after 4–5 days if the bleeding does not recur.

Prerequisites for expectant management

Before the expectant management can be undertaken, the following conditions need to be fulfilled:

- Fetal maturity is not achieved (fetus < 36 weeks of gestation).
- Bleeding has stopped and there is no active bleeding.
- The fetus is not in distress
- The mother's vital signs are stable
- Patient is not in labor.

Steps of expectant management

The following steps need to be undertaken:

- Admission to the hospital.
- Bed rest must be advised.
- The women must be advised to avoid sexual intercourse.
- Blood investigations need to be done: Blood grouping and crossmatching, hematocrit and coagulation studies.
- Placenta to be localized by an ultrasound scan.
- Once the active bleeding has stopped, cervix needs to be inspected with a speculum.
- The fetal monitoring should be done using DFMC, ultrasound measurements of fetal growth and NST.

Cesarean Section

Indications for emergency cesarean section in cases of placental abruption are as follows:

- Appearance of fetal distress.
- Bleeding continues to occur despite of artificial rupture of membranes and oxytocin infusion.
- Labor doesn't seem to progress well, despite artificial rupture of membranes and oxytocin infusion.
- Deterioration of maternal or fetal condition
- Presence of fetal malpresentation.
- Associated obstetric factors
- Appearance of a complication (DIC, oliguria, etc)

Complications

MATERNAL

Maternal Shock due to Severe Bleeding

Placental abruption is a serious complication of pregnancy that requires immediate medical attention. Placental abruption can cause life-threatening hemorrhage for both mother and baby.

Maternal Death

Severe bleeding, shock and DIC associated with placental abruption can result in maternal death.

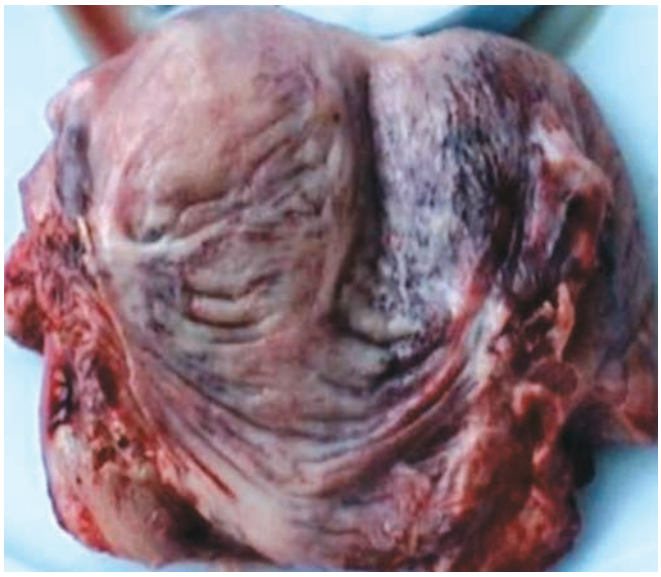


Fig. 4.12: Couvelaire uterus

Renal Failure

Severe shock resulting from grade 3 placental abruption and/or DIC can be responsible for development of renal failure.

Couvelaire Uterus or Uteroplacental Apoplexy

This condition has been found to be associated with severe forms of concealed placental abruption and is characterized by massive intravasation of blood into the uterine musculature upto the level of serosa (figure 4.12). The blood gets infiltrated between the bundles of muscle fibers. As a result, the uterus becomes port wine in color. This is likely to interfere with uterine contractions and may predispose to the development of severe postpartum hemorrhage. However couvelaire uterus per se is not an indication for cesarean hysterectomy.

In couvelaire uterus, there can be effusions of blood beneath the tubal serosa, connective tissues of broad ligaments, substance of the ovaries as well as free blood in the peritoneal cavity. These myometrial hemorrhages may interfere with uterine contractions to produce PPH.

Risk of Recurrence of Abruption in Future Pregnancies

Recurrence risk of placental abruption varies from 8% to 15%.

Postpartum Uterine Atony and Postpartum Hemorrhage

Disseminated Intravascular Coagulopathy (DIC)

DIC is a syndrome associated with both thrombosis and hemorrhage. The pathophysiology of DIC is shown in flow chart 4.5. In DIC, initially there is activation of the coagulation pathways, both intrinsic and extrinsic (flow chart 4.6), due to thromboplastin released from the decidual fragments and placental separation. As the process of coagulation continues, it results in consumption of various clotting factors and widespread deposition of fibrin. This can result in development of hypoxia, ischemia and necrosis, which ultimately results in end stage organ damage, especially renal and hepatic failure. This consumptive coagulopathy and activation of the fibrinolytic system (flow chart 4.7) results in development of hypofibrinogenemia (< 150 mg/dl), elevation in the levels of FDP (fibrin degradation products), increased levels of D-dimers and variable decrease in the levels of various coagulation factors and platelets. As a result of consumptive coagulopathy and activation of fibrinolytic system, bleeding takes place. Massive bleeding and end stage organ failure in patients with DIC is ultimately responsible for producing death.

Causes of DIC

Besides placental abruption, there are many causes which may be responsible for producing DIC. Some of these causes for DIC are listed in table 4.8.

Clinical presentation

Most common sign of DIC is bleeding. It can be manifested in form of ecchymosis, petechiae and purpura. There can be oozing or frank bleeding from multiple sites. Extremities may become cool and mottled. Pleural and pericardial involvement may be responsible for producing dyspnea and chest pain respectively. Hematuria is commonly produced. Bleeding and renal failure are the most important manifestations in cases with DIC.

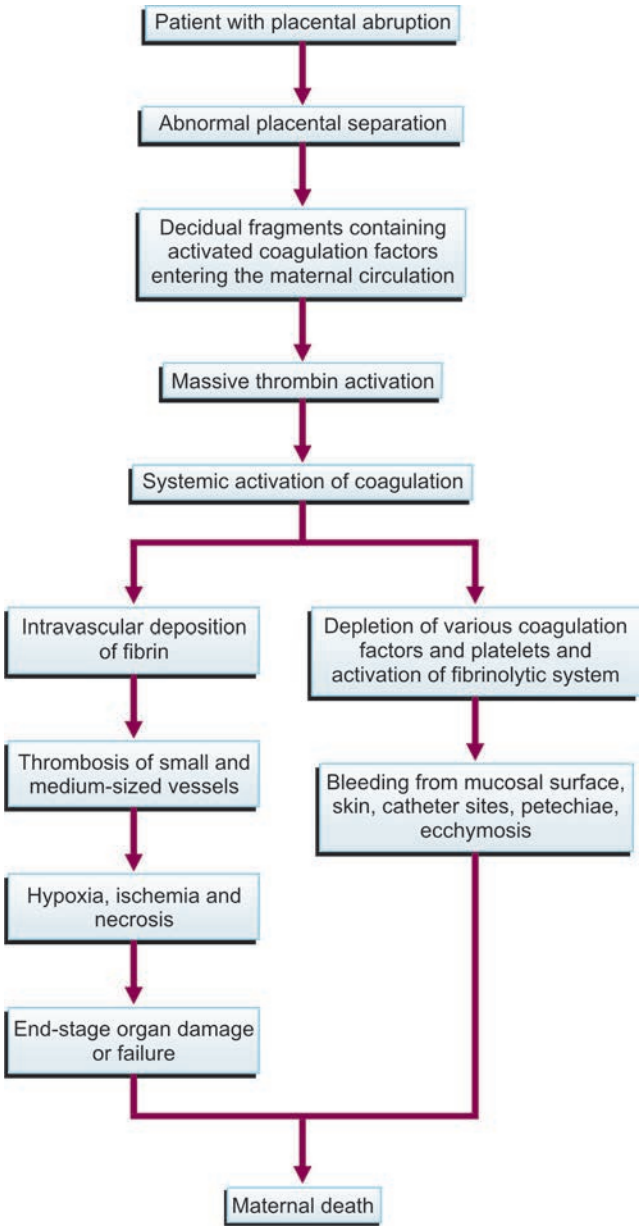
Diagnosis

In the cases of DIC, the coagulation profile is mainly affected. Abnormal results of various tests in coagulation profile in patients with DIC are shown in table 4.9. Fibrinogen levels

Table 4.8: Various causes for DIC

Obstetrical causes (placental abruption, septic abortion, amniotic fluid embolism, intrauterine death)
Infection (bacterial, viral, parasitic, rickettsial and mycotic)
Malignancy (metastatic tumors including those in colon, lungs, breast, prostate, etc)
Transfusion reactions (ABO incompatibility)
Vascular disorders (giant hemangiomas, aneurysm, prosthetic grafts, etc)
Massive tissue injury (trauma/burns etc)
Miscellaneous (snake bites, iron toxicity, pancreatitis, etc)

Flow chart 4.5: Pathophysiology of DIC



are reduced; prothrombin time, APTT (activated partial thromboplastin time) and thrombin time are prolonged; platelet levels are reduced and levels of D-dimer and Fibrinogen degradation products (FDP) are increased.

*Prothrombin time***:** It is the time taken by the blood to clot after addition of tissue thromboplastin. It indicates the amount of prothrombin present in the blood.

Activated Partial Thromboplastin Time: Time taken for the blood to clot after addition of phospholipids and calcium.

Thrombin time: Time taken for blood to clot after adding thrombin to it.

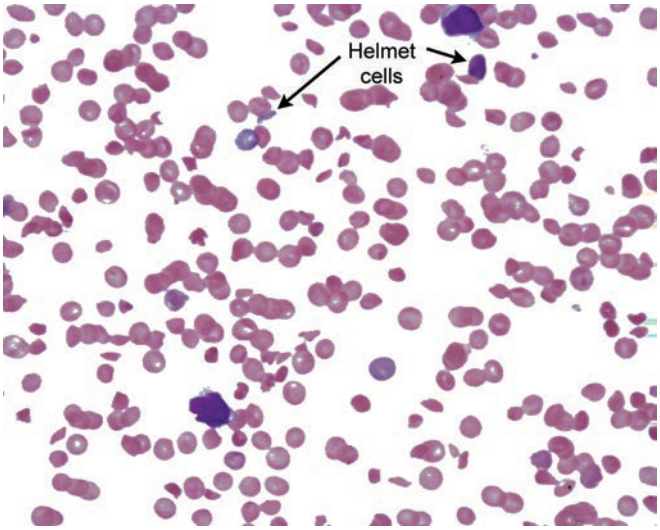


Fig. 4.13: Peripheral smear in patient with DIC, suggestive of hemolytic anemia. The black arrows point towards the helmet cells

Table 4.9: Abnormal results of coagulation profile in cases of DIC

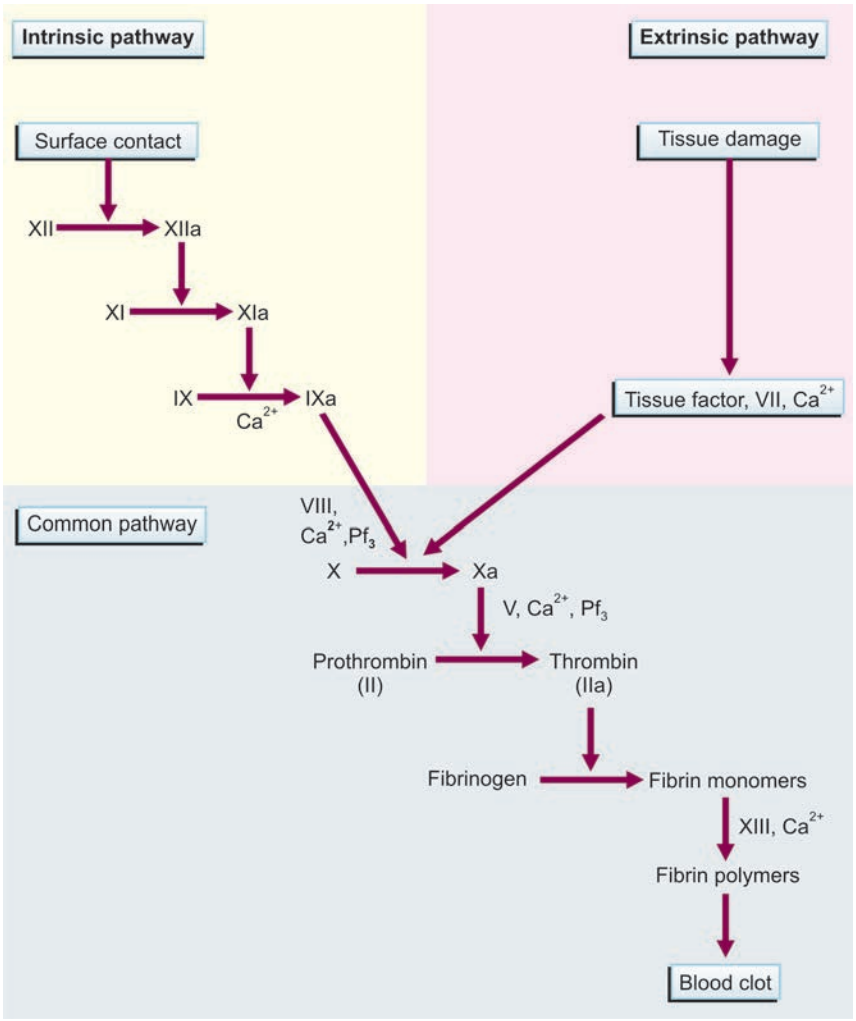
Test	*Normal results*	*DIC*
Fibrinogen	150–600 mg/dl	Reduced (< 150 mg/dl)
Prothrombin time	11–16 seconds	Prolonged
APTT (activated partial thromboplastin time)	22–37 seconds	Prolonged
Thrombin time (TT)	15–25 seconds	Prolonged
Platelet count	1.2–1.5 lakh/mm^3	Reduced
D-dimer	< 0.5 mg/L	Increased (> 0.5 mg/L)
FDP	Less than 10 µg/dl	Increased (> 10 µg/dl)

The findings on peripheral smear (figure 4.13) in patients with DIC are suggestive of microangiopathic hemolytic anemia. The peripheral smear shows presence of multiple helmet cells, fragmented RBC's, microspherocytes and schistocytes and paucity of platelet cells.

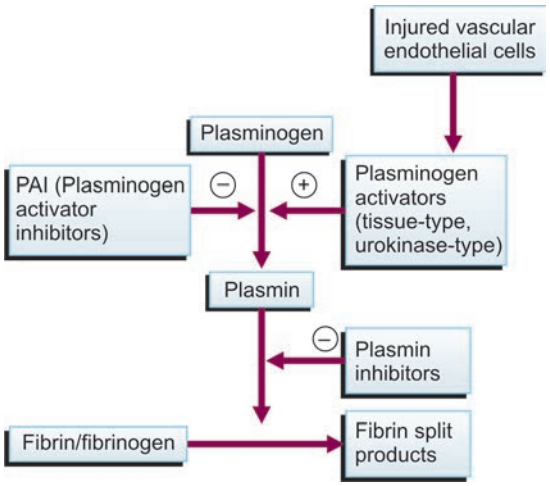
Treatment of DIC

Treatment of DIC mainly involves the treatment of the underlying cause. Platelets can be transfused in patients at high risk of bleeding, e.g. those who need to undergo surgery. Replacement therapy with fresh frozen plasma may also be administered. Fresh frozen plasma is usually administered to maintain fibrinogen levels above 150 mg/dl. Fresh frozen plasma (FFP) usually contains the clotting factors V, VIII, XIII and antithrombin III. Usual dose of fresh frozen plasma is 10–15 mg/kg body weight. Indications for administration

Flow chart 4.6: Coagulation pathways



Flow chart 4.7: Fibrinolytic pathway



of FFP include prolongation of prothrombin time and fibrinogen levels less than 50 mg/dl. Transfusion of platelets, fibrinogen concentrates and cryoprecipitate is also sometimes given. Cryoprecipitate is composed of fibrinogen and factor VIII. The use of heparin in cases of DIC is largely controversial and is supposed to worsen the bleeding.

FETAL COMPLICATIONS

Fetal Distress

Placental abruption can deprive the baby of oxygen and nutrients and cause heavy bleeding in the mother. Left untreated, placental abruption puts both mother and baby in jeopardy.

Decreased oxygen to the brain leads to later development of neurological or behavioral problems. In severe cases, stillbirth is possible.

Premature Delivery

Stillbirth and Fetal Death

Placental abruption is an important cause of fetal distress, asphyxia and ultimately intrauterine death. Premature delivery in cases with placental abruption is an important cause of fetal morbidity.

Important Questions and Answers

Q.1. What should be the initial steps for management in the above mentioned patient?

Ans. The initial step in the management of this case is the emergency active resuscitation of the mother as an emergency. The other steps which need to be taken include the following:

- Two intravenous infusion lines are usually needed, one of which can be a central venous pressure line.
- Blood needs to be sent for the following investigations: CBC, ABO and Rh typing and cross-matching and blood coagulation profile.
- Two units of fresh frozen plasma and at least four units of whole blood need to be urgently arranged and cross-matched. This is usually needed for effective resuscitation.
- The pulse rate and blood pressure must be checked every 15 minutes until the patient's condition stabilizes and every half hourly thereafter.
- A Foley's catheter must be inserted into the bladder and half hourly input-output charting needs to be done.
- An urgent ultrasound examination needs to be performed to confirm placental position, fetal viability and presentation.
- Pain relief in the form of intramuscular injection of pethidine must be administered.

Q.2. In this case, on ultrasound examination a retroplacental clot was observed and placenta was located posteriorly in the upper uterine segment. CTG trace showed non-reassuring fetal heart trace. What would be the next step in management in this case?

Ans. In this case a diagnosis of placental abruption in association with fetal distress was made. The baby needs to be delivered as soon as possible. Since the diagnosis of placenta previa has been excluded, a vaginal examination can be safely performed. Further management needs to de decided based on the findings of the vaginal examination. If the cervix is 9 cm or more dilated and the fetal head is on the pelvic floor, ARM can be done and oxytocin infusion can be started so that the fetus can be delivered vaginally as quickly as possible. If the cervical dilatation is found to be less than 9 cm, an emergency cesarean section must be performed as soon as the patient has been resuscitated. Immediately before starting the cesarean section, the fetal heart sounds must be auscultated.

Q.3. What is the most likely cause of antepartum hemorrhage with fetal distress?

Ans. The most likely cause of antepartum hemorrhage in association with fetal distress is placental abruption. Intrauterine death also can commonly occur in cases of placental abruption, where as it is relatively less common in cases of placenta previa.

Q.4. Why is an antepartum hemorrhage of unknown cause always regarded in a serious light?

Ans. There is a possibility that abruptio placentae is present. If the abruptio placentae is going to extend, intrauterine death may result. The risk of such an event is greatest during the 24 hours following the bleed.

Q.5. How would you manage this patient if a fetal heart beat is not heard?

Ans. If placental separation is so severe that the fetus is dead, vaginal delivery is preferred unless hemorrhage is so severe that it cannot be managed even by vigorous blood replacement or there is the presence of some other obstetrical factor. In this case, the membranes should be ruptured and the fetus delivered vaginally, if possible.

Q.6. What is the most probable cause of the blood stained vaginal discharge? How can the cause of the vaginitis be diagnosed?

Ans. The most common cause of blood stained vaginal discharge is trichomonas vaginitis. This can usually be confirmed by a speculum examination. During the speculum examination, a sample of the discharge should be taken and a wet smear made. Trichomonal organisms seen on the wet smear are probably the cause of vaginitis. Abruption placenta is another cause of blood stained amniotic fluid which could be responsible for producing blood stained vaginal discharge in this case.

Q.7. How would you treat a patient with Trichomonal vaginitis?

Ans. Single dose of 2 g metronidazole (Flagyl) is given orally to both the patient and her partner.

Q.8. What are the likely causes for renal failure in patients with placental abruption?

Ans. In cases with placental abruption, the renal failure could result from numerous causes including the following:

- Acute tubular necrosis.
- Massive hemorrhage resulting in impaired renal perfusion.
- Frequent coexistence of preeclampsia which is an important cause of renal vasospasm.

Q.9. What are the causes of PPH in a case of placental abruption?

Ans. If the woman has suffered a placental abruption, there might be presence of intramuscular hemorrhages within the uterine musculature, which may prevent effective uterine contractions thereby resulting in development of PPH. Due to onset of DIC in cases with severe placental abruption, there might be failure of coagulation due to which the blood may fail to clot. This may be another cause for PPH.

Q.10. What steps should be taken to prevent the occurrence of PPH?

Ans. Active management of the third stage of labor is the most important step for the prevention of PPH. This incorporates the following steps:

- 0.5 mg of ergometrine must be administered at the delivery of anterior shoulder. This can be supplemented with five units of oxytocin, if required. If necessary, these drugs may be repeated several times.
- An intravenous line must be running and typed and cross-matched blood should be available. Any time severe hemorrhage occurs, or the mother appears to be in shock, blood must be transfused immediately.
- Bimanual compression of the uterus may be tried after ruling out the traumatic causes of bleeding.

Bibliography

1. Ananth CV, Savitz DA, Luther ER. Maternal Cigarette Smoking as a Risk Factor for Placental Abruption, Placenta Previa and Uterine Bleeding in Pregnancy. Am J Epidemiol. 1996;144: 881-9.
2. Lijoi, AF, Brady J. Vasa Previa Diagnosis and Management. J Am Board Fam Pract. 2003;16:543-8.
3. RCOG. Placenta previa and placenta previa accreta: Diagnosis and management. Guideline No. 27. Revised October 2005.
4. Scott JS. Antepartum Hemorrhage-1. BMJ. 1964:1163-65.
5. Silver R, Depp R, Sabbagha RE, Dooley SL, Socol ML, Tamura RK. Placenta previa: Aggressive expectant management. Am J Obstet Gynecol. 1984;150(1):15-22.
6. SOGC clinical practice guideline. Diagnosis and Management of Placenta Previa. No. 189, March 2007.

Chapter

5

Twin Pregnancy

Case Study

A 24-year-old G2P1L1 with 36 completed weeks of gestation and previous history of normal vaginal delivery at term presented for an ANC check-up. There is no history of taking any fertility treatment. She gives history of being diagnosed with twin gestation on an ultrasound examination done at 8 weeks.

Introduction

Development of two or more embryos simultaneously in a pregnant uterus is termed as multifetal gestation. Development of two fetuses simultaneously is known as twin gestation (figure 5.1); development of three fetuses simultaneously as triplets; four fetuses as quadruplets; five fetuses as quintuplets and so on…

The incidence of twin gestation is about one per 80 live births. The incidence varies among different countries and ethnic groups, with the incidence being highest in African countries, lowest in Japan and intermediate in Caucasians.

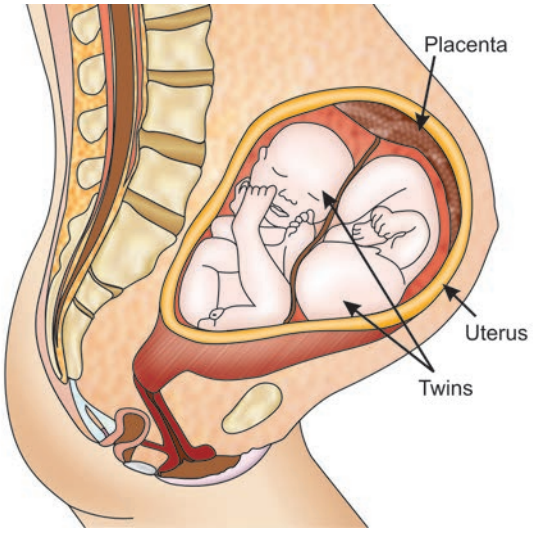


Fig. 5.1: Twin gestation

According to the Hellen's rule, the frequency of twins is 1 in 80; frequency of triplets 1 in 80^2; frequency of quadruplets 1 in 80^3 and so on. The exact cause of multifetal gestation is not known.

TYPES OF TWIN GESTATION

Multifetal gestation can be of two types: Monozygotic twins and Dizygotic twins (figure 5.2). The difference between these two are described in table 5.1.

Dizygotic Twins

When two or more ova are fertilized by sperms, the result is development of dizygotic twins or non-identical twins or fraternal twins (figures 5.3A and 5.4). As a result of being fertilized by two separate sperms, the two embryos can be of different sexes. Furthermore, in dizygotic twins the two embryos have separate placentae and there is no communication between the fetal vessels of the two embryos.

Monozygotic Twins

Monozygotic twins are formed due to the division of a single fertilized egg (figures 5.3B and 5.4). In monozygotic multiple pregnancies, different types can result depending on the timing of the division of the ovum.

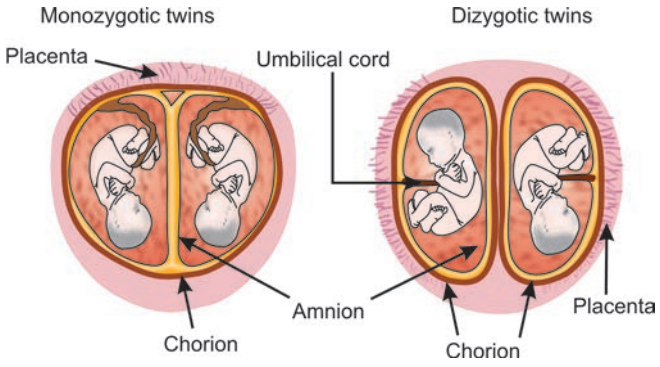


Fig. 5.2: Difference between monozygotic and dizygotic twins

Table 5.1: Difference between monozygotic and dizygotic twins

Parameter	*Monozygotic twins (identical twins)*	*Dizygotic twins (nonidentical or fraternal twins)*
Etiology	Division of a fertilized ovum into two	Fertilization of two or more ova by sperms
Sex	Same	Can be different
Placenta	Single	Each fetus has a separate placenta
Communication between fetal vessels	Present	Absent
Genetic features (DNA finger printing)	Same	Different
Blood group	Same	Different
Skin grafting	Acceptance by the other twin	Rejection by the twin
Intervening membrane between the two fetuses	Composed of three layers: A fused chorion in the middle surrounded by amnion on two sides	Composed of four layers: Two chorions in the middle surrounded by amnion on two sides
Fetal growth and congenital malformation	More common	Less common
Incidence	Comprises of one-third of total cases of twins	Comprises of two-third of total cases of twins

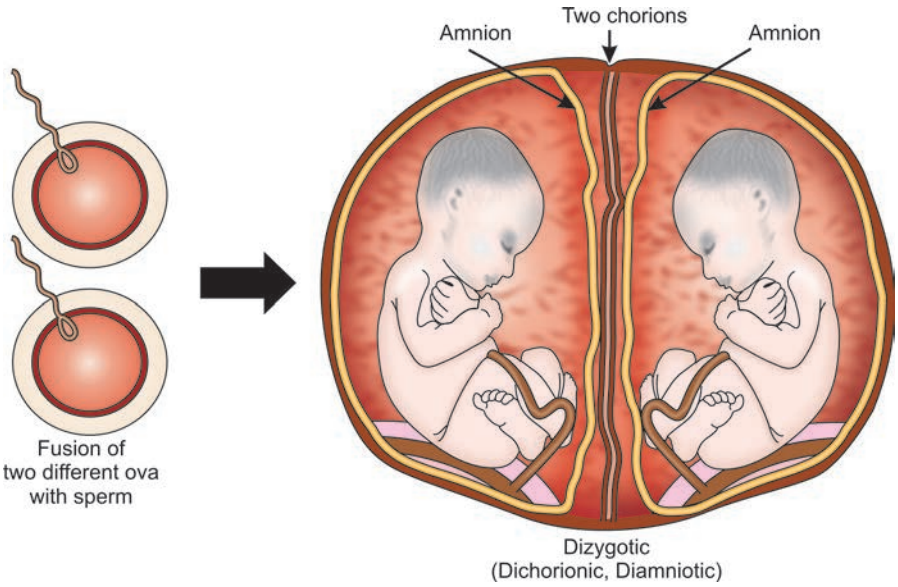


Fig. 5.3A: Formation of dizygotic twins

Different types of monozygotic twins

Diamniotic dichorionic monozygotic twin pregnancy (figure 5.5A): The embryo splits at or before three days of gestation. This results in development of two chorions and two amnions. There is development of two distinct placentae or a single fused placenta. This type of monozygotic twin accounts for nearly 8% of all twin gestations.

Diamniotic monochorionic monozygotic twin pregnancy (figure 5.5B): The cleavage division is delayed until the formation of inner cell mass and the embryo splits between four to seven days of gestation. This results in development of a single chorion and two amnions. Nearly 20% of all twins are of this type.

Monoamniotic monochorionic monozygotic twin pregnancy (figure 5.5C): The embryo splits between eight to twelve days of gestation. This results in development of one chorion and one amnion. Such types of monozygotic twins are rare, accounting for less than 1% of all twin gestations.

Conjoined or Siamese monozygotic twin pregnancy: The embryo splits at or after 13 days of gestation, resulting in development of conjoined twins, which share a particular body part with each other. Development of such type of monozygotic twins is extremely rare. Different types of conjoined twins, which can result are shown in figures 5.6A and B and table 5.2. The conjoined twins are diagnosed by ultrasonographic features (figure 5.7), some of which are as:

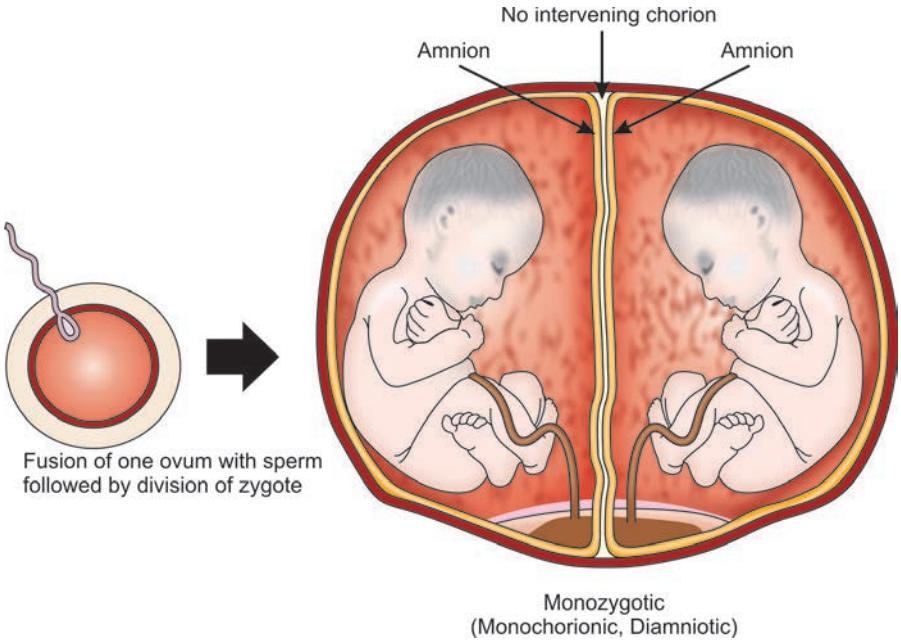


Fig. 5.3B: Formation of monozygotic twins

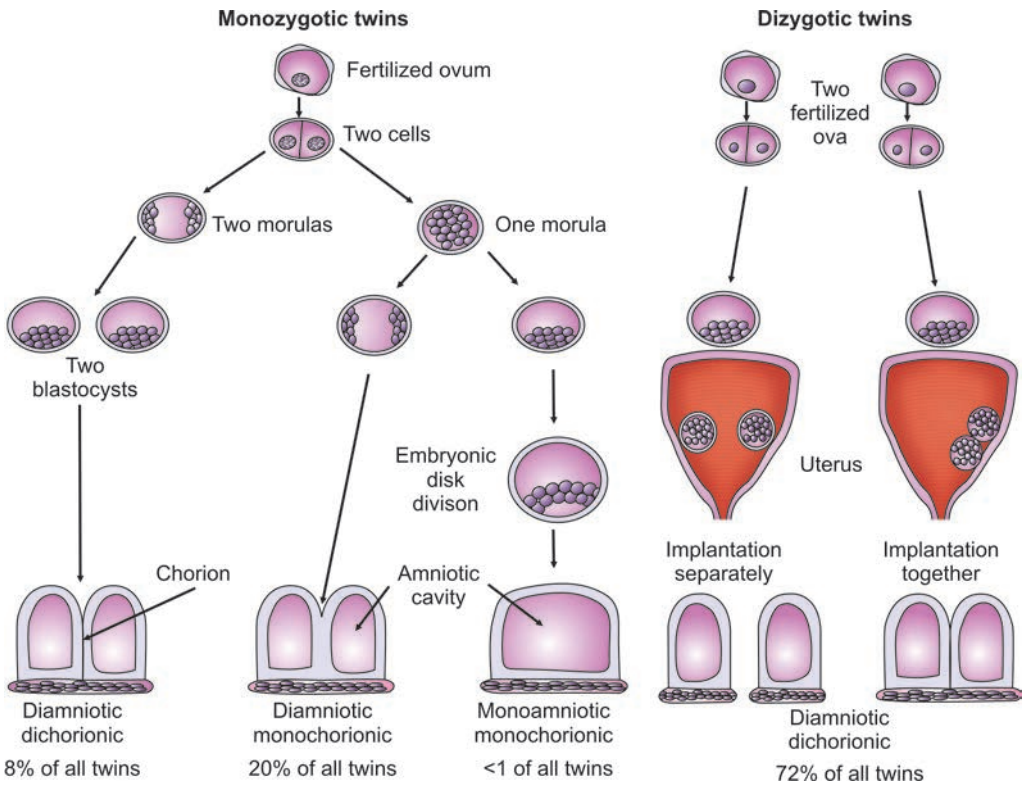


Fig. 5.4: Formation of monozygotic and dizygotic twins

- Both the twins appear to be facing one another, with their heads being at the same plane and level.
- The thoracic cages of both the twins appear to be unusually close to one another.
- Repeat ultrasound examination done at an interval of few days or even few weeks is unable to show any change in the relative positions of the fetuses.
- The fetal heads may appear to be unusually hyperextended.

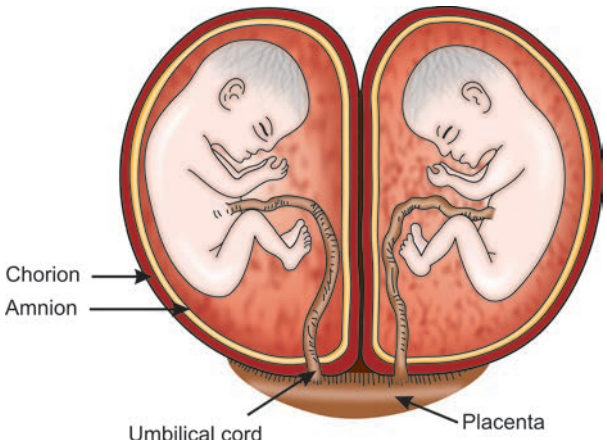


Fig. 5.5A: Diamniotic dichorionic monozygotic twin pregnancy

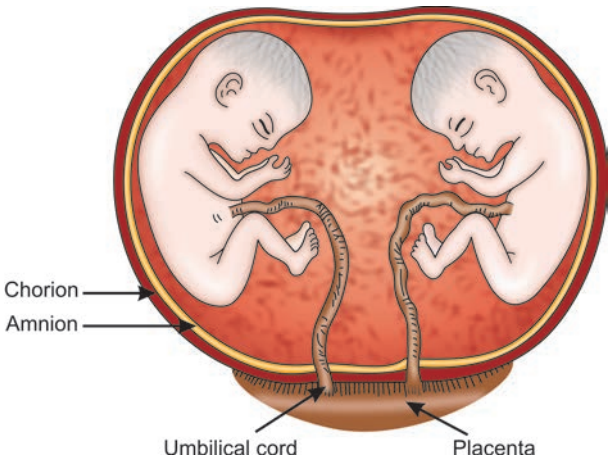


Fig. 5.5C: Monoamniotic monochorionic monozygotic twin pregnancy

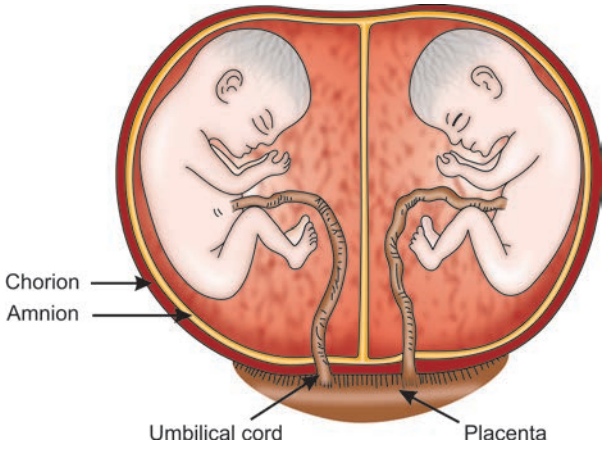


Fig. 5.5B: Diamniotic monochorionic monozygotic twin pregnancy

Table 5.2: Different types of Siamese twins

Type of Siamese twin	*Description*
Thoracophagus	Joined at the chest
Omphalophagus	Joined at the anterior abdominal wall
Craniophagus	Joined at the head
Pyophagus	Joined at the buttocks
Ischiophagus	Joined at the ischium

If the pregnancy is allowed to continue, delivery by cesarean section is the only option followed by surgical separation of the babies after birth.

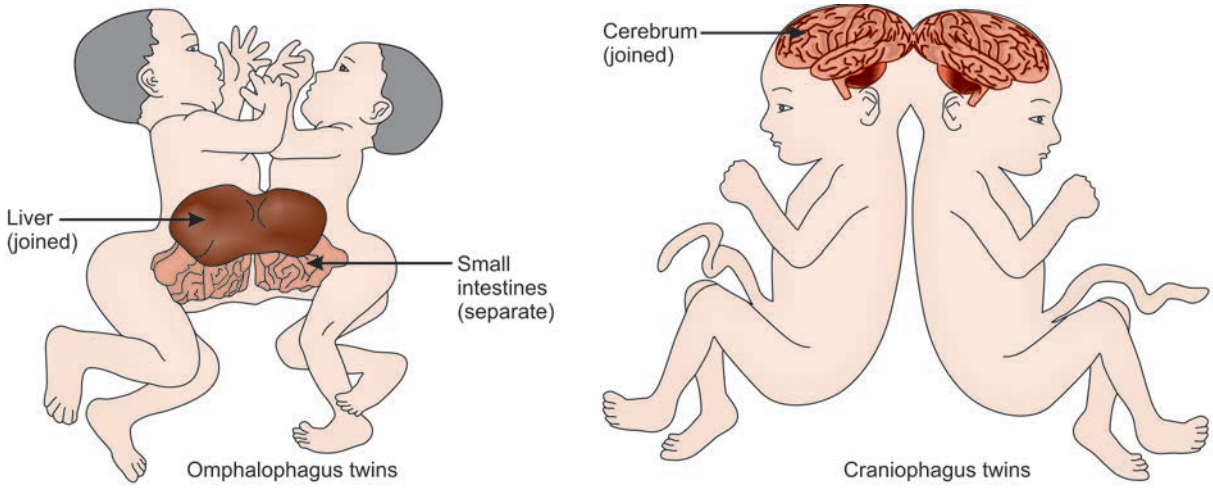


Fig. 5.6A: Different types of conjoined twins

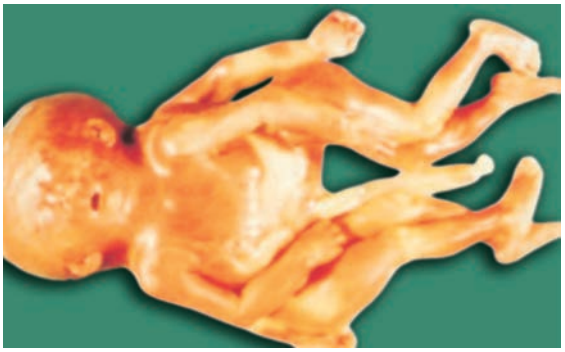


Fig. 5.6B: Autopsy specimen of craniophagus twins

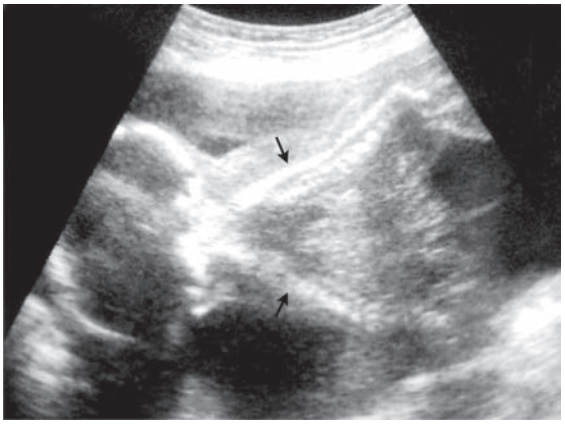


Fig. 5.7: Ultrasound appearance of conjoined twins fused in the regions of skull and anterior chest wall

History

RISK FACTORS

The risk factors which are most likely to result in twin pregnancies and need to be elicited while taking the history include the following:

- Increased maternal age and parity
- Previous history of twin gestation
- Family history of twin gestation (especially on maternal side)
- Conception following a long period of infertility.
- Pregnancy attained through use of assisted reproductive technology (in vitro fertilization or use of clomiphine citrate).
- Racial origin (twin gestation is more common among the women of West African ancestry, less common in those of Japanese ancestry).
- History of using progestational agents or combined oral contraceptives. These are the drugs which are prone to reduce the tubal mobility.
- Previous history of twin gestation.

CLINICAL PRESENTATION

The woman may experience exaggeration of symptoms of early pregnancy, including symptoms like nausea, piles, varicosities, heartburn, shortness of breath, backache, ankle swelling, piles, varicose veins, etc due to a higher levels of circulating hormones. Pregnancy complications like preterm labor, preeclampsia, placenta previa, polyhydramnios, anemia etc are also more common in twin pregnancies. Nearly all multiple pregnancies are now diagnosed in the first trimester by ultrasound. However, some twins die and are absorbed in the first half of pregnancy resulting in "the disappearing twin" syndrome. With increasing period of gestation, the woman may experience increased frequency of heartburn; indigestion and urinary frequency as the enlarging uterus presses on other organs. Back pain is common because of the extra load of the enlarging uterus in combination with the relaxation of muscles and ligaments produced by the pregnancy hormones. The women with mulitifetal gestation may experience early onset of preeclampsia.

General Physical Examination

The signs of anemia may be exaggerated in a woman with multifetal gestation and she may exhibit pallor of extreme degrees. There may be early onset of preeclampsia in these women. As a result they may show high blood pressure and proteinuria before twenty weeks of gestation.

Specific Systemic Examination

ABDOMINAL EXAMINATION

Inspection

Abdominal overdistension (barrel shaped abdomen)

Palpation

- The uterus may be palpable abdominally earlier than 12 weeks gestation.
- In the second half of pregnancy, the women may present with a uterine size more than the period of gestation and/or higher than expected weight gain in comparison to singleton pregnancies. Height of the uterus is greater than period of amenorrhea (fundal height is typically 5 cm greater than the period of amenorrhea in the second trimester).
- Abdominal girth at the level of umbilicus greater than the normal abdominal girth at term.
- Palpation of multiple fetal parts (e.g. palpation of two fetal heads).
- Presence of hydramnios.

Table 5.3: Differential diagnosis of multifetal gestation
Hydramnios
Wrong dates
Hydatidiform mole
Uterine fibroids
Adnexal masses
Fetal macrosomia

Auscultation

Two FHS can be auscultated, located at two separate spots separated by a silent area in between.

Differential Diagnosis

Other causes for fundal height being more than period of amenorrhea are listed in table 5.3. Ultrasound examination can help in ruling out various other conditions which cause the fundal height to be more than the period of gestation and also help in confirming the diagnosis of multifetal gestation.

Management

Management comprising of investigations and definitive obstetric management is discussed below.

Investigations

Routine ANC investigations

See chapter 1

Ultrasound examination

- *Multiple fetuses*: Presence of two or more fetuses or gestational sacs (figures 5.8A and B).
- *Multiple placentas*: There may be two placentas lying close to one another or presence of a single large placenta with a thick dividing membrane. This dividing layer could be composed of maximum upto four membranes (two layers of chorion fused in the middle, surrounded by amnion).
- *Twin peak sign*: Pregnancies in which a single placental mass is identified, it may be difficult to distinguish one large placenta from two placentas, lying side by side or fused. Examining the point of origin of dividing membrane on the placental surface may help in clarifying the situation. If a triangular projection of the placental tissue is seen to extend beyond the chorionic surface between the layers of the dividing membrane, this might imply the presence of two fused placentas. This sign may be observed on the ultrasound and is termed as "twin-peak" sign.

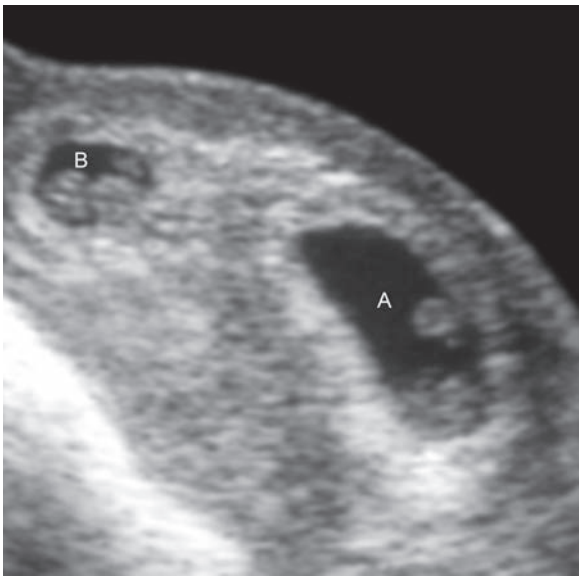


Fig. 5.8A: Presence of two gestational sacs on ultrasound, with sac A=7.6 weeks and sac B=5.7 weeks

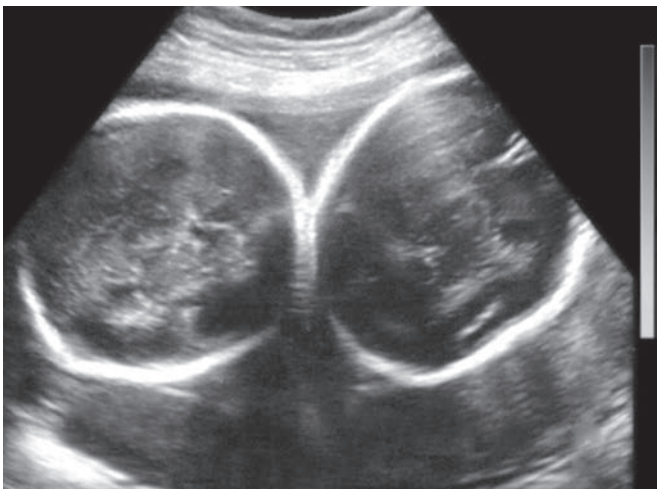


Fig. 5.8B: Ultrasound of the same patient at 30 weeks of gestation, showing two fetal heads

Treatment/Obstetric Management

PREVENTION

Primary Prevention

Methods of primary prevention aim at preventing the occurrence of twin pregnancies in the first place. These include,

limiting the number of embryos transferred in IVF and close counseling/monitoring of women using ovulation induction therapies. Since 2001, the Human Fertilisation and Embryology Authority (UK) has recommended that the maximum number of embryos to be transferred per cycle of IVF must be limited to two.

Secondary Prevention

The methods of secondary prevention aim at reducing the occurrence of twin gestation and other higher order pregnancies, once the formation of multiple gestational sacs has already occurred. This method mainly involves the procedure of multifetal pregnancy reduction (MFPR). This option, however, may not be acceptable to all individuals with a past history of infertility. MFPR is performed early in pregnancy, usually between 9 and 12 weeks. In this procedure, potassium chloride is injected into the selected fetuses under either a transabdominal or transvaginal ultrasound guidance. MFPR may be associated with many risks, including the miscarriage of remaining fetuses, emotional consequences for the parents and rarely infection.

MANAGEMENT IN THE ANTENATAL PERIOD

Steps for Prevention of Preterm Labor

Since preterm labor is the common complication associated with multifetal gestation, steps should be taken to avoid the risk of preterm labor. Some of these are as follows:

- Bed rest,
- Administration of tocolytic agents (beta-mimetic agents, calcium channel blockers, etc),
- Regular monitoring of uterine activity, if possible using external cardiotocography in which uterine contractions along with the fetal heart rate are continuously monitored.
- Prophylactic cervical cerclage: The success of this procedure has not yet been proven.
- The women should be advised to contact her midwife/or obstetrician as soon as she experiences a contraction.

However the routine use of any of these strategies: Beta mimetics, cervical cerclage and bed rest has not been supported by good evidence.

Increased Daily Requirement for Dietary Calories, Proteins and Mineral Supplements

There is an increase in requirement for total dietary calories and proteins. There is an additional calorie requirement to the extent of 300 kcal per day above that required for a normal singleton gestation or 600 kilocalories more in comparison with the nonpregnant state. There is a requirement for increased iron and folic acid supplements in order to meet the demands of twin pregnancy. Iron requirement must be increased to the extent of 60–100 mg per day and folic acid to 1 mg per day. Calcium also needs to be prescribed above the requirements for a normal singleton gestation.

Increased Frequency of Antenatal Visits

The patient should be advised to visit the ANC clinic every two weeks, especially if some problem is anticipated. Attention should be focused on evaluation of blood pressure, proteinurea, uterine fundus height and fetal movements. The patient should be advised to maintain a daily fetal movement count chart (DFMC chart). The fetal growth should be monitored using an ultrasound examination every 3–4 weeks. Vaginal and bladder infections should be recognized and treated promptly to prevent the risk of preterm labor. The patient should be advised to stop doing extraneous activities and rest in the lateral decubitus position for a minimum of 2 hours each morning and afternoon.

Increased Fetal Surveillance

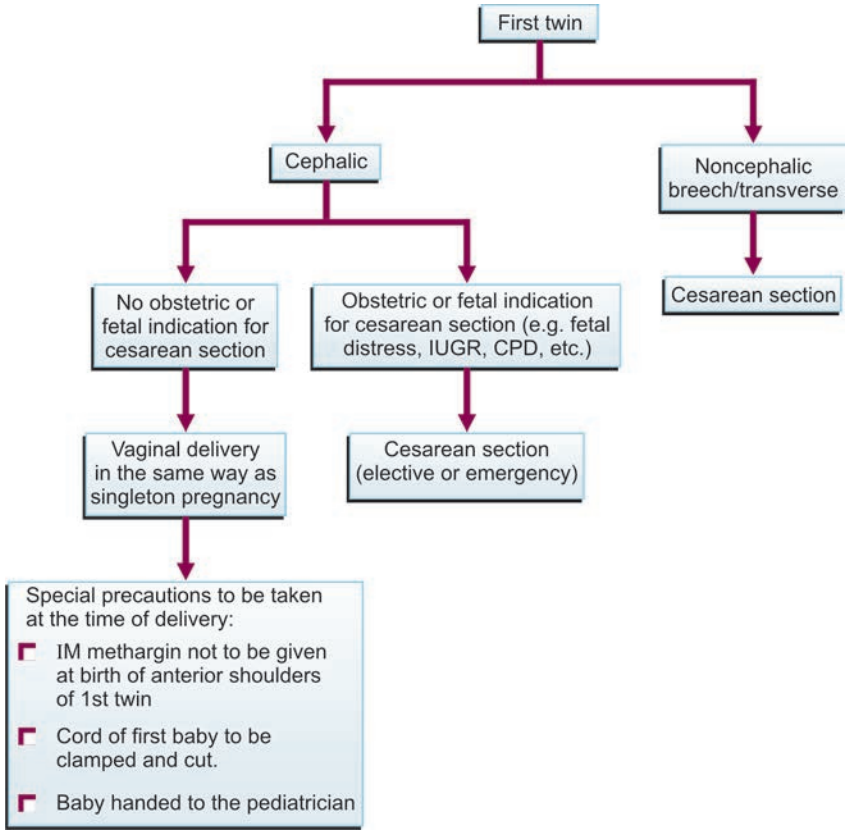
Since presence of multifetal gestation can produce numerous complications for the fetuses, which can result in significant neonatal morbidity and mortality, stringent fetal surveillance becomes mandatory. Fetal monitoring can be done with the help of serial ultrasound examination, BBP, NST, AFI and Doppler ultrasound examinations.

MANAGEMENT IN THE INTRAPARTUM PERIOD (Flow charts 5.1A and B)

The following precautions need to be observed in the intrapartum period:

- Blood to be arranged and kept crossmatched.
- Pediatrician/anesthesiologist needs to be informed.
- Patient should be advised to stay in bed as far as possible in order to prevent premature rupture of membranes.
- Labor should be monitored with help of a partogram and the heart rate of both the fetuses must be monitored preferably using a cardiotocogram. If the membranes have ruptured, the first twin can be monitored with help of internal cardiotocography, where as the second twin can be monitored with help of external cardiotocography (figure 5.9).
- Prophylactic administration of corticosteroids for attaining pulmonary maturity in cases of anticipated preterm deliveries.
- IV access in the mother must be established.
- Careful fetal monitoring.

Flow chart 5.1A: Intrapartum management of first twin



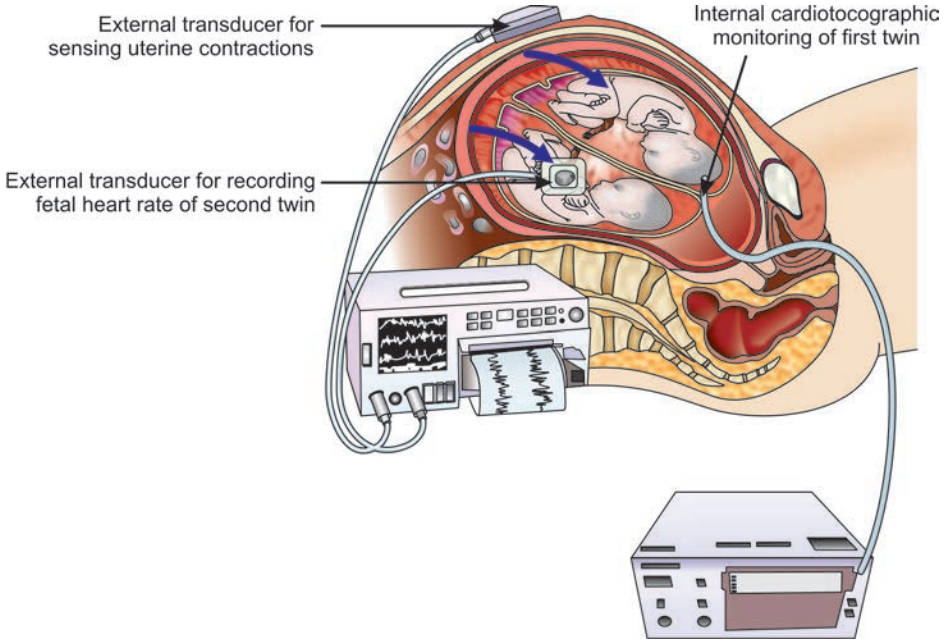
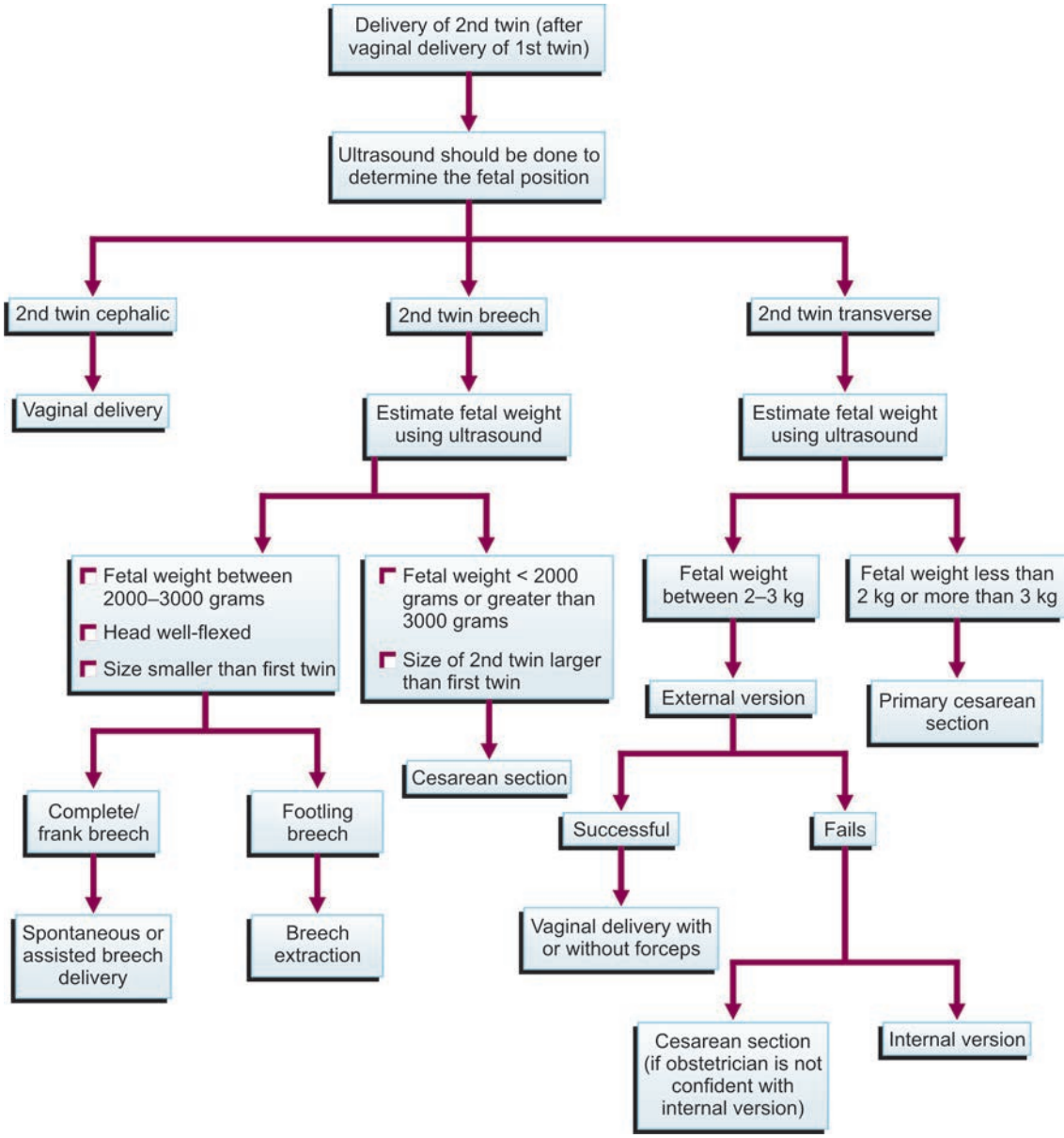


Fig. 5.9: Internal electronic monitoring of the first twin and external electronic monitoring of the second twin

Flow chart 5.1B: Intrapartum management of the second twin



- Epidural analgesia for relief from pain is preferred as it can be rapidly extended in caudal direction in case a procedure like internal podalic version or cesarean section is required.
- Vaginal examination must be performed soon after the rupture of membranes to exclude cord prolapse and to confirm the presentation of first twin.
- The labor ward where the deliveries of the babies have to take place should be equipped with ultrasound machine and other fetal monitoring equipment.
- Two health care professionals (one obsetetrician and one pediatrician) should be available for each anticipated fetus. At least one of these persons should be well-versed in neonatal resuscitation.

MANAGEMENT AT THE TIME OF DELIVERY

Delivery of the First Baby

- Delivery of the first baby should be conducted according to guidelines for normal pregnancy.
- Ergometrine is not to be given at the birth of first baby.
- Cord of the first baby should be clamped and cut to prevent exanguination of the second twin in case communicating blood vessels between the two twins exist.

Delivery of Second Baby

The various types of twin presentations which are possible are shown in figures 5.10A to E and table 5.4.

After the delivery of the first baby, an abdominal and vaginal examination should be performed to confirm the lie, presentation and FHS of the second baby. External version can be attempted at the time of abdominal examination, in case the lie is transverse. Vaginal examination also helps in diagnosing cord prolapse if present.

Table 5.4: Various types of twin presentations

Types of twin presentation	*Frequency*
Both vertex (figure 5.10A)	40%
1st vertex, second breech (figure 5.10B)	25%
1st breech, 2nd vertex (figure 5.10C)	7%
1st and second breech	9%
1st vertex, 2nd transverse	7%
1 breech 2nd transverse (figure 5.10D)	3%
Both transverse (figure 5.10E)	3%

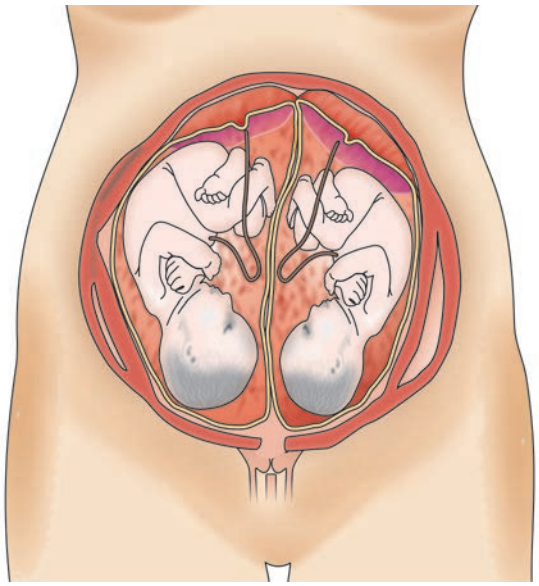


Fig. 5.10A: Type of twin presentation, with both the fetuses in vertex presentation

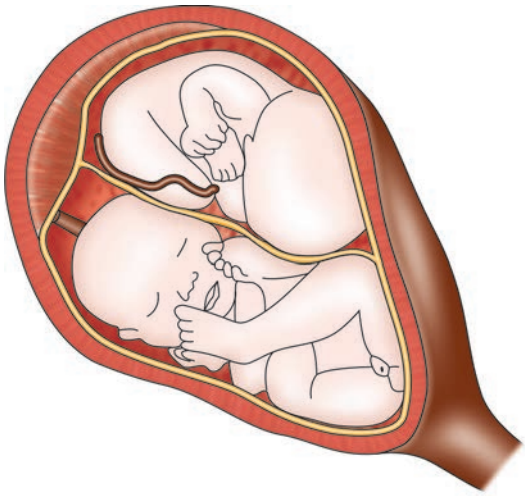


Fig. 5.10C: Type of twin presentation, with 1st fetus as breech and 2nd as vertex

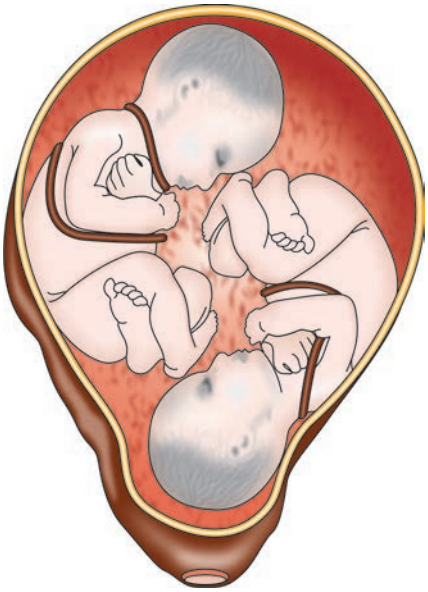


Fig. 5.10B: Type of twin presentation, with 1st fetus as vertex and 2nd as breech

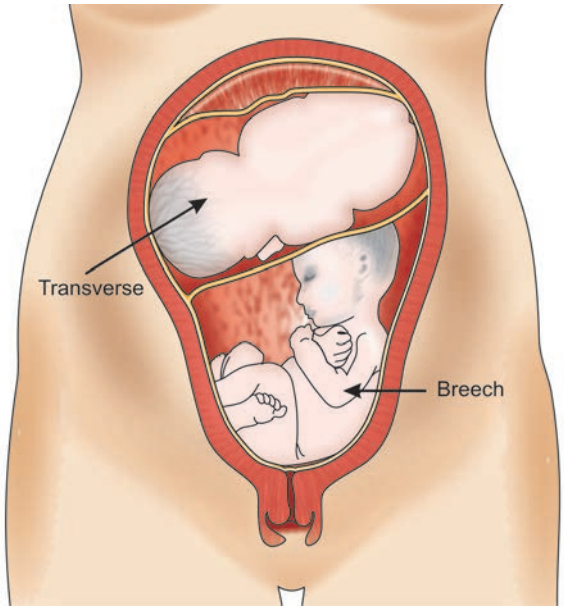


Fig. 5.10D: Type of twin presentation, with 1st fetus as breech and 2nd as transverse

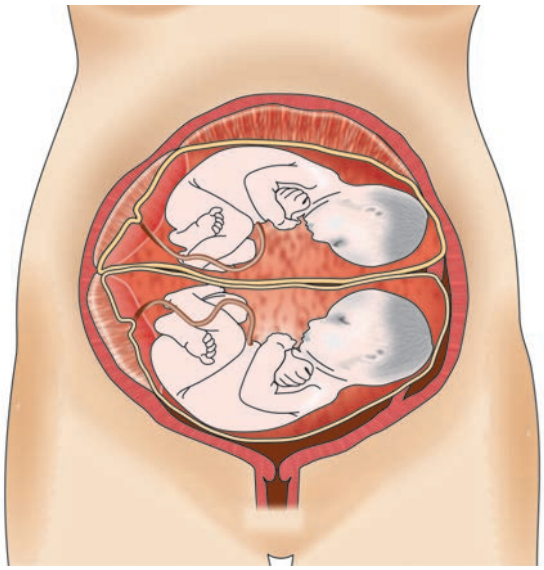


Fig. 5.10E: Type of twin presentation, with both fetuses in transverse

Table 5.5: Indications for urgent delivery of second twin

Severe bleeding per vaginum
Cord prolapse of second baby
Fetal distress of second baby
Inadvertent use of intravenous ergometrine with the delivery of anterior shoulder of the first baby
Delivery of the first baby under general anesthesia

Timing the delivery of second twin

According to the ACOG (1998), the interval between the delivery of twins is not critical in determining the outcome of twins delivered. The obstetrician must still try to expedite the delivery of second twin as far as possible. However an urgent delivery of the fetus is not required unless the conditions mentioned in table 5.5 are present. If either of the conditions mentioned in table 5.5 is present, the obstetrician needs to expedite the delivery as far as possible.

Mode of Delivery of Second Twin

Depending on the presentation of second twin, various options can be adopted as shown in flow chart 5.1B.

Lie is longitudinal

Cephalic: Low rupture of membranes is done after fixing the presenting part on the pelvic brim. If the patient is not having good contractions labor can be induced with help of syntocinon. If the head has reached pelvic brim, i.e., the head has engaged and is not progressing beyond this point, outlet forceps or vacuum can be applied.

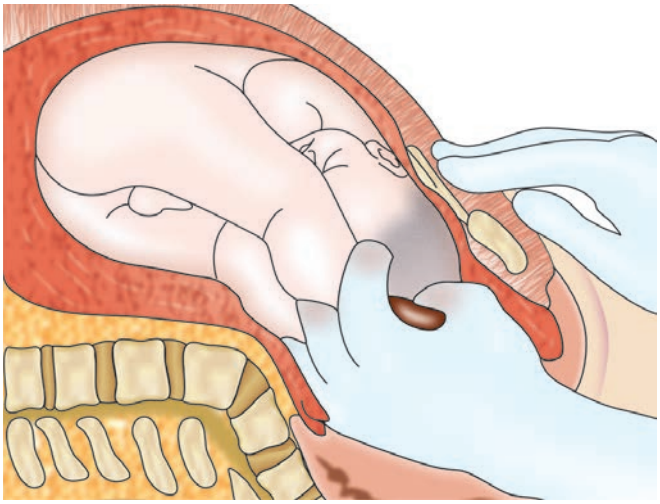


Fig. 5.11: Technique for internal podalic version

Breech: In case of breech presentation, delivery is completed by breech extraction (see chapter 2).

Lie is transverse

If the lie is transverse, external version must be attempted in order to correct the fetal lie. If the external version fails, internal version under general anesthesia can be attempted. The only indication for internal version in modern obstetrics is the transverse lie of second twin.

Technique for Internal Podalic Version

The technique of internal version is shown in figure 5.11. The procedure must be ideally performed under general anesthesia with the uterus sufficiently relaxed. Under all aseptic precautions the obstetrician introduces one of his/her hands into the uterine cavity in a cone shaped manner. The hand is passed along the breech to ultimately grasp the fetal foot which is identified by its heel. While the foot is gradually brought down, obstetrician's other hand present externally over the abdomen helps in gradually pushing the cephalic pole upwards. Rest of the delivery is completed by breech extraction. Following the delivery of the baby, routine exploration of the cervico-vaginal canal must be done to exclude out any injuries.

Delivery of the Placenta

Following the delivery of the babies, placenta is delivered:

- Placental tissue must be examined carefully in order to determine the zygosity of the twins. If the dividing membrane between the two placentas is composed of two layers of chorion in-between, surrounded by amnion on two sides, the zygosity is most likely dizygotic; even though monozygosity is possible.

Table 5.6: Indication for cesarean section in cases of multiple gestation

Obstetric indications	*Fetal indication*	*Indication specific to twin gestation*
Placenta previa	Twin with IUGR	Monochorionic twins with TTTS
Previous cesarean section	First fetus with noncephalic presentation	Locking of twins
Contracted pelvis		Conjoined twins

- Cord blood is to be collected after delivery of both the twins. Determination of the blood group of the twins also helps in confirming the zygosity.

Indications for Cesarean Section in Twin Pregnancy

Cesarean section is not required in routine clinical practice for every case of twin gestation. However in case of presence of an obstetric, or fetal indication as shown in table 5.6, a cesarean delivery may be required. There is no need for a routine cesarean section in all cases of second twin with noncephalic presentation. Some of the fetal indications for twin gestation are same as that for singleton pregnancy and include the following: First fetus with noncephalic presentation, (i.e., the first fetus shows either breech or transverse presentation), fetal distress, IUGR fetuses, etc. There are some indications, specific to twin gestation, for cesarean section which are as follows: Monochorionic twins with twin to twin transfusion syndrome (TTTS); conjoined twins; locking of twins etc. The locking of twins usually takes place when the first fetus presents as breech, where as the second twin presents as cephalic presentation. The after coming head of the fetus in breech presentation locks between the neck and chin of the second fetus. Cesarean section is usually recommended in case the potential for locking is identified. Sometimes cesarean delivery of second twin in noncephalic presentation may be required even if the first twin in cephalic presentation was delivered vaginally. This is especially the case if the clinician present at the time of delivery of second twin, which is in transverse presentation, is not well-versed in internal manipulation procedures like internal podalic version.

Management of Third Stage of Labor

There is an eminent risk for postpartum hemorrhage due to uterine atony.

Some of steps which can be taken to prevent postpatum hemorrhage include the following:

- Intravenous methargin (0.2mg) must not be administered with the delivery of anterior shoulder of first twin as this can result in the trapping of second twin inside the uterine cavity.
- However intravenous methargin must be definitely administered with the delivery of anterior shoulder of the second twin. Oxytocin drip can be continued for about one hour following delivery.
- Delivery of placenta must be by controlled cord traction.
- In case of excessive blood loss, blood transfusion may be required.

Complications

MATERNAL COMPLICATIONS

During Antenatal Period

Multifetal gestation is associated with increased frequency of pregnancy-related complications in the antenatal period such as:

- Spontaneous abortion
- Anemia: Due to increased iron requirement by two fetuses, early appearance of anemia is a common complication. This problem can be avoided by increasing the dose of daily iron supplementation.
- Fatty liver of pregnancy: It is rare complication that occurs more often in multifetal than in singleton pregnancies.
- Hyperemesis gravidarum
- Polyhydramnios
- Preeclampsia
- Antepartum hemorrhage
- Preterm labor
- Varicosities, dependent edema

During Labor

Multifetal gestation is also associated with a higher rate of complications during labor, such as:

- Fetal malpresentation
- Vasa previa
- Cord prolapse
- Premature separation of placenta, resulting in abruption placenta
- Cord entanglement
- Postpartum hemorrhage
- Dysfunctional uterine contractions
- Increased operative interference

Puerperium

Multifetal gestation can also result in a high rate of complications during the puerperium including complications like:

- Subinvolution

- Infection
- Failure of lactation

FETAL COMPLICATIONS

Fetal Complications Due to Twin Gestation

- Miscarriage
- Prematurity: Premature labor (onset before 37 completed weeks of gestation) is the main risk of twin pregnancy, probably resulting from overstretching of the uterine cavity. The mean period of gestation for twins has been estimated as 37 weeks and for triplets as 31 weeks. The most frequent neonatal complications of preterm birth are hypothermia, respiratory difficulties, persistant ductus arteriosus, intracranial bleeding, hypoglycemia, necrotizing entrocolitis, infections and retinopathy of prematurity, low birth weight babies, etc.
- Congenital anomalies: A two-four fold increase in the risk of congenital abnormalities has been found to be associated with multiple pregnancies, especially the monozygotic twin pregnancies.
- Intrauterine death
- Intrauterine growth retardation often resulting in low birth weight babies
- Low birth weight babies due to intrauterine growth retardation and preterm delivery.

FETAL COMPLICATIONS SPECIFIC TO TWIN GESTATION

Discordant Growth

Discordancy refers to the difference in growth rates between the two twins. Grade I discordant growth indicates a difference of 15% to 20%, whereas grade II discordant growth indicates a difference of greater than 25%. As a result of discordant growth, there can be discrepancy in the weight of the two twins and a discrepancy of 20% or more is usually considered to be significant. This difference is expressed as percentage of the larger twin's weight. The smaller twin is at high risk for perinatal complications.

Several ultrasound criteria have been used to diagnose discordant twin growth before birth. Initially the diagnosis was based on the presence of a biparietal diameter difference of 6 mm of greater. Later it was found that biparietal diameter measurements were inaccurate and a difference of 5% or more in head circumference was recommended as the criterion for diagnosis of discordant growth. Even later, it was proposed that a difference of 20 mm in abdominal circumference should be used. However, recently the criteria used most frequently is a difference of 15% to 25% in estimated fetal weight (EFW).

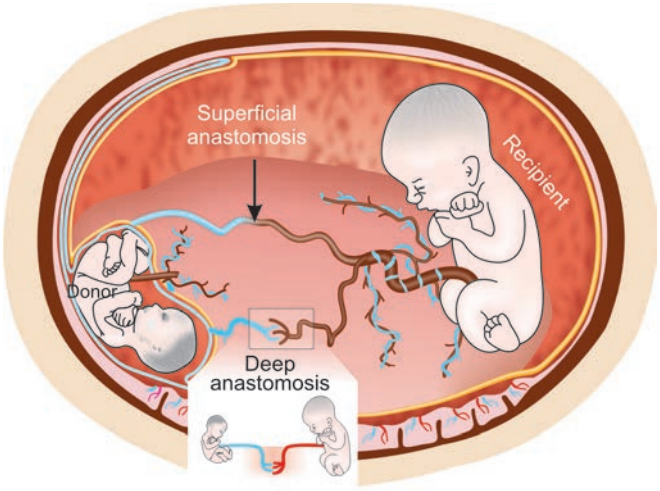


Fig. 5.12: Twin to twin transfusion syndrome

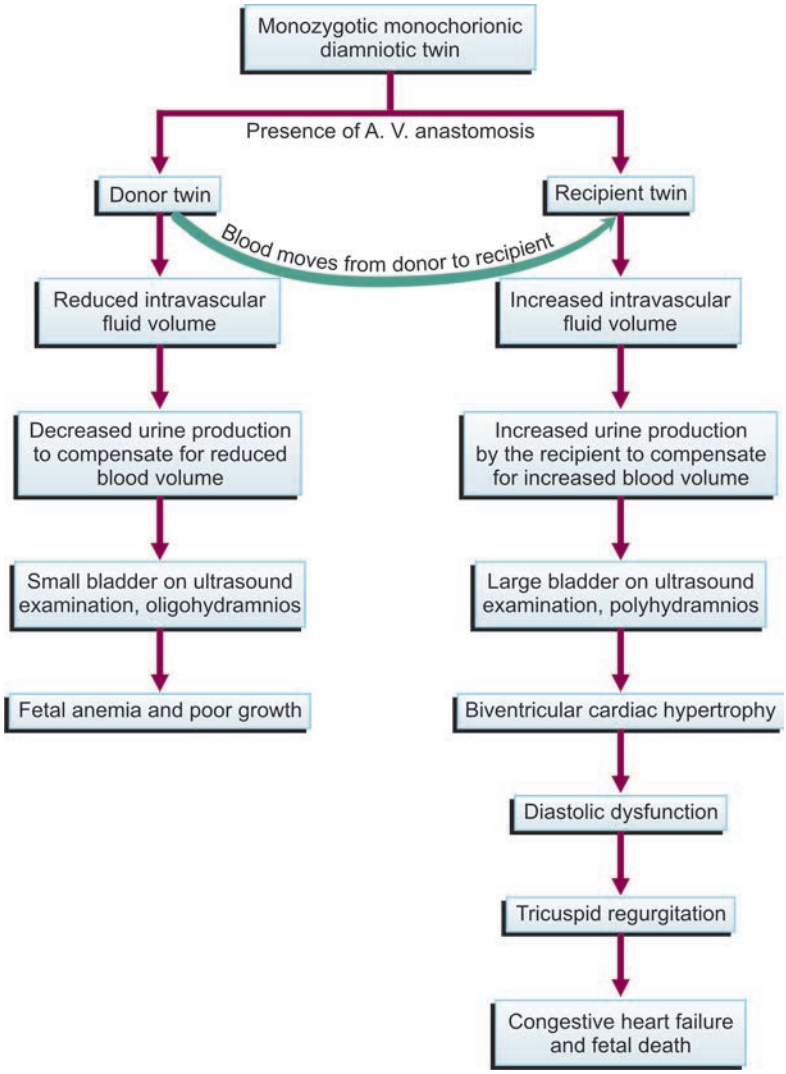
The causes of discordant growth may include factors like unequal placental mass, genetic syndromes (neural tube defects, cardiac abnormalities, chromosomal defects, etc) and TTT syndrome. Growth discordancy because of TTT syndrome is limited to monochorionic twins. While discordant growth due to unequal placental mass or genetic syndromes can occur in both monochorionic and dichorionic twins, that due to TTT syndrome is largely limited to monochorionic twins.

Twin to Twin Transfusion

This is a rare complication that can occur in monozygotic monochorionic, diamniotic twins, which causes the blood to pass from one twin to the other (figure 5.12). This usually occurs due to the presence of placental vascular communication. The placental vascular anastomoses responsible for the development of TTS could be from artery to artery (A-A); artery to vein (A-V); or from vein to vein (V-V).

As a result of the vascular communication, one of the twins, which donates blood (donor twin) becomes thin and undernourished, while the other twin who receives blood (recipient twin) grows at the expense of donor twin. The donor twin in TTTS usually shows poor growth, oliguria, anemia and hyperproteinemia, low or absent liquor, resulting in development of oligohydramnios, etc (flow chart 5.2). With the severe disease, the donor may not produce any urine, resulting in nonvisualization of urinary bladder on ultrasound examination. In these cases, the twin may become wrapped by its amniotic membrane, resulting in the formation of a "stuck" twin. On the other hand, the recipient twin shows

Flow chart 5.2: Pathogenesis of twin to twin transfusion syndrome



polyuria, polyhydramnios and an enlarged urinary bladder. In the long run, this twin frequently develops polycythemia, biventricular cardiac hypertrophy and diastolic dysfunction with tricuspid regurgitation. The death of this twin eventually occurs due to congestive heart failure.

Ultrasound findings

The fundamental diagnostic criterion in TTTS is the finding of oligohydramnios in one twin and polyhydramnios in the other twin belonging to monochorionic twin gestation. The criterion for the diagnosis of oligohydramnios is no fluid or a pocket of fluid less than 2 cm in its largest diameter. The criterion for the diagnosis of polyhydramnios is a pocket of fluid 8 cm or more in its largest diameter.

80% to 90% of cases of TTTS if left untreated, prior to 24 weeks of gestation are associated with the loss of one or both twins. In case of death of one of the twins occurs, the blood vessel connections in the placenta can place the surviving twin at risk for long-term brain damage.

Quintero stages of TTTS

- *Stage I:* A small amount of amniotic fluid (oligohydramnios) is found around the donor twin and a large amount of amniotic fluid (polyhydramnios) is found around the recipient twin.
- *Stage II:* In addition to the presence of above findings, there is absence of bladder in the donor twin on ultrasound examination. In these cases laser photocoagulation may be helpful.
- *Stage III:* In addition to the characteristics of Stages I and II, Doppler studies are critically abnormal. Critically abnormal Doppler studies are defined as absent/reverse

end diastolic velocity in the umbilical artery, reverse flow in the ductus venosus, or pulsatile flow in the umbilical vein. Laser photocoagulation is recommended in this situation.

- *Stage IV:* In addition to all of the above findings, the recipient twin shows evidence of heart failure and fetal hydrops. Laser photocoagulation may be attempted, but the chance of survival in this stage is much lower.
- *Stage V:* In addition to all of the above findings, one of the twins has died. Usually the donor twin is the first to die, but death can occur first in either of the twins.

Treatment options

Since more advanced stages of TTTS have a worse prognosis in comparison to the earlier stages, when severe TTTS occurs at a very early gestational age (prior to 16 weeks), the option of termination of the pregnancy can be considered. The various therapies that are presently available, either involve balancing the fluid volumes between the two sacs or interrupting the communication of blood vessels between the twins. The treatment options that are currently available are described below in details:

Reduction amniocentesis: Serial amniocentesis involves the removal of the excessive amount of amniotic fluid from the sac of the recipient twin through the process of amniocentesis. This technique may be useful for milder cases of TTTS that occur later in pregnancy. The procedure is generally not thought to be effective for more advanced stages of TTTS (Stages III and IV). As a general rule no more than five liters of amniotic fluid is removed at any one time. The procedure is usually by completed within 30 minutes or less. However, the procedure may only temporarily restore the balance in the amniotic fluid in both twins' sacs as the fluid levels may return back within a few days. Thus, the procedure might required to be repeated after every few days. The procedure of repeated amniocenteses for the treatment of TTTS can result in numerous complications such as premature labor, premature rupture of the membranes and rarely infection or an abruption. Pregnancies managed with serial reduction amniocentesis on an average deliver by 29 to 30 weeks of gestation.

Septostomy (microseptostomy): Septostomy involves the creation of a hole in the membrane between the fetal sacs using a needle. This causes the movement of the fluid from the amniotic sac of the recipient into the sac with absent or low fluid (donor's sac). Though the risk for complications like infection, premature labor and premature rupture of the membranes are rare, septostomy does carry the additional potential risk for the hole between the two sacs to become too large. Sometimes it can cause the entire separating membrane to get disrupted, allowing the babies to share the same amniotic space. In the worst case, this could result in entanglement of the umbilical cords of the two twins, resulting in the death of one or both the fetuses. However the advantage of septostomy over amnioreduction is that the patients undergoing septostomy typically require fewer procedures in comparison to those treated with amnioreduction.

Selective laser ablation of the placental anastomotic vessels: In more advanced stages of TTTS (Stage II and higher) ablation of the communicating vessels on the placental surface using laser beams under ultrasound guidance can act as a curative procedure. A fetoscope is introduced in the amniotic cavity after administration of adequate anesthesia to the patient in order to directly visualize the blood vessels on the surface of the placenta. Vessels that are found to communicate between the twins are then ablated using laser light energy.

Being a more invasive procedure in comparison to amnioreduction or septostomy, laser ablation is associated with a higher risk of complications such as premature contractions, premature rupture of the membranes (15% to 20% of cases), placental separation (2%) and infection. In order to prevent these complications, tocolyics to prevent uterine contractions and antibiotics to prevent infection may be given both before and after the procedure. In addition, laser therapy may be associated with unique risks since the laser energy may cause certain areas of the placenta or blood vessels on the surface of the placenta to bleed.

Selective cord coagulation: In this procedure, under ultrasound guidance, one of the twins is purposefully sacrificed in order to save the life of other twin. This procedure is used when laser ablation of the connecting vessels is not possible or if one of the twins is so close to death that laser ablation is unlikely to be successful. By stopping the flow in the cord of the dying twin, the other twin can be protected from the consequences of its sibling's death. In this procedure, the umbilical cord is grasped and electrical current is applied to coagulate the blood vessels in the cord in order to stop the blood flow through them. Complications of this procedure include premature delivery and premature rupture of the membranes.

Acardiac Twin or Twin Reversed Arterial Perfusion (TRAP) Syndrome

This is an unusual form of TTTS, occurring in about 1 in 15,000 pregnancies. In these monochorionic twins, one twin develops normally while the other twin fails to develop a heart as well as other body structures. This abnormal twin, called an acardiac fetus, shows characteristic features, in which the cardiac structures are absent or nonfunctioning and the head, upper body and upper extremities are poorly developed. The lower body and lower extremities are, however, more or less normal. The acardiac twin acts as a recipient and

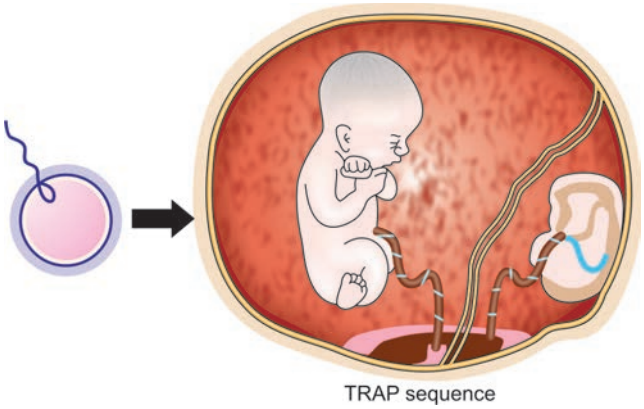


Fig. 5.13: Twin reversed arterial perfusion

depends on the normal donor (pump) twin for obtaining its blood supply via transplacental anastomoses and retrograde perfusion of the acardiac umbilical cord. Perfusion of the malformed (acardiac) fetus occurs via artery-to-artery and vein-to-vein anastomoses between the fetuses. Deoxygenated umbilical arterial blood from the donor flows into the umbilical artery of the recipient, with its direction reversed. In these pregnancies, the umbilical cord from the acardiac twin branches directly from the umbilical cord of the normal twin. This blood flow is reversed from the normal direction leading to the name for this condition – twin reversed arterial perfusion syndrome; TRAP (figure 5.13). As a result, there is better perfusion of the lower part of the deformed body. On the other hand, the upper part of the body, showing lack of head, heart and upper extremities remains poorly perfused. Normal twin (donor) eventually develops high output failure because it is responsible for maintaining the circulation of both the twins. Thus the circulatory load of the donor twin may become extremely large resulting in heart failure. Doppler verification of reversed flow in the umbilical cord of the acardiac fetus helps confirms the diagnosis. In some cases, the blood flow from the pump twin to the acardiac twin stops on its own and the acardiac twin stops growing. In other cases, the flow continues and the acardiac twin continues to increase in size. This eventually leads to heart failure and polyhydramnios in the pump twin. Without treatment, more than 50% of cases of TRAP will result in the death of the pump twin. Radiofrequency ablation of a major blood vessel in the acardiac fetus often serves as the therapeutic strategy of choice. This procedure helps in stopping the blood flow and as a result the pump twin (normal twin) has to no longer send the blood to the acardiac twin.

Conjoined Twins

Conjoined twins are the least common form of monozygotic twinning, which is always associated with monochorionic monoamniotic twins. Detailed description of conjoined twins has been done earlier in the text.

Long Term Complications

Complications related to multiple gestations do not end with the birth of the babies. Long term complications like language and speech delay, cognitive delay or motor problems, behavioral problems and difficulty in parent-child interactions all appear to be more commonly associated with babies born as a result of multifetal gestation.

Important Questions and Answers

Q.1. What would be the further course of management in this case?

Ans. At the time of this antenatal visit, the obstetrician must perform an abdominal examination to detect presentation and wellbeing of both the fetuses. This should be followed by an untrasound examination to confirm the findings of the abdominal examination. Further management needs to be decided based on the lie and presentation of both the fetuses.

Q.2. On ultrasound examination both fetuses are healthy; the first fetus is in cephalic presentation, while the second fetus shows breech presentation. How should the labor be planned in such case?

Ans. Since the first fetus shows a cephalic presentation, in absence of any other obstetric indication for cesarean section, the patient can be posted for normal vaginal delivery.

Q.3. Following the delivery of first twin an ultrasound examination was performed. A fetus with breech presentation, having an estimated fetal weight of 2.4 Kg was diagnosed on ultrasound examination. What should be the next step of management?

Ans. The second twin can be delivered by breech vaginal delivery. In case of footling breech, the fetus can be delivered by breech extraction, while in case of complete or frank breech presentation, spontaneous or assisted vaginal breech delivery can be attempted.

Q.4. What should be the anticipated time of delivery in this case?

Ans. The obstetrician should wait for spontaneous onset of labor. Since the patients with twin gestation can commonly experience preterm delivery, these patient should be warned about its occurence well in advance and must be counseled to report to the hospital as soon as she experiences labor pains or has spontaneous rupture of membranes.

Q.5. What is the cause for increased risk of PPH in twin gestation?

Ans. Severe postpartum bleeding following the delivery of twin is usually the consequence of uterine atony due to large uterine size.

Chances of perineal injury resulting from trauma are small due to small size of the babies. However, there is increased used of instrumental delivery, which may be the cause of perineal injury and accompanying PPH.

Q.6. What are precautions, which should be taken at the time of cesarean section in case of twins?

Ans. The following precautions must be taken at the time of cesarean section in case of twin gestation:

- Since hypotension can easily develop in women with twins, they must be placed in left lateral position to avoid the risk of hypotension at the time of surgery.
- A transverse incision over the skin and uterus must be given liberally.
- Precautions must be taken to prevent the occurrence of PPH.

Q.7. Why are women with mutifetal gestation at an increased risk of development of gestational diabetes?

Ans. Increased frequency of gestational diabetes in women with multifetal pregnancy is probably due to the large placental mass producing large amount of human placental lactogen, a hormone, which is a competitive inhibitor of insulin action.

Bibliography

1. Armson BA, O'Connell C, Persad V et al. Determinants of perinatal mortality and serious neonatal morbidity in the second twin. Obstet Gynecol. 2006;108 (3 Pt 1):556-64.
2. Bdolah Y, Lam C, Rajkumar A, et al. Twin pregnancy and the risk of preeclampsia: Bigger placenta or relative ischemia? Am J Obstet Gynecol. 2008;198(4):428.e1-6.
3. Bhide A, Thilaganathan B. What prenatal diagnosis should be offered in multiple pregnancy? Best Pract Res Clin Obstet Gynaecol. 2004;18(4):531-42.
4. Campbell DM. Multiple pregnancy. Baillieres Clin Obstet Gynaecol. 1990;4(1):109-27.
5. Di Renzo GC, Luzietti R, Gerli S, Clerici G. The ten commandments in multiple pregnancies. Twin Res. 2001;4(3):159-64.
6. Dodd JM, Crowther CA. Evidence based care for women with a multiple pregnancy. Best Pract Res Clin Obstet Gynaecol. 2005; 19(1):131-53.
7. Dodd JM, Crowther CA. Reduction of the number of fetuses for women with triplet and higher order multiple pregnancies. Cochrane Database Syst Rev. 2003;(2):CD003932.
8. Egan JF, Borgida AF. Multifetal gestations: The importance of ultrasound. Obstet Gynecol Clin North Am. 2004;31(1): 141-58.
9. Evans MI, Kaufman MI, Urban AJ, et al. Fetal reduction from twins to a singleton: a reasonable consideration? Obstet Gynecol. 2004;104(1):102-9.
10. Fundamentals of Obstetrics and Gynaecology. 7th edition. Llewellyn-Jones D. Mosby 1999.
11. Hughey MJ, Olive DL. Routine ultrasound detection and management of twin pregnancies. J Reprod Med. 1985;30(5):427-30.
12. Hunter LP. Twin gestation: The antepartum management. J Perinat Neonatal Nurs. 1989;3(1):1-13.
13. Modena AB, Berghella V. Antepartum management of multifetal pregnancies. Clin Perinatol. 2005;32(2):443-54, vii.
14. Ozturk O, Templeton A. Invitro fertilization and risk of multiple pregnancy. Lancet. 2002;359(9302):232.
15. Pons JC, Hoffmann P, Bringer S, Deutsch V, Lisik F, Schaal JP. Management of twin pregnancy. Rev Prat. 2006;56(20):2227-35.
16. Quintero R, Morales W, Allen M et al. Staging of twin to twin transfusion syndrome. J Perinatol. 1999;19:550-555.
17. Robyr R, Quarello E, Ville Y. Management of fetofetal transfusion syndrome. Prenat Diagn. 2005;25(9):786-95.
18. Crowther CA. Hospitalization and bed rest for multiple pregnancy. Cochrane Database Syst Rev. 2001;(1):CD000110.
19. Rustico MA, Baietti MG, Coviello D, et al. Managing twins discordant for fetal anomaly. Prenat Diagn. 2005;25(9):766-71.
20. Schmitz T, Carnavalet Cde C, Azria E, et al. Neonatal outcomes of twin pregnancy according to the planned mode of delivery. Obstet Gynecol. 2008;111(3):695-703.
21. Smith-Levitin M, Skupski DW, Chervenak FA. Multifetal pregnancies. Curr Opin Obstet Gynecol. 1995;7(6):465-71.
22. Smith GC, Fleming KM, White IR. Birth order of twins and risk of perinatal death related to delivery in England, Northern Ireland and Wales, 1994-2003: Retrospective cohort study. BMJ. 2007;334(7593): 576.
23. Sperling L, Kiil C, Larsen LU, Brocks V, Wojdemann KR, Qvist I, Schwartz M, Jørgensen C, Espersen G, Skajaa K, Bang J, Tabor A. Detection of chromosomal abnormalities, congenital abnormalities and transfusion syndrome in twins. Ultrasound Obstet Gynecol. 2007;29(5):517-26.
24. Su LL. Monoamniotic twins: Diagnosis and management. Acta Obstet Gynecol Scand. 2002;81(11):995-1000.
25. Sutcliffe AG, Derom C. Follow-up of twins: Health, behaviour, speech, language outcomes and implications for parents. Early Hum Dev. 2006;82(6):379-86.
26. Sławatyński A, Leszczyńska-Gorzelak B, Oleszczuk J, Szymula D, Zych I.Ultrasonic diagnosis in the first trimester of multiple pregnancy. Ginekol Pol. 2000;71(11):1458-63.
27. Taylor MJ. The management of multiple pregnancy. Early Hum Dev. 2006;82(6):365-70.
28. Wimalasundera RC, Trew G, Fisk NM. Reducing the incidence of twins and triplets. Best Pract Res Clin Obstet Gynaecol. 2003;17(2):309-29.

Chapter 6 Rh Negative Pregnancy

Case Study

34-year-old patient Rh negative G3P2L1 with history of previous pregnancy being affected by anemia presents for antenatal check-up. She gives history of receiving some kind of injection related to Rh negative blood (probably Rh immunoglobulins) in the previous pregnancy.

Introduction

Blood groups were discovered by Landsteiner. Two major classification systems are used for grouping blood. They are based on the presence of different antigens in the blood cells. These systems are the "ABO system" and the "rhesus system."

ABO CLASSIFICATION

According to the ABO system, the blood groups can be classified as blood group A, B, AB and O (table 6.1).

Blood Group A

These people contain antigen A in their blood cells and antibody anti-B in their plasma. People with blood group A can receive and give blood to people with blood group A only (provided they are compatible for Rh factor).

Blood Group B

These people contain antigen B in their blood cells and antibody anti-A in their plasma. People with blood group B can receive and give blood to people with blood group B only (provided they are compatible for Rh factor).

Table 6.1: ABO system and blood groups

Blood group	*RBC antigen*	*Plasma antibody*	*RBC choice*	*Plasma choice*
A	A	Anti-B	A, O	A, AB
B	B	Anti-A	B, O	B, AB
AB	A, B	None	A, B, AB, O	AB
O	none	Anti-A, anti-B	O	O, A, B, AB

Blood Group AB

These people contain both antigens A and B in their blood cells and none of the antibodies in their plasma. People with blood group AB are known as "universal recipients" as they can receive blood from any person belonging to any of the ABO group (with matching rhesus status). This is so as their blood does not contain any antibodies so there cannot be any reaction with any of the antigens present in the donor's blood.

Blood Group O

These people contain none of the antigen (A or B) in their blood cells but contain both the antibodies (anti-A and anti-B) in their plasma. People with blood group O are known as "universal donors" as they can donate their blood to a person belonging to any of the ABO group (with matching rhesus status). Thus people with O blood type can donate blood to people with blood group A, B, AB or O (however compatibility with other antigens like rhesus needs to be matched). This is so as their blood does not contain any antigens so there is no reaction with any antibodies present in the recipient's blood.

RHESUS CLASSIFICATION

After the ABO blood group system, the next most important blood group system is rhesus (Rh) blood group system. Though the Rh system contains 5 main antigens (C, c, D, E and e), antigen D is considered to be the most immunogenic. There is no specific antiserum for "d" antigen. The letter "d" indicates the absence of a discernible allelic product. According to the rhesus classification, the blood groups can be basically classified as Rh positive and Rh negative (table 6.2).

The major Rh system antigen is the D antigen and it is found in 85% of the population. Anti-D antibodies are IgG antibodies that bind to the surface of the red cells resulting

Table 6.2: Rh system and blood grouping

Rh group	*Rh antigen*	*Rh antibody*	*RBC choice*	*Plasma choice*
Rh positive	D positive	none	Positive or negative	Either
Rh negative	D negative	anti-D	Negative	Either

Table 6.3: Halotypes for three rhesus antigens

Haplotype	*Fisher system*	*Rh status*
CDe	R1	Rh positive
cDE	R2	Rh positive
CDE	Rz	Rh positive
cDe	Ro	Rh positive
Cde	r'	Rh positive
cdE	r"	Rh positive
CdE	Ry	Rh positive
cde	r	Rh negative

in deformation of cells. These deformed red cells, are then sequestered in the spleen resulting in delayed extravascular hemolysis. It is now known that the Rh system is very complex and there are other antigens besides D antigen. Some important Rhesus antigens include: C, D and E. Since there are two possible alleles for each antigen: c or C; d or D; and e or E, one haplotype consisting of c/C, d/D and e/E is inherited from each parent. The resulting rhesus type of the individual depends on their inherited genotype. The haplotypes are given a code based on Fisher system in the table 6.3 below.

If an individual's Rh genotype contains at least one of the C, D, E antigens, they are Rhesus positive. Only individuals with the genotype cde/cde (rr) are rhesus negative. For blood transfusion purposes, donors possessing C or E, even in Rh genotypes r'r (Cde/cde) and r''r (cdE/cde) are classified as Rh positive. Thus based on rhesus classification system, two main types of blood groups are possible: Rh positive and Rh negative.

Rh Positive

These people contain Rh antigen in their blood cells. RBC's of such individuals are agglutinated by antiserum against D antigen.

Rh Negative

These people do not contain Rh antigens in their blood cells. RBCs of such individuals are not agglutinated by the antiserum. Individuals with Rh negative blood normally do not have antibodies against Rh antigens. However these people may develop "anti-Rh" antibodies if they receive exposure to Rh antigens (e.g. transfusion of Rh positive blood in a person with Rh negative status). Thus, people with Rh positive blood can safely receive blood from people with Rh negative blood. But people with Rh negative blood must not receive blood from Rh positive people as they will develop anti-Rh antibodies on receiving Rh positive blood. If these people receive Rh positive blood the second time, there will be a reaction between the Rh antigens of the donor and the anti-Rh antibodies already present in the recipient.

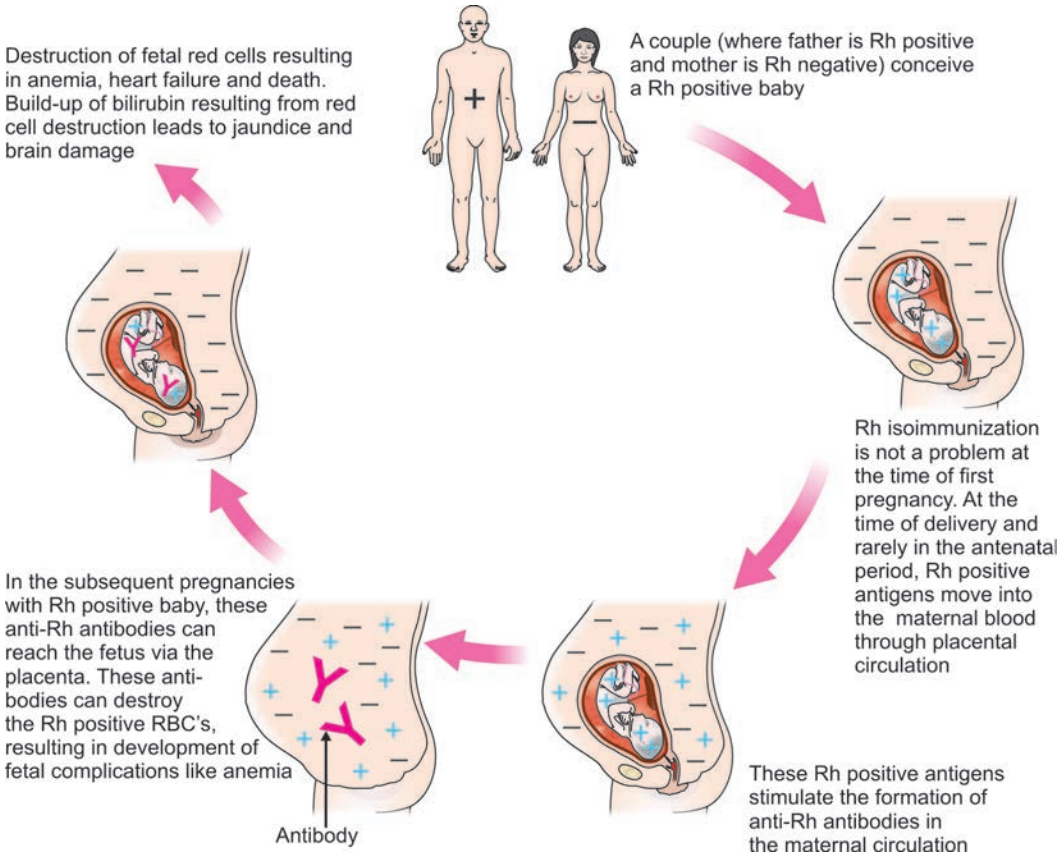
The above mentioned scenario can also occur in Rh negative women if they bear a Rh positive child. Therefore, transfusion of Rh positive, ABO compatible blood products should always be avoided in Rh negative women of childbearing age to prevent the formation of anti-D antibodies prior to pregnancy. However, inevitable Rh incompatibility occurs when Rh negative mother carries a Rh positive child.

Rh INCOMPATIBILITY DISEASE

Due to difference in blood groups between the mother and fetus, two types of incompatibility diseases can occur: Rh incompatibility disease (flow chart 6.1) and ABO incompatibility disease. Both diseases have similar symptoms, but Rh disease is much more severe, because anti-Rh antibodies cross over the placenta more readily than anti-A or anti-B antibodies. Rh incompatibility may develop when a woman with Rh negative blood marries a man with Rh positive blood and conceives a fetus with Rh positive blood group (who has inherited the Rh factor gene from the father). Rh positive fetal red blood cells from the fetus leak across the placenta and enter the woman's circulation. Throughout the pregnancy, small amounts of fetal blood can enter the maternal circulation (feto-maternal hemorrhage), with the greatest transfer occurring at the time of delivery or during the third trimester. This transfer stimulates maternal antibody production against the Rh factor, which is called isoimmunization. The process of sensitization has no adverse health effects for the mother.

During the time of first Rh positive pregnancy, the production of maternal anti-Rh antibodies is relatively slow and usually does not affect that pregnancy. Rh incompatibility is not a factor in a first pregnancy, because few fetal blood cells reach the mother's bloodstream until delivery. The antibodies that form after delivery cannot affect the first child. However, if the mother is exposed to the Rh D antigens during subsequent pregnancies, the immune response is quicker and much greater. The anti-D antibodies produced by the mother can cross the placenta and bind to Rh D antigen on the surface of fetal red blood cells, causing lysis of the fetal RBCs, resulting in development of hemolytic anemia. Severe anemia can lead to fetal heart failure, fluid retention and hydrops and

Flow chart 6.1: Pathogenesis of Rh isoimmunization



intrauterine death. Depending on the degree of erythrocyte destruction, various types of fetal hemolytic diseases can result. An umbrella term for these hemolytic disorders is known as "erythroblastosis fetalis." Clinical manifestations of erythroblastosis fetalis include hydrops fetalis, icterus gravis neonatorum and congenital anemia of the newborn. Hemolysis often results in hyperbilirubinemia. Low levels of jaundice are not harmful but, if left untreated, higher levels may develop resulting in damage to specific areas of the neonatal brain, causing permanent brain damage (kernicterus). This can lead to a range of neurodevelopmental problems, such as cerebral palsy, deafness and motor and speech delay. Postnatal jaundice can be treated with phototherapy (figure 6.1) and exchange transfusion.

Isoimmunization depends on the volume of fetal blood entering the maternal circulation and usually occurs when at least 0.1 ml of fetal blood enters the maternal circulation. Chances of Rh isoimmunization in antenatal period due to feto-maternal hemorrhage are about 1% to 5%, whereas that during the end of third trimester and at the time of labor are about 10% to 15%. Isoimmunization can also occur following medical interventions such as chorionic villus sampling, amniocentesis, external cephalic version, etc and other medical events like, pregnancy terminations, late miscarriages, antepartum hemorrhage and abdominal trauma, which can cause feto-maternal hemorrhage.

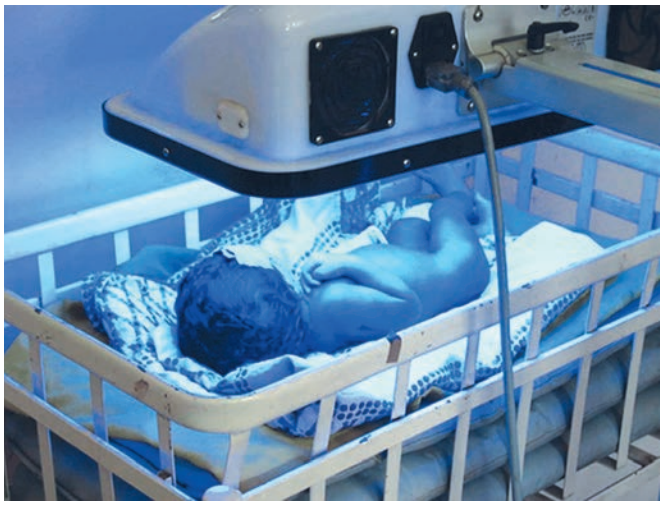


Fig. 6.1: A newborn baby with mild degree of postnatal jaundice being treated with phototherapy

History

RISK FACTORS

The following risk factors must be elicited on history:

Maternal History

- Rh negative (dd) blood type
- Younger (<16 years) or older (>35 years) maternal age
- Rh negative women partnered with Rh positive father
- History of previous blood transfusion

Obstetric History

- History of jaundice, congenital malformations, still births or intrauterine deaths in previous pregnancies
- Previous history of hydrops fetalis
- Previous history of feto-maternal transfusion
- History of receiving anti-Rh immunoglobulins in previous pregnancies.
- Decrease in fetal movements
- History of unrecognized miscarriage with transplacental hemorrhage

It is important to elicit detailed obstetric history from the patient. Previous history of neonatal deaths or stillbirths and history of previous successive fetuses affected by jaundice, anemia, etc is quite suggestive of Rh isoimmunization. Women may typically give a history of having received injection of anti-Rh immunoglobulins in previous pregnancies or following miscarriage and invasive procedures like amniocentesis, CVS, etc.

General Physical Examination

No specific finding is observed on general physical examination.

Specific Systemic Examination

No specific finding is observed on specific systemic examination.

ABDOMINAL EXAMINATION

Normal abdominal and vaginal examination should be carried out as described in chapter 1.

Management

Management comprising of investigations and definitive obstetric management is discussed next.

Investigations

Blood Grouping

Routine antenatal investigations including ABO and Rh typing must be performed in all women at the time of their first antenatal visit.

Maternal antibody screening, which helps in detecting the presence of anti-D antibodies, must be performed in all pregnant women who turn up to be Rh negative. In this test the maternal serum is incubated with Rh positive erythrocytes and Coomb's serum (antiglobulin antibodies). The red cells will agglutinate if Rh antibodies are present in the maternal plasma.

Kleihauer-Betke Test

This is a blood test usually performed in Rh negative mothers, for measuring the amount of fetal hemoglobin transferred from a fetus to mother's bloodstream as a result of feto-maternal hemorrhage. It is based on the principle that fetal hemoglobin is resistant to acid. In this test maternal blood smear is exposed to an acidic solution (citric acid phosphate buffer). The acid is able to elute adult hemoglobin, but not fetal hemoglobin, from the red blood cells. As a result, on subsequent staining the fetal cells (containing fetal hemoglobin) appear rose-pink in color, while adult red blood cells appear as "ghosts."

Kleihauer-Betke test is normally not useful and is usually not done to determine the requirement for Rh immunoglobulins.

Rx Treatment/Obstetric Management

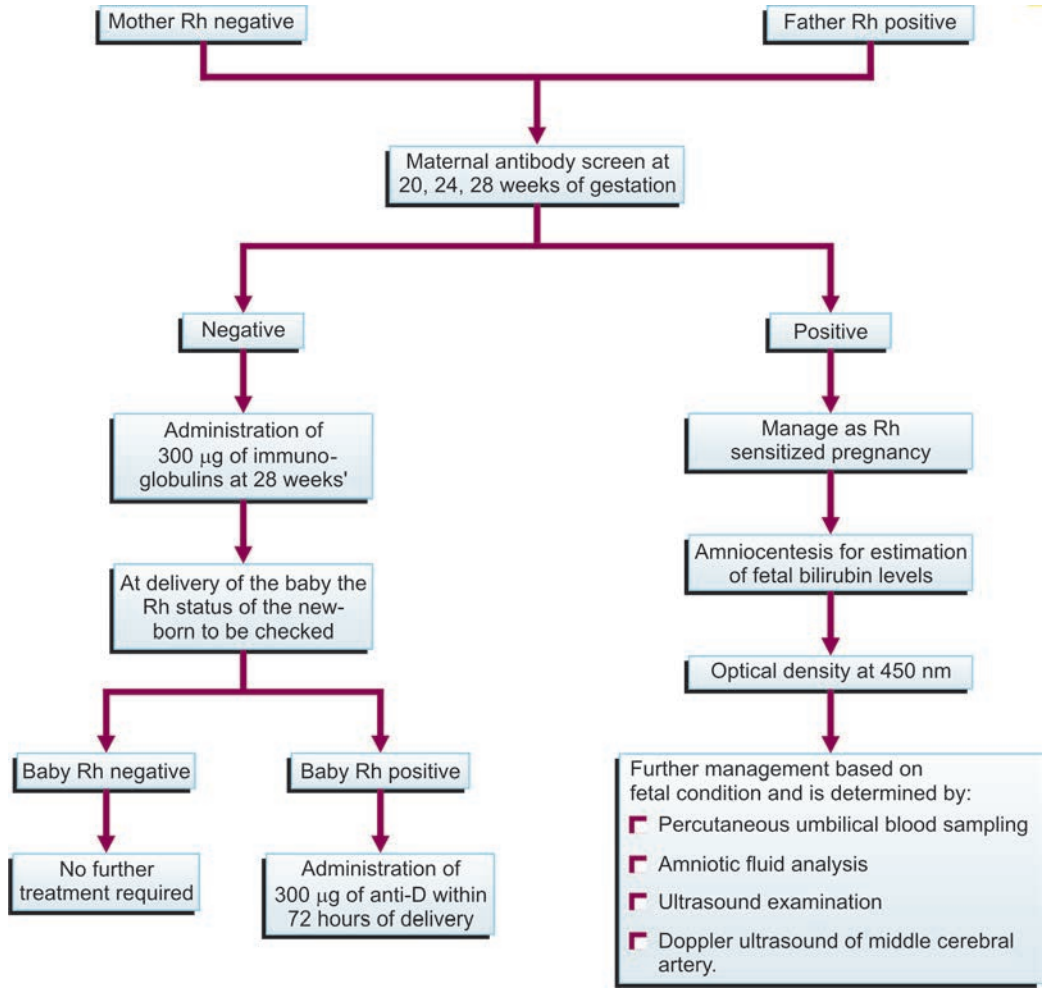
ANTENATAL MANAGEMENT

In the antenatal period, the women can be divided into two groups: Rh negative nonimmunized women and the Rh negative immunized women. In the nonimmunized women, the objective of the antenatal management is prevention of Rh alloimmunization. In women who are already alloimmunized, the objective of management is early detection and treatment of anemia in the fetus. Management of both these cases would be discussed in details below:

Management of Rh Negative Nonimmunized Women (Flow chart 6.2)

These women do not show any antibodies in their blood at the time of the initial prenatal evaluation. In these patients the first step in the management should be the determination

Flow chart 6.2: Management of Rh negative nonimmunized women



of the blood group of the baby's father. If the father's blood group is Rh negative, there is no possibility that the baby would be Rh positive. Such pregnancies should be managed like normal ones and no further testing of Rh antibodies is required.

If the father is Rh positive, there is 50% to 100% chance that the baby born would be Rh positive, depending on whether the father is homozygous or heterozygous for the Rh antigen. In such cases, it is important to detect the development of the antibodies in the mother during the antenatal period. The maternal antibody screen in order to detect the presence of the antibodies needs to be carried out at 20, 24 and 28 weeks of gestation. The indirect Coombs test is done to measure the presence of antibodies in the maternal blood. While the direct Coombs test helps in detecting the antibodies that are bound to the surface of red blood cells; the indirect Coombs test detects antibodies against RBCs that are present unbound in the patient's serum. Negative antibody titer on indirect Coomb's test can help identify the fetus that is not at risk.

In case the antibody screen turns out to be positive, the woman must be further managed as Rh sensitized pregnancy. In case, the antibody screen is negative, the patient should be administered 300 μg of immunoglobulins at 28 weeks of gestation in order to neutralize the fetal Rh antigens. This dose of anti-D immunoglobulins is capable of neutralizing 30 ml of fetal blood which is equivalent to approximately 15 ml of fetal red blood cells. This is able to prevent alloimunization in about 90% of the cases. Administration of these anti-Rh antibodies help in blocking the recognition of fetal Rh positive cells by the mother's body by neutralization of maternal antibodies before they can destroy the fetal Rh positive cells (figure 6.2).

In the remaining 10% cases, administration of anti-D immunoglobulins may be ineffective due to large volumes of feto-maternal hemorrhage. If a massive feto-maternal

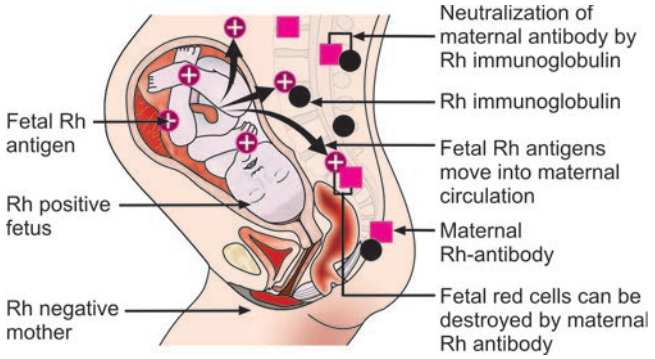


Fig. 6.2: Mechanism of action of anti-D immunoglobulins

Table 6.4: Criteria for administration of second dose of anti-D immunoglobulins to Rh negative nonimmunized women

The baby born is Rh positive
Direct Coombs test on the umbilical cord blood is negative
The cross match between the anti-D immunoglobulins and mother's red cells is compatible

hemorrhage has occurred, additional injections of Rh immunoglobulins may be required.

The woman's eligibility for the second dose of the anti-D immunoglobulins needs to be determined at the time of the delivery of the baby (table 6.4). Once the anti-D immunoglobulins have been administered to the mother, the anti-D antibodies in her blood would be detected on antibody screening. However, the antibody titer would not be greater than 4 at term in these cases. If the antibody titer is greater than 4, it probably is due to alloimmunization rather than due to administration of the anti-D immunoglobulins.

The maximal protective effect of anti-D immunoglobulins is observed if they are administered within 12 hours of delivery. However, they can be administered until 4 weeks of delivery. Since the maximum chances of feto-maternal hemorrhage occur at the time of delivery, administration of anti-D immunoglobulins to eligible mothers post-delivery helps in reducing the incidence of alloimmunization from 15% to about 1–2%. Anti-D immunoglobulins must also be administered to all the negative nonimmunized women following spontaneous or induced abortions, amniocentesis and the ectopic pregnancies.

Rh Negative Immunized Women (Flow charts 6.3A and B)

In Rh immunized women the main objective of the management is to diagnose and treat fetal anemia as soon as possible. This can be done through the following ways:

- *Measurement of the peak systolic velocity (PSV) of the fetal middle cerebral artery:* This is done by Doppler ultrasound.
- *Amniocentesis and amniotic fluid analysis:* This involves determination of bilirubin concentration in the amniotic fluid.
- *Ultrasound examination of the fetus.*
- *Percutaneous Umbilical cord blood sampling (PUBS)* (cordocentesis)

In cases of Rh immunized woman also, it is important to determine the blood group of the husband. If the husband is Rh negative, no further testing is required. In case the father is Rh positive, further management needs to decided depending on whether the woman has a history of previously affected babies or not.

First affected pregnancy (No previous history of affected pregnancies)

Risk of fetal anemia is proportional to maternal anti-Rh antibodies titer in the first affected pregnancy. This relationship is lost in the subsequent pregnancies. In case of first affected pregnancy, the maternal antibody titers must be determined at monthly intervals. If the antibody titer remains under the critical level (usually 32) up to 36 weeks of gestation, the woman may be continued until the term. The pregnancy should not be allowed to get post dated and she should be induced between 38–40 weeks of gestation. If there is a sudden rise in the antibody titer at any time, the following needs to be done:

34 or more completed weeks: Induction and delivery

Less than 34 weeks: Amniocentesis to determine pulmonary maturity and serum bilirubin levels must be done. If the bilirubin levels are below 0.05 or lungs are immature, pregnancy should be allowed to continue and amniocentesis should be done at weekly intervals. Such babies are unlikely to develop severe hemolytic diseases and should be delivered as soon as lungs have attained maturity.

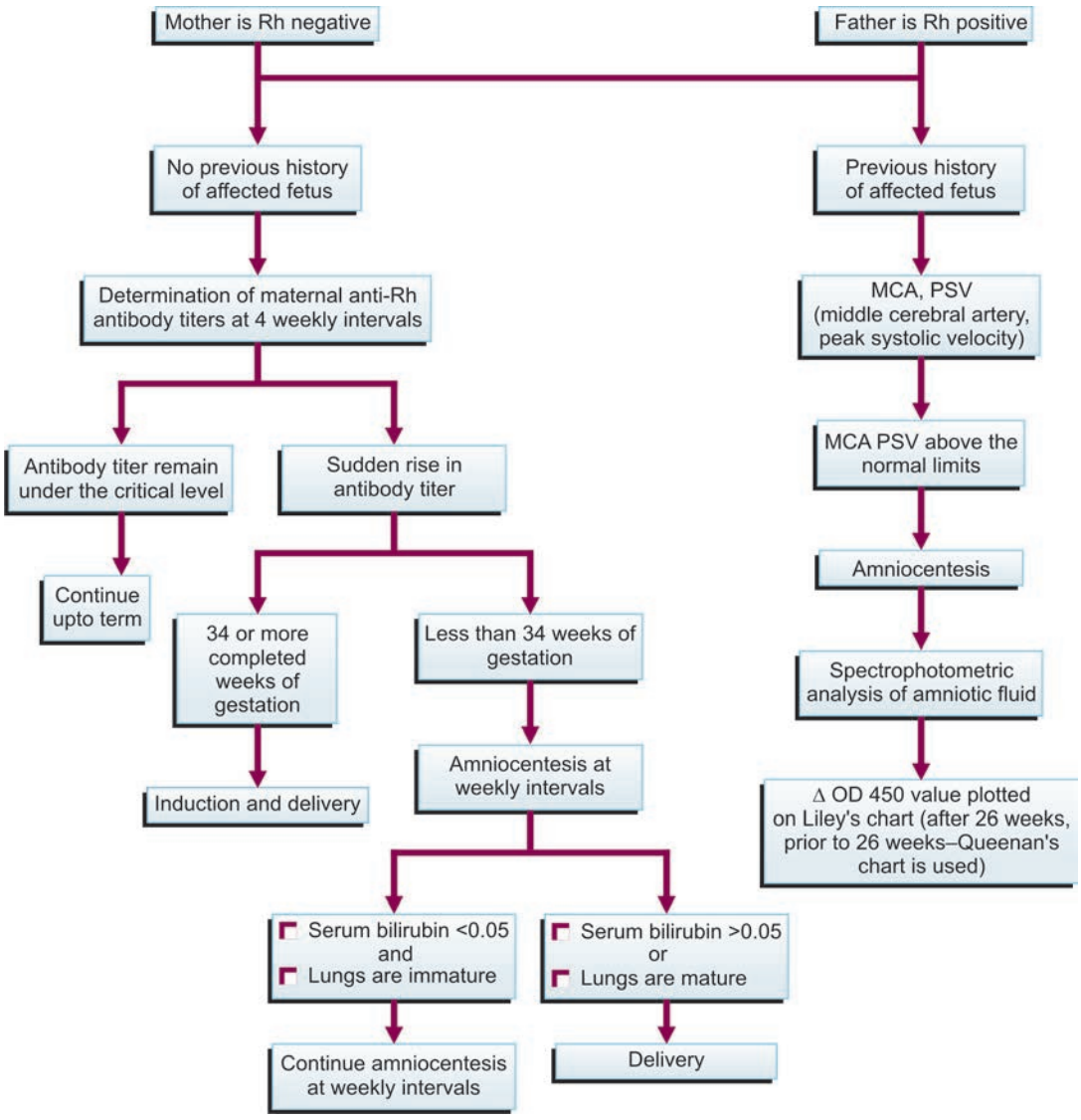
Women with a history of previously affected pregnancy

In these cases, anti-D titers are unable to predict the development of fetal anemia. Therefore other tests are required to predict the development of fetal anemia. Some of these tests are as follows:

Ultrasound

Ultrasound examination in the first trimester helps in an accurate estimation of the gestational age. Following that, serial ultrasounds and amniotic fluid analysis help in determining fetal progress. The ultrasound may reveal the evidence of hydrops fetalis and fetal anemia. There could be presence of polyhydramnios and increased placental thickness (greater than 4 cm). The fetus may show pericardial effusion, ascites or pleural effusion and/or echogenic bowel. There could be spenomegaly and hepatomegaly along with the dilatation of cardiac chambers.

Flow chart 6.3A: Antenatal management of immunized Rh negative pregnancy



Some tests for estimation of fetal hemoglobin include immunofluorescent flow cytometry or DNA analysis using PCR.

Tests for fetal surveillance

The earliest warning of fetal anemia may be experienced by the mother in the form of reduced fetal body movements. External cardiotocography may show evidence of sinusoidal fetal heart rate patterns (figure 6.3) and fetal biophysical profile may be affected.

Middle cerebral artery peak systolic velocity (MCA PSV) on Doppler ultrasound

This is a non invasive method for detection of fetal anemia. The peak systolic flow in fetal middle cerebral vessels is

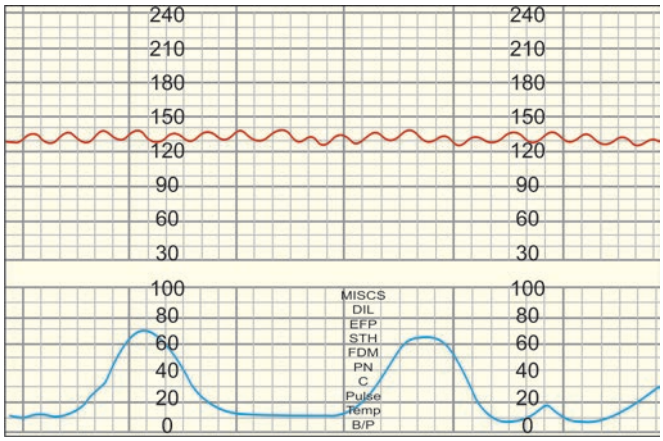
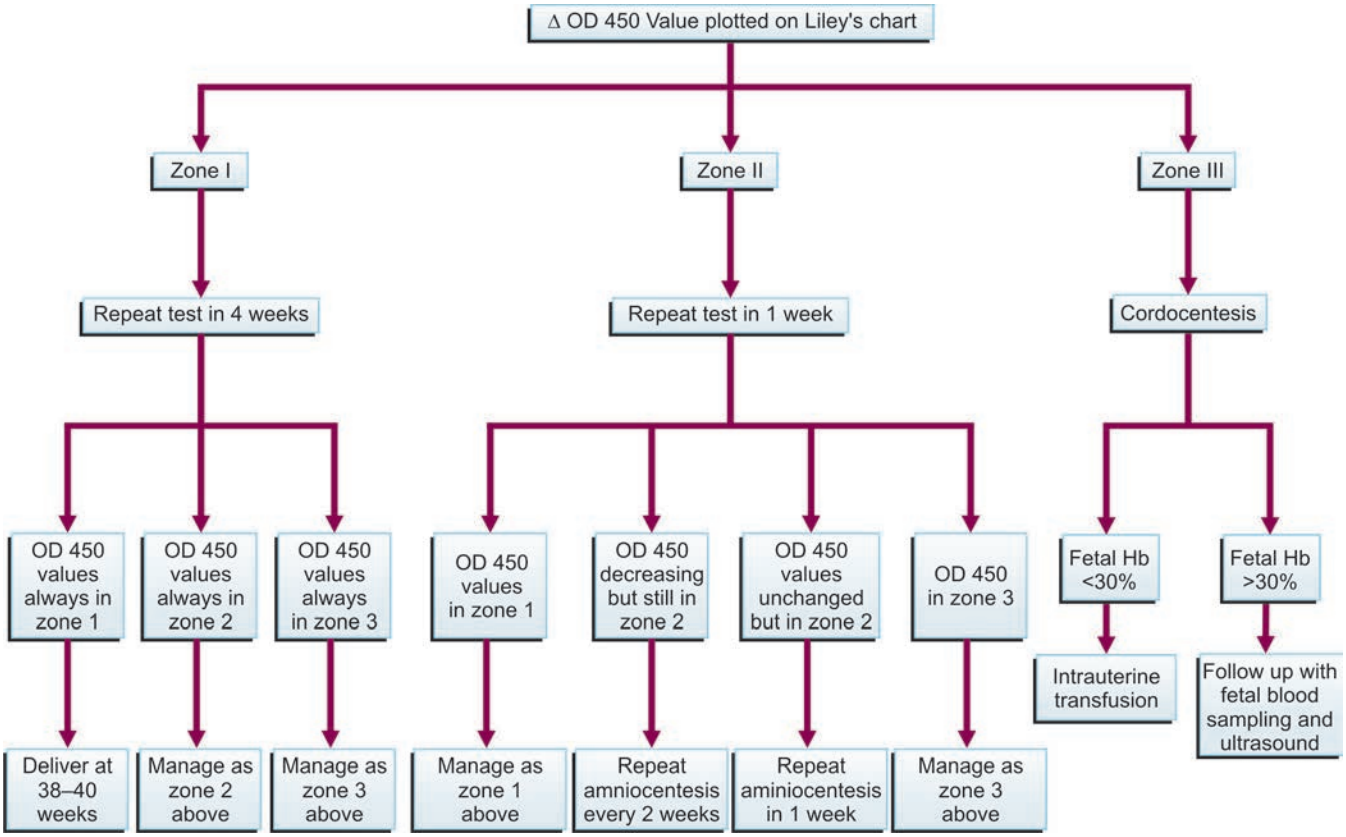


Fig. 6.3: Sinusoidal fetal heart rate pattern on cardiotocography

Flow chart 6.3B: Intrapartum management of immunized Rh negative pregnancy



directly proportional to the amount of fetal hemoglobin. Though abnormally elevated MCA PSV can be considered to have a high sensitivity (almost approaching 100%) in prediction of fetal anemia, it also has a false positive rate of approximately 12%. Therefore an elevated MCA PSV must be followed by a cordocentesis and if required, an intrauterine transfusion.

Amniocentesis

The process of amniocentesis is useful for obtaining the amniotic fluid sample which is then subjected to bilirubin levels estimation. If bilirubin levels in amniotic fluid remains normal, the pregnancy can be allowed to continue to term and the clinician can await spontaneous labor. If bilirubin levels are elevated, indicating impending intrauterine death, the fetus can be given intrauterine blood transfusions at ten-day to two-week intervals, generally until 35 to 36 weeks of gestation, following which the delivery is usually performed by 37–38 weeks.

Amniotic fluid bilirubin estimation: Amniocentesis is usually performed at 20 weeks. However an earlier amniocentesis may be performed at 16 weeks if the woman gives a history of previous baby being affected by hydrops or ultrasound examination shows evidence of a hydropic baby.

In order to determine the bilirubin concentration of the amniotic fluid sample, 5 to 10 ml of amniotic fluid sample is centrifuged at 4000 rpm for 20 minutes and than analyzed by spectrophotometric analysis. Optical density readings (OD) of normal amniotic fluid when analyzed by spectrometry form an almost straight line between 350 and 650 nm. If bilirubin is present in the amniotic fluid, a peak occurs at 450 mm. The size of this peak is proportional to the amount of bilirubin in amniotic fluid. Instead of doing continuous spectrophotometry, optical density readings are selectively measured at 375 nm, 450 nm and 525 nm. The results are then plotted on a semilogarithmic paper and a straight line is drawn between the readings at 375 and 525 nm. The ΔOD 450 values are calculated next, which are equal to the difference between the expected value (point at which the line crosses the 450 nm mark) and the actual reading at this wavelength. The ΔOD 450 values are then plotted on Liley's chart (figure 6.4).

Zone 3 on the Liley's curve corresponds to severely affected infants, zone 2 to moderately affected infants and zone 1 to unaffected or mildly affected infants.

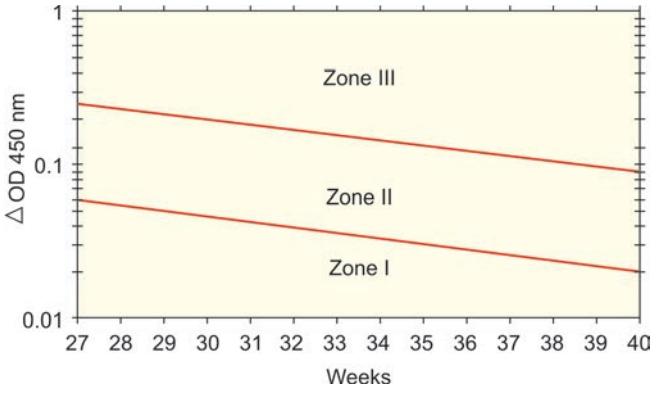


Fig. 6.4: Liley's chart

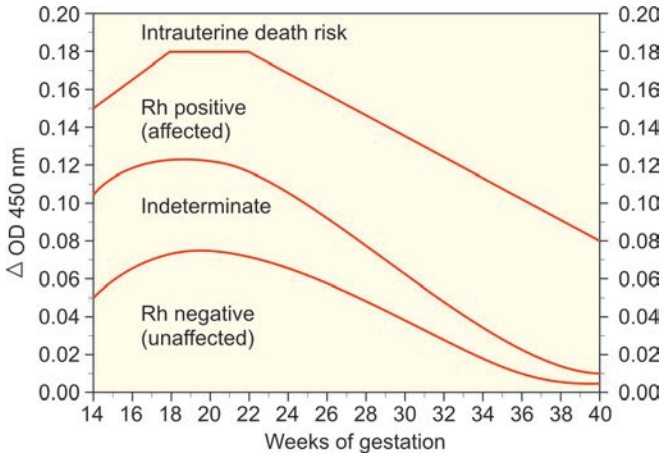


Fig. 6.5: Queenan's chart

Amniotic fluid ΔOD 450 lies in zone 1: If the amniotic fluid ΔOD 450 lies in zone 1, the fetus is either unaffected or mildly affected and there is no danger of intrauterine death. In such cases the procedure should be repeated in 4 weeks. If the repeated ΔOD 450 values remain in the zone 1, the infant should be delivered at the term. It is anticipated that a healthy or a mildly affected fetus would be born.

Amniotic fluid ΔOD 450 lies in zone 2: If at anytime, the ΔOD 450 value lies in the zone 2, the procedure needs to be repeated at weekly intervals. If during the repeated test the ΔOD 450 values come to lie in the zone 1, the test needs to be repeated again after 4 weeks. If during the repeated tests the ΔOD 450 values show a decreasing trend but still within the zone 2, amniocentesis must be again repeated after two weeks. If during the repeated test the ΔOD 450 values show a horizontal trend (values similar to previous one) and still lie within the zone 2, amniocentesis needs to be repeated again after 2 weeks. If the horizontal trend continues on successive repeated amniocentesis examinations, it indicates that the fetus could be moderately to severely affected. In these cases cordocentesis and evaluation of fetal hematocrit is required.

Amniotic fluid ΔOD 450 lies in Zone 3: If at any time, the OD 450 values lies in the zone 3 or show a rising trend (moves from zone 1 or 2 to zone 3), the fetus is in imminent danger of the intrauterine death. In these cases cordocentesis must be done and fetal hemoglobin values must be determined. If fetal hematocrit values are less than 30%, intrauterine transfusion is indicated.

The only disadvantage of Liley's curve is that it is inaccurate before 26 weeks of gestation.

Another chart called Queenan chart (figure 6.5) is sometimes is used. It has been found to be more accurate in comparison to the Liley's curve. It can be used for the fetal assessment, starting from 14 weeks of gestation upto 40 weeks and the graph has been divided into four zones. The first zone in this curve corresponds to a non affected fetus. As the ΔOD 450 values move to higher zones, the chances of having an affected fetus also correspondingly increase. The values in the upper zone correspond to the higher risk of the fetal death. After 26 weeks of gestation, Liley's graph can be used.

Percutaneous umbilical cord blood sampling (PUBS) or cordocentesis

Cordocentesis, also sometimes called percutaneous umbilical cord blood sampling (PUBS), is a diagnostic test which aims at detection of fetal anomalies (e.g. chromosomal anomalies like Down's syndrome; blood disorders like hemolytic anemia, etc) through direct examination of fetal blood. Cordocentesis is usually performed during 18–24 weeks of pregnancy. In cases of Rh negative immunized women, the procedure of cordocentesis helps in estimating the fetal hemoglobin and hematocrit levels.

Procedure: The procedure of cordocentesis involves the following steps (figure 6.6):

- Cordocentesis must be performed only after the woman has given informed consent. Before performing the procedure, the obstetrician must counsel the patient regarding the procedure, indications, advantages, disadvantages and the risks involved to the patient and her partner.
- Maternal blood group including Rh factor needs to be determined before performing the procedure. If the mother is Rh negative, she should be administered Rh immunoglobulins.
- Preprocedure ultrasound evaluation: A comprehensive preprocedure ultrasound examination preferably and a Doppler analysis must be done to determine the location where the umbilical cord inserts into the placenta.
- Strict asepsis should be maintained at the time of the procedure.
- A thin needle (20–22 Gauge) must be inserted through the abdomen and uterine walls into the umbilical cord under

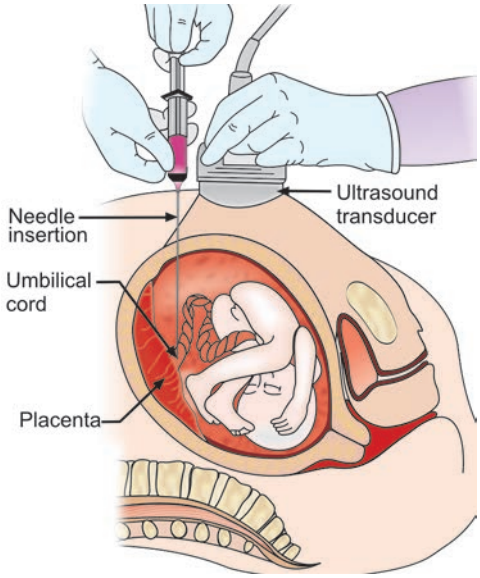


Fig. 6.6: Procedure of cordocentesis

the "continuous ultrasound control." The needle is then inserted into the umbilical cord to retrieve a small sample of fetal blood.

- The sample is sent to the laboratory for analysis, and results are usually available within 72 hours.

Risks of Cordocentesis: Though generally considered as a safe procedure, cordocentesis is an invasive procedure, which must be performed after adequate counselling of the parents regarding its advantages and risks. Some potential side effects related to the procedure of cordocentesis include:

- There is a 1% to 2% risk of miscarriage
- Blood loss from the puncture site
- Infection
- Drop in fetal heart rate
- Premature rupture of membranes

The patient must be asked to consult her healthcare provider, in case she experiences symptoms like fever, pain, vaginal bleeding, reduced fetal movements, leakage of amniotic fluid per vaginum etc, following the procedure.

INTRAPARTUM MANAGEMENT

Precautions to be Taken at the Time of Delivery

Following steps must be taken to minimize the chances of feto-maternal bleeding during the time of delivery:

- Prophylatic ergometrine with the delivery of the anterior shoulder, routinely administered as a step under active management of the third stage of the labor, must be withheld.
- If the manual removal of the placenta is required, it should be performed gently in order to minimize the chances of the feto-maternal bleeding.
- Rh positive blood transfusion must be preferably avoided in Rh negative woman right from birth uptil menopause.
- Any abdominal maneuver like external version/abdominal palpation etc should be done gently.
- Any invasive procedure like amniocentesis, chorionic villus sampling etc should be followed by administration of anti-Rh immunoglobulins. Except for first trimester abortion where the dose required in 50 μg, in all other situations the dose of Rh immunoglobulins required is 300 μg.
- Careful fetal monitoring needs to be performed during the time of labor.
- Delivery should be as nontraumatic as possible. The placenta should not be removed manually to avoid squeezing of fetal cells into the maternal circulation.
- The clinician should remain vigilant regarding the possibility for the occurrence of PPH since ergometrine is usually withheld.
- Umbilical cord should be clamped as soon as possible to minimize the chances of feto-maternal hemorrhage.
- About 15 to 20 cm of cord length should be left intact with the fetus. This may prove useful for exchange transfusion.
- About 5 ml of cord blood should be collected and sent to the lab for tests like ABO and Rh typing; direct Coomb's test; serum bilirubin levels; hemoglobin estimation and peripheral smear.
- At the time of cesarean section, all precautions should be taken to prevent any spillage of blood into the peritoneal cavity. As far as possible, manual removal of the placenta should not be done.
- A newborn with erythroblastosis should be attended to immediately by a pediatrician who must be prepared to perform an exchange transfusion at once if required.
- In case preterm delivery is required, mother must be administered an intramuscular dose of corticosteroids.

Timing of Delivery (Flow chart 6.4)

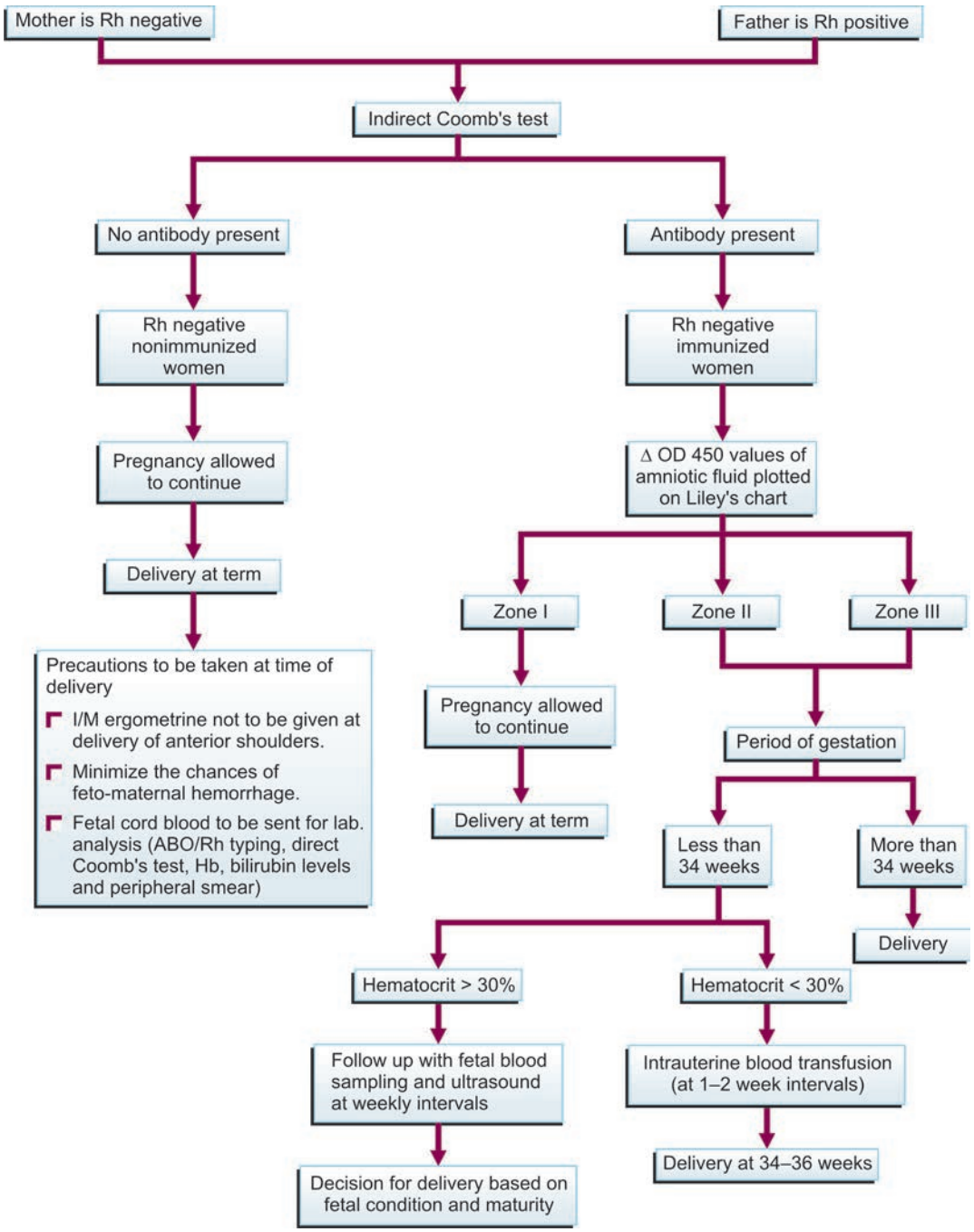
Rh negative nonimmunized women

In Rh negative nonimmunized women, the pregnancy must be allowed to continue upto term. However, the tendency to overrun the expected date of delivery must be curtailed.

Rh negative immunized women

As discussed previously, if there is no sign of fetal hemolytic disease on Liley's chart (Δ OD 450 values lie within the zone 1) the pregnancy can continue upto 38–40 weeks. In

Flow chart 6.4: Deciding the timing for delivery in Rh negative women



case there is evidence of fetal hemolytic disease (Liley's zone II or III), early termination of pregnancy must be considered. If the period of gestation is 36 weeks or more, the labor must be induced. If the period of gestation is less than 36 weeks, cordocentesis must be done to determine fetal hemoglobin levels and hematocrit. If hematocrit is less than 30%, fetal intrauterine blood transfusion at 10–14 days intervals, generally until 35 to 36 weeks gestation, must be performed. Following the intrauterine blood transfusion, delivery is usually performed by 37–38 weeks of gestation.

Treatment of Fetal Anemia

Treatment of the baby born with hemolytic anemia comprises of the following options:

- In utero transfusion, if fetal anemia is severe
- Exchange transfusion after birth

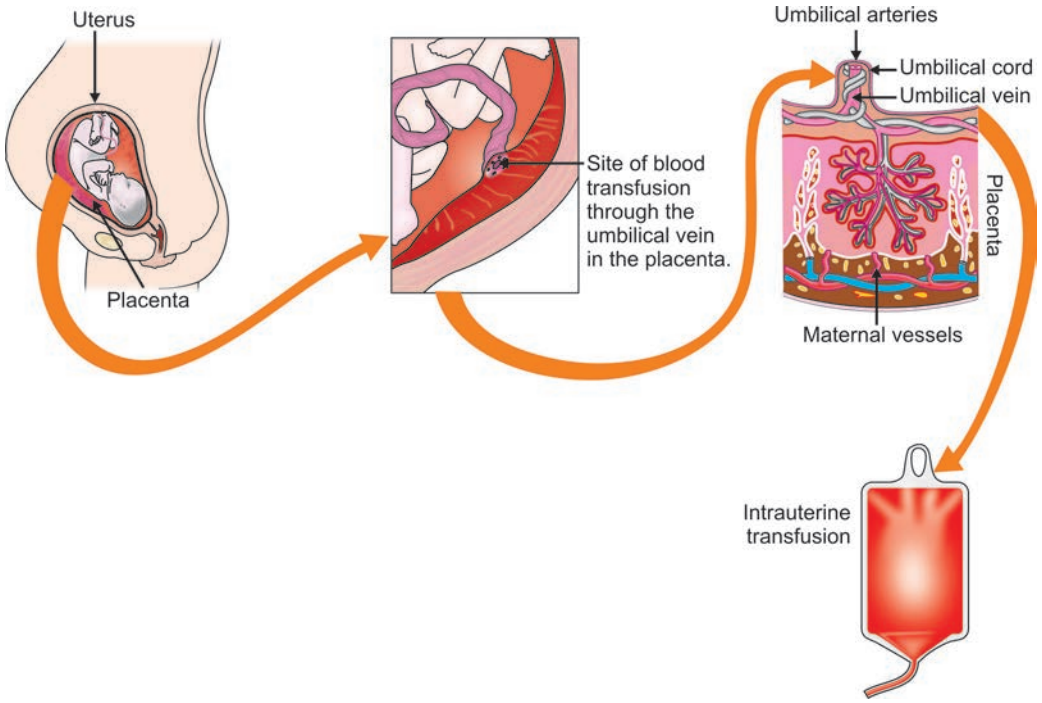


Fig. 6.7: Process of exchange transfusion

Fetal intrauterine blood transfusion

There are two techniques that are used to deliver intrauterine blood transfusion to a baby before birth: These include intraperitoneal transfusion and intravascular transfusion. One or more transfusions may be necessary to treat the episode of anemia, hyperbilirubinemia, and bleeding. The amount of blood to be transfused (in milliliters) is calculated by multiplying number of weeks of gestation over 20 with ten. For e.g. at 34 weeks of gestation the amount of blood required to be transfused would be equal to (34–20) × 10 = 140 ml. The transfusion process can be repeated at weekly or two weekly intervals. Following the process of transfusion, fetal surveillance in form of biweekly CTG and weekly ultrasound examinations in order to ensure fetal wellbeing must be performed.

Intraperitoneal Transfusion: With this method, a needle is inserted through the mother's abdomen and uterus into the baby's peritoneal cavity under ultrasound guidance. Red blood cells injected into the baby's abdominal cavity are absorbed by the subdiaphragmatic lymphatics into the bloodstream. Rh negative packed red cells of the blood group type O, having the hematocrit of 80% that have been crossmatched with the mother are usually transfused.

Intravascular blood transfusion: In this method, Rh negative packed red cells of the blood group type O, having the hematocrit of 80% that have been crossmatched with the mother are usually transfused through the fetal umbilical vein.

Exchange transfusion

Exchange transfusion is a potentially lifesaving procedure that is done to counteract the effects of serious jaundice related to hemolytic anemia in a newborn child born to the mother with Rh incompatibility. This procedure helps in correcting neonatal anemia and congestive heart failure. It also helps in removing the circulatory antibodies. The procedure of exchange transfusion involves slow removal of the baby's blood and its replacement with fresh donor blood or plasma (figure 6.7).

Prerequisites for the procedure:

- If a severely affected infant with Rh hemolytic disease is anticipated at birth, it may be necessary to arrange ABO compatible (with the baby), Rh negative whole blood with the specific volume. If ABO compatible blood is not available, O negative blood can be used. The blood should be crossmatched with the infant's serum. The total volume exchange should not exceed one adult unit of blood (450–500 ml). The volume of blood to be exchanged is calculated using the following formula:

$$\text{Volume exchanged (ml)} = \frac{\text{Blood Volume (ml)} \times (\text{Hb desired} - \text{Hb initial})}{(\text{Hb Donor} - \text{Hb Initial})}$$

(Where blood volume = 70–90 ml/kg for term and 85–110 ml/kg for preterm infants).

- If possible, the infant should be nil per orally (NPO) and have his/her stomach contents aspirated prior to the procedure.
- The exchange transfusion should be done using sterile technique, with the infant placed under a radiant warmer.
- The donor blood should be warmed using the blood warmer to a temperature not exceeding 37°C.
- The infant's blood pressure, respiratory rate, heart rate and general condition should be monitored during the exchange transfusion according to the standard nursing protocol.
- At the beginning of the exchange transfusion, the first blood sample withdrawn should be sent for various investigations including total bilirubin (both direct and indirect); hemoglobin and hematocrit; glucose and calcium levels.

Procedure: The procedure of exchange transfusion comprises of the following steps:

- Since an exchange transfusion requires the infant's blood to be removed and replaced, in most cases a plastic catheter is passed through the umbilical vein into the inferior vena cava.
- The exchange transfusion is done in cycles; each one usually lasting for a few minutes.
- In each cycle, about 5 to 20 ml of infant's blood is slowly withdrawn through a peripheral artery and at the same time an equal amount of fresh, prewarmed blood or plasma is injected into the infant's body through the umbilical vein. This cycle is repeated until the required volume of blood has been replaced. Two types of techniques can be used for the procedure of exchange transfusion: Two catheter push-pull technique or one catheter push-pull technique. In the two catheter technique, blood is removed from the peripheral artery, while fresh blood is infused through a vein at the same rate. In the one catheter push-pull technique, a single catheter is placed, usually in the umbilical vein.
- At the end of an exchange transfusion, blood should be sent for the following investigations: Estimation of the levels of sodium, glucose, calcium, total and direct bilirubin, hemoglobin and hematocrit.
- At the end of an exchange transfusion, the umbilical vein catheter is usually removed. In the event of a subsequent exchange, a new catheter can be inserted. The umbilicus must be inspected at frequent intervals for any evidence of bleeding.
- Hypoglycemia may sometimes occur in the first or second hour following an exchange transfusion due to increased insulin secretion. It is therefore necessary to monitor blood glucose levels for the first several hours after exchange.
- The serum bilirubin concentration may rise by two hours after completion of the exchange transfusion. Therefore, the serum bilirubin concentration should be monitored at two to four hours intervals after exchange. In case the serum bilirubin levels continue to remain elevated, phototherapy may be used.
- The infant may be fed after two to four hours following the procedure of exchange transfusion.

Risks: The possible complications of the procedure include the following:

- Formation of blood clots and risk of thrombosis.
- Alteration in the blood chemistry resulting in abnormalities like hyperkalemia, hypokalemia, hypocalcemia, hypoglycemia and metabolic acidosis.
- Heart and lung problems
- Infection
- Shock due to inadequate replacement of blood.

Complications

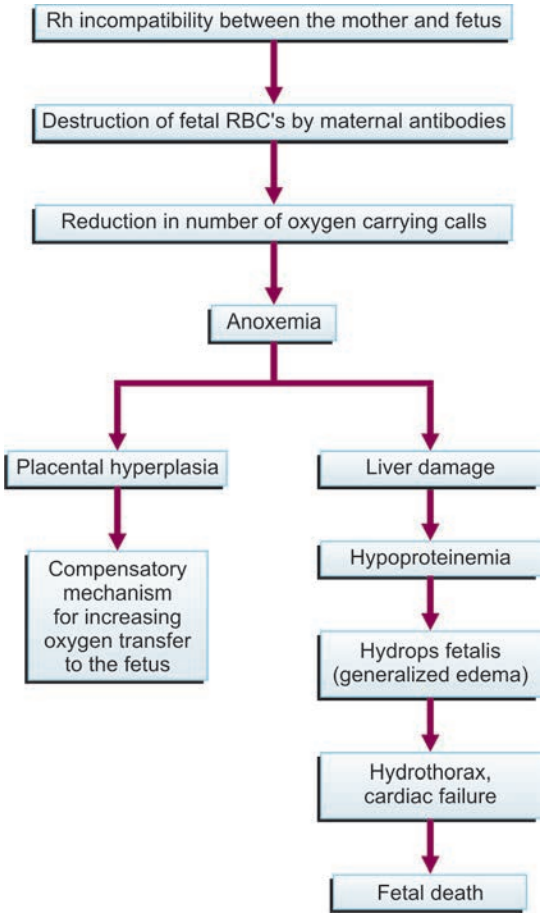
FETAL COMPLICATIONS

The various complications that can develop in the fetus or newborn baby due to Rh isoimmunization are shown in flow chart 6.5 and are also described below in details.

Erythroblastosis Fetalis

Erythroblastosis fetalis, also known as hemolytic disease of the newborn is an umbrella term used to denote various hemolytic disorders resulting due to Rh incompatibility. Clinical manifestations of erythroblastosis fetalis include hydrops fetalis, icterus gravis neonatorum and congenital anemia of the newborn. Erythroblastosis fetalis is a disease in the fetus or newborn caused by transplacental transmission of maternal antibodies, usually resulting from maternal and fetal blood group incompatibility. Hemolysis produced due to Rh incompatibility may produce profound anemia, which may even result in fetal death in utero. As a compensatory mechanism to anemia, the fetal bone marrow starts producing immature erythroblasts into the fetal peripheral circulation, causing erythroblastosis fetalis. The overproduction of erythroblasts can produce enlargement of liver and spleen resulting in development of hepatomegaly and splenomegaly respectively. Excessive destruction of RBC's results in excessive production of bilirubin, which is responsible for producing hyperbilirubinemia and jaundice. Uncontrollable hyperbilirubinemia results in deposition of bilirubin in the brain resulting in permanent damage and development of kernicterus, which can lead to deafness, speech problems, cerebral palsy, or mental retardation.

Flow chart 6.5: Various fetal complications arising from Rh isoimmunization.



Hydrops Fetalis

This is a condition, characterized by an accumulation of fluids within the baby's body (figure 6.8), resulting in development of ascites, pleural effusion, pericardial effusion, skin edema, etc. In many cases, it may also cause polyhydramnios and placental edema. Pleural effusion may interfere with the normal process of breathing, whereas pericardial effusion may be associated with congestive heart failure. Various mechanisms for the formation of fetal hydrops are listed in table 6.5. The fetus is particularly susceptible to interstitial fluid accumulation due to increased capillary permeability, hypoproteinemia and obstruction to lymphatic return.

Recently, factors other than Rh isoimmunization have been found to be associated with development of fetal hydrops. The term nonimmune hydrops has been introduced to identify those cases of fetal hydrops, caused by factors other than Rh isoimmunization. Some of the causes for nonimmune hydrops are listed in table 6.6.

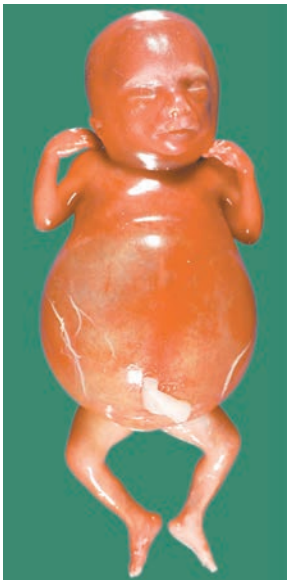


Fig. 6.8: Hydrops fetalis associated with fetal ascites and skin edema

Table 6.5: Pathophysiological mechanisms responsible for development of fetal hydrops

Reduced intravascular oncotic pressure resulting in interstitial fluid accumulation
Increased capillary hydrostatic pressure
Reduced lymphatic return
Elevation of CVP
Elevations in the levels of aldosterone, renin, norepinephrine, and angiotensin I
Increase in the levels of atrial natriuretic peptide
Reduced nitric oxide production due to injury of fetal vascular endothelial cells

MATERNAL

Maternal complications such as history of recurrent miscarriages and intrauterine deaths can occur.

Complications such as abortion and preterm labor are related to procedures such as fetal cord blood sampling.

Important Questions and Answers

Q.1. What would be the next step of management in the above mentioned case study?

Ans. This woman should be managed as a case of Rh negative sensitized pregnancy with a history of previously affected pregnancy. Amniocentesis for the estimation of fetal bilirubin levels was performed. Spectrophotometric analysis of amnotic fluid was performed and ΔOD 450 values

Table 6.6: Causes of nonimmune hydrops

Infectious causes	*Genetic syndromes*	*Metabolic disorders*	*Chromosomal abnormalities*
Infection with parovirus	Myotonic dystrophy (autosomal dominant)	Glycogen-storage disease, type IV	Beckwith-Wiedemann syndrome (trisomy 11p15)
Cytomegalovirus infection	Noonan syndrome (autosomal dominant with variable penetrance)	Lysosomal storage diseases (Gaucher disease, Niemann-Pick disease, etc)	Cri-du-chat syndrome (chromosomes 4 and 5)
Toxoplasmosis	Sjögren syndrome (uncertain inheritance)	Hypothyroidism and hyperthyroidism	Trisomy 21 (Down syndrome)
Coxsackie virus type B	Tuberous sclerosis (autosomal dominant)		Turner syndrome (45, X)
Intrathoracic tumors	*Abdominal tumors*	*Other conditions*	
Pericardial teratoma	Metabolic nephroma	Placental choriocarcinoma	
Rhabdomyoma	Polycystic kidneys	Placental chorangioma	
Mediastinal teratoma	Neuroblastoma	Cystic hygroma	
Pulmonary fibrosarcoma	Hepatoblastoma	Intussusception	
Leiomyosarcoma	Ovarian cyst	Intracranial teratoma	

were plotted on Liley's chart. The values were in zone I and remained in zone I even when a repeat amniocentesis was performed after four weeks. This implies that the infant needs to be delivered at term in anticipation of the delivery of a healthy fetus.

Q.2. Can Rh positive ABO compatible blood be transfused to a Rh negative individual?

Ans. Rh positive ABO compatible blood can be transfused to Rh negative males in case of emergency as a life saving procedure. However such transfusions must be avoided in Rh negative females from birth until menopause due to the risk of acceleration of the process of Rh isoimmunization process in case the Rh negative woman marries an Rh positive man and conceives an Rh positive child.

Q.3. What are other causes for hydrops fetalis besides Rh isoimmunization?

Ans. See table 6.6

Bibliography

1. NICE technology appraisal guidance 156. (2008). Routine antenatal anti-D prophylaxis for women who are rhesus D negative. Review of NICE technology appraisal guidance 41.
2. Santiago MD, Rezende CA, Cabral AC, Leite HV, Vitral ZN, Apocalypse IM. Blood volume calculation required for the correction of fetal anemia in pregnant women with alloimmunization. Rev Bras Ginecol Obstet. 2008;30(4):196-200.
3. Slotnick, Robert N. "Isoimmunization." In: Manual of Obstetrics. K. Niswander and A. Evans (eds). Philadelphia: Lippincott, Wilkins & Wilkins, 2000.

Chapter 7

Previous Cesarean Section

Case Study

24-year-old G2 P2 L1 attended the booking antenatal clinic with a previous history of a cesarean section at term due to breech presentation. She is sure of her last menstrual period and her period of gestation is 14 weeks both by dates and on abdominal examination.

Introduction

Definition

Cesarean Section (CS) is removal of a fetus from the uterus by abdominal and uterine incisions, after 28 weeks of pregnancy. If the removal of fetus is done before 28 weeks of pregnancy, the procedure is known as hysterotomy. Presently, there has been a considerable rise in the rate of cesarean delivery. Some of the common indications for cesarean delivery are described in table 7.1. Pregnant women with a previous section may be offered either planned VBAC or ERCS (elective repeat caesarean section). VBAC stands for vaginal birth after cesarean, which refers to vaginal birth following one or more cesarean births. More than 80% of women will be able to have a vaginal birth following a cesarean delivery. Maternal request for cesarean section, on its own is not an indication for CS. The clinician needs to discuss and explore the specific reasons for this choice with the patient and her partner. The risks and benefits of both cesarean section and vaginal delivery need to be explained. If the woman is just being apprehensive and fearful of the normal vaginal delivery due to the pain involved, she needs to be adequately counseled. If the clinician feels that the woman's request is unreasonable, he/she can decline her request or may refer her for a second opinion. Some of the conditions where routine use of cesarean section is not required are mentioned in table 7.2.

Table 7.1: Indications for a cesarean section

A term singleton breech (if external cephalic version is contraindicated or has failed)
A twin pregnancy with first twin in noncephalic presentation
HIV positive women (to reduce the risk of mother-child HIV transmission
Grade 3 and 4 placenta previa
Both HIV and hepatitis C
Primary genital herpes in the third trimester
Fetal distress
Dystocia (secondary arrest of cervical dilatation, arrest of descent, cephalopelvic disprortion, etc).

History

Detailed history regarding the reason for previous cesarean delivery needs to be taken.

The following questions regarding the previous cesarean section need to be asked:

- What was the indication for the surgery?
- Was it repetitive or a nonrepetitive cause (for e.g. if the indication for cesarean delivery is breech presentation, it is a nonrepetitive cause). However cephalopelvic disproportion can be a repetitive cause requiring a repeat cesarean section during future pregnancies.
- Was the cesarean section elective one or an emergency surgery?
- Place where the previous surgery was performed.
- The period of gestation at which the CS was performed and the skill of the obstetrician who had performed the surgery.

Table 7.2: Indications not requiring a routine cesarean section

Preterm birth
A twin pregnancy with first twin having a cephalic presentation
An IUGR baby
Infection with hepatitis B virus
Infection with hepatitis C virus
Recurrent genital herpes in the third trimester

- What was the type of the scar given (classical or the lower segment)?
- Were there any technical difficulties encountered during the procedure? Was there any lateral extension of the uterine scar or uncontrolled bleeding during the surgery?
- Previous history of any other uterine surgery, especially myomectomy for myoma uterus needs to be enquired. This is especially important as vaginal delivery following myomectomy may be complicated by uterine rupture.

General Physical Examination

- The patient must be considered high risk and frequent antenatal checkups are required.
- The patient should be instructed to report to the clinician in case she experiences pain over the scar, reduced fetal movements or bleeding per vaginum anytime during the pregnancy.

Specific Systemic Examination

Besides the routine obstetric abdominal examination (as described in chapter 1), careful examination of the abdominal scar and elicitation of scar tenderness is important. The scar tenderness is palpated using the ulnar border of right hand in the region above the public symphysis for a few centimeters.

Management

In the past, management of the patient with a history of cesarean scar was considered as "once a cesarean, always a cesarean." This dictum has now been changed to "once a cesarean always hospitalization." Since the management of cases with previous history of cesarean section is still controversial, this dictum is also sometimes changed to "once a cesarean always a controversy." The management options for the patient with previous history of cesarean delivery are presented in flow chart 7.1.

Investigations

Routine ANC investigations including blood grouping (ABO and Rh typing); complete blood count; and ultrasound examination.

Treatment/Obstetric Management

There are two options for delivery in these patients:

- Vaginal birth after cesarean delivery
- Elective repeat cesarean section

Table 7.3: Criteria for VBAC

Previous history of one uncomplicated lower segment transverse cesarean section
Low transverse incision on the uterus
Pelvis is adequate
Patient is willing for VBAC
Facilities for continuous fetal monitoring during labor are available
No other contraindication for cesarean section
VBAC should be undertaken in settings where facilities for emergency cesarean section are present

VAGINAL BIRTH AFTER CESAREAN DELIVERY

Women with a prior history of one uncomplicated lower segment transverse cesarean section, in an otherwise uncomplicated pregnancy at term, with no contraindication to vaginal birth, can be given the option of planned VBAC or an ERCS.

Criteria for VBAC

Decision regarding VBAC must be individualized and must be taken only if the criteria for VBAC, enumerated in table 7.3 are fulfilled. The decision for VBAC is usually taken after considering the following parameters:

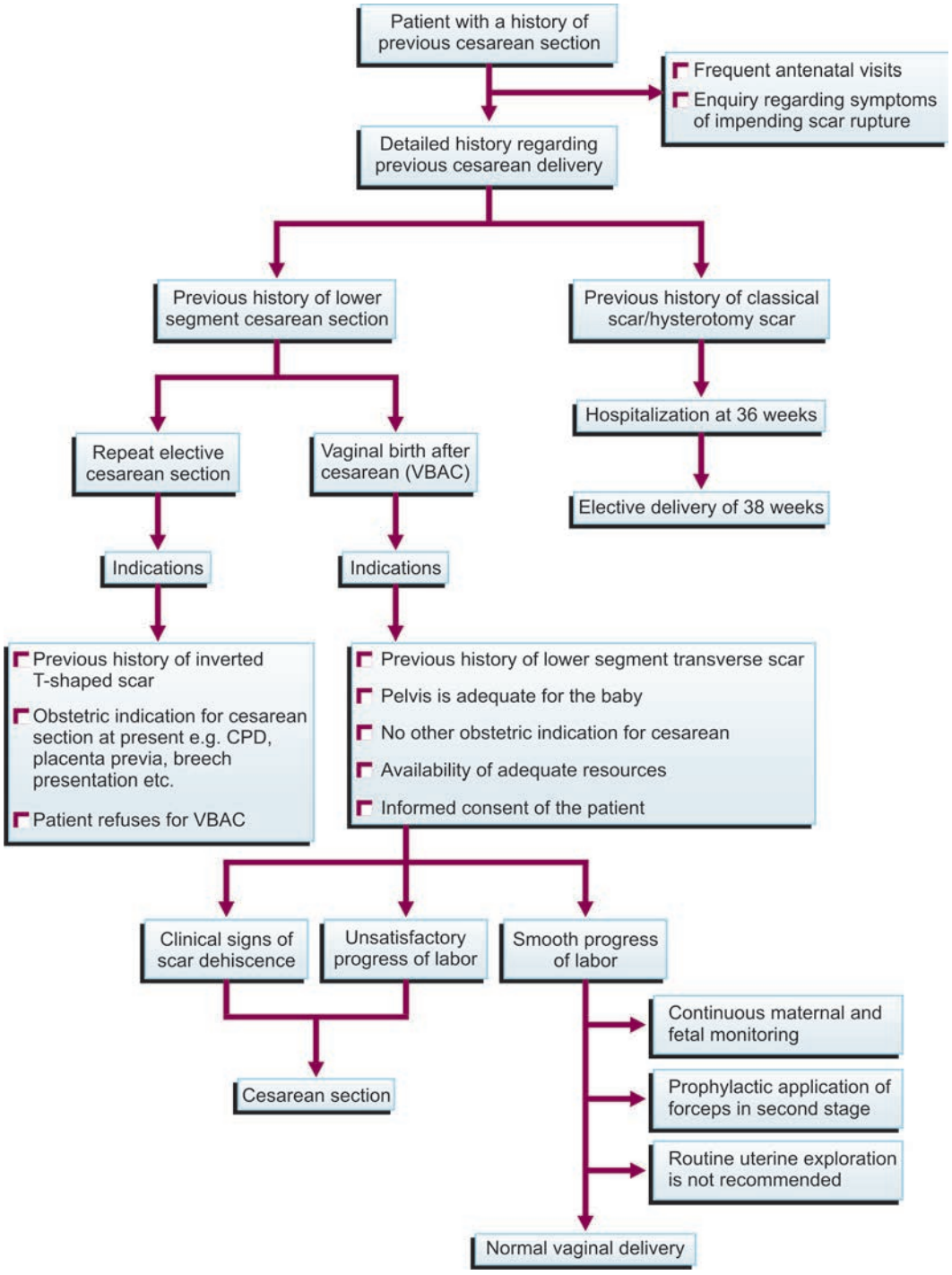
Indication for the previous cesarean (recurrent or a nonrecurrent cause): If the indication of previous cesarean section was a nonrecurrent cause (e.g. fetal distress or non progress of labor), which may or may not recur in future pregnancies, the option of VBAC can be considered. However if the indication for previous cesarean is a recurrent cause like cephalopelvic disproportion, the option of ERCS would be more suitable.

Any associated obstetrical complications in the present pregnancy: If the present pregnancy is associated with some other obstetrical indication for cesarean section (e.g. grade III, IV placenta previa; breech presentation etc), the patient must be considered for ERCS.

Ultrasound estimated weight of the baby: If the ultrasound estimated fetal weight is ≥ 4.0 Kg, the option of ERCS should be considered due to the increased risk of shoulder dystocia and fetal injuries with vaginal deliveries.

Number of the previous sections: According to recommendations by RCOG (2007), women with the history of previous two uncomplicated low transverse cesarean section can be considered for the planned VBAC. Though this practice is commonly employed in developed countries, in developing countries, including India with limited health care settings, this is rarely practiced.

Flow chart 7.1: Management of a patient with a previous history of cesarean section



Strength of the scar as elicited from history and the clinical examination: If the scar appears to be healthy and strong as elicited from the history and clinical examination, the option of VBAC can be considered. In developing countries including India, women with a history of previous two or more cesarean section is considered as an indication for ERCS.

Informed consent of the patients: If the clinician is satisfied after taking patient's history and conducting a clinical examination that the patient appears to be a candidate for

VBAC, this option must be discussed with the patient. VBAC should be undertaken only if the patient is herself satisfied with the decision and is willing to give an informed consent for the same.

Advantages of VBAC

The vaginal birth after cesarean section is associated with the following advantages:

- Prevention of surgery related complications including death.
- Prevention of blood loss
- Prevention of infection
- Prevention of injury to various organs including bowel, urinary bladder, etc.
- Prevention of thromboembolism
- Breastfeeding is generally easier after a vaginal birth
- Vaginal birth is usually associated with reduced health care costs in comparison to cesarean births.
- VBAC is also associated with lower fetal mortality and morbidity in comparison to elective repeat cesareans.

Contraindications for VBAC

VBAC is contraindicated in the presence of the following conditions:

- Previous history of the classical or T-shaped uterine incision.
- History of previous two or more lower segment uterine scars in the past.
- Presence of an obstetric indication for cesarean including CPD, placenta previa, malpresentation etc.
- Limited resource setting, where it might not be possible to continuously monitor the patient.
- Patient refuses to give consent for VBAC.

Risk of VBAC

- If VBAC turns out to be unsuccessful, an emergency cesarean section may be required.
- There is a risk of the scar dehiscence and rupture.
- Increased risk of maternal and perinatal mortality in case of scar rupture.
- Failure of vaginal trial may end up in requirement for an emergency cesarean section. It may also cause uterine rupture, or pelvic floor dysfunction.

Counseling of Women for VBAC

Women who want VBAC should be encouraged and supported. They should be counseled regarding the advantages and disadvantages of both the procedures. They should also be informed about the slightly increased chances of uterine rupture during VBAC in comparison with ERCS (about 1 per 10,000 risk of uterine rupture in cases with ERCS vs. 50 per 10,000 with VBAC). Though occurrence of intrapartum fetal death is rare, it is slightly more in cases with VBAC compared with those with ERCS (about 10 per 10,000 for VBAC vs. 1 per 10,000 for ERCS).

Intrapartum Management

The following steps must be observed during the intrapartum period:

- Blood should be sent for grouping, crossmatching and complete blood count (including hemoglobin and hematocrit levels). One unit of blood should be arranged.
- IV access to be established and ringer lactate can be started.
- Clinical monitoring of the mother for the signs of scar dehiscence needs to be done. This includes monitoring of vitals, especially the pulse rate and scar tenderness, which must be done every 15 minutes.
- Careful monitoring of fetal heart rate, preferably using continuous external CTG. There is no role of intermittent auscultation in these cases.
- Facilities for emergency cesarean section should be available. Pediatrician, anesthetist and the OT staff must be informed well in advance, because they may be required at any time.
- The use of prostaglandins for induction of labor in women with the previous history of cesarean section must be best avoided. Induction of labor using prostaglandins in patients with previous history of cesarean section is associated with a small but statistically significant increased risk of uterine rupture compared to cases where non-prostaglandins are used. (Risk of uterine rupture of 80 per 10,000 in cases where non-prostaglandins are used, vs. 240 per 10,000 cases where prostaglandins are used). Therefore induction and/or augmentation in such patients must be preceded by careful obstetric assessment.
- Epidural analgesia can be safely given at the time of labor.
- Intrapartum monitoring regarding the progress of labor must be done using a partogram (figure 7.1)
- Second stage of labor can be cut short by using prophylactic forceps or ventouse.
- Routine uterine exploration following VBAC is not recommended. If the patient shows signs of uterine rupture including tachycardia, hypotension, vaginal bleeding, etc, uterine exploration may be done. Laparotomy may be required if a uterine rent is found on the uterine exploration.

The most important complication associated in a patient with previous history of cesarean section is the possibility of scar rupture during future pregnancies, especially if given trial

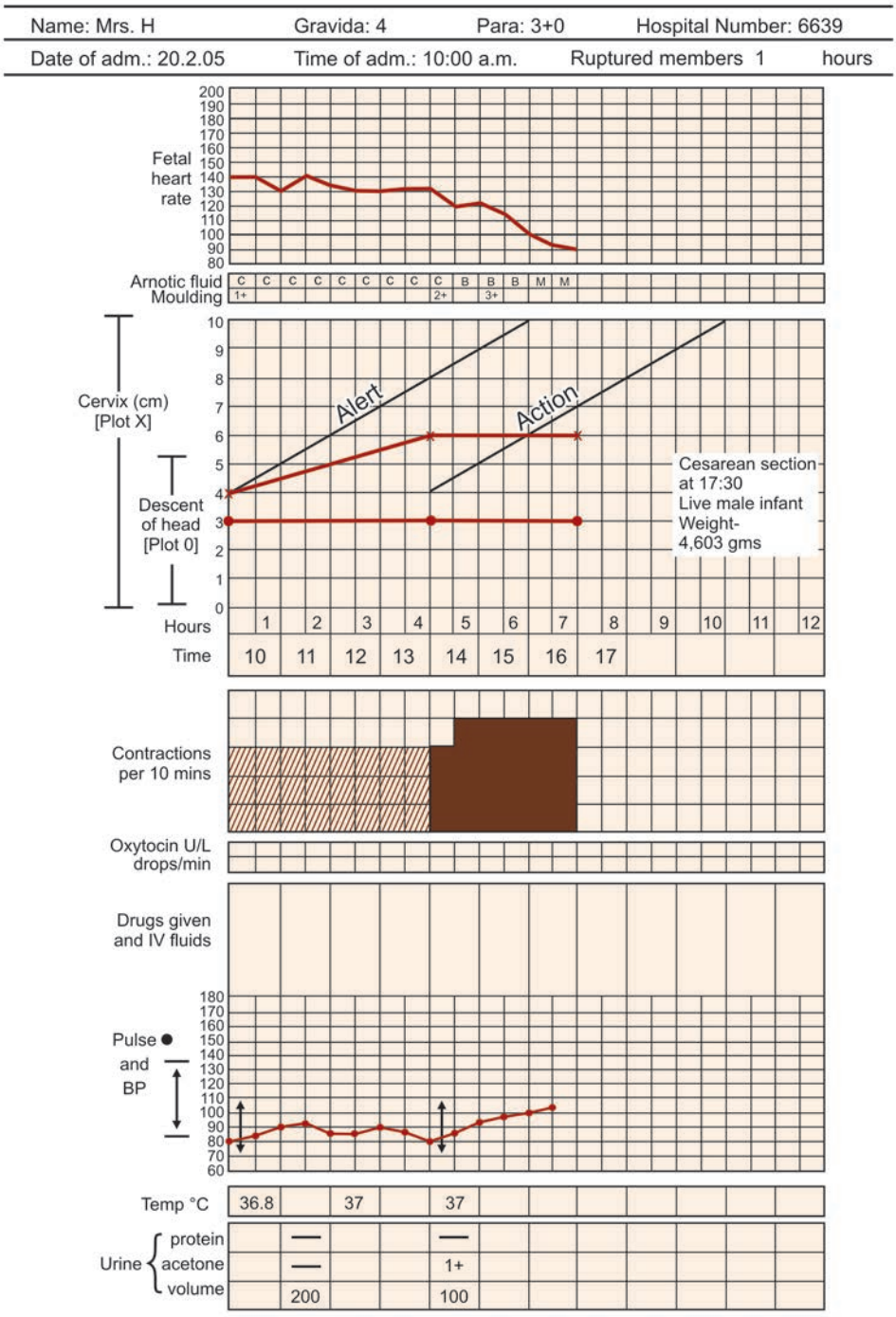


Fig. 7.1: Monitoring the progress of labor using a partogram

for vaginal delivery. Thus, it is the prime duty of the obstetrician to remain vigilant and at the earliest detect the signs related to impending scar rupture. Symptoms of impending scar rupture during the labor include the following:

- Dull suprapubic pain or severe abdominal pain, especially if persisting in between the uterine contractions.
- Slight vaginal bleeding or hematuria.
- Bladder tenesmus or frequent desire to pass urine.
- Unexplained maternal tachycardia.
- Maternal hypotension.
- Abnormal fetal heart rate pattern.
- Scar tenderness.
- Chest pain or shoulder tip pain, or sudden onset of shortness of breath.

Table 7.4: Advantages of cesarean delivery

Reduced incidence of perineal pain
Reduced incidence of urinary incontinence
Reduced incidence of uterovaginal prolapse

On vaginal examination, there may be a failure of normal descent of the presenting part and the presenting part may remain high up. There also may be a sudden loss of station of the presenting part.

None of the above mentioned signs and symptoms are definite proof of the impending scar rupture. However presence of any of these symptoms must raise caution in the clinician's mind and he/she must become more vigilant.

ELECTIVE REPEAT CESAREAN SECTION

For the physician, ERCS may offer a few advantages including convenience, saving of time, increased monetary compensation and reduced fear of legal litigation in case of complications with VBAC. Though, cesarean section is safe, it is a major surgical intervention and would be therefore associated with some complications in comparison to normal vaginal delivery. The clinician must counsel the women regarding increased risks of complications like cardiac arrests, thromboembolism and major infections in comparison to those who deliver vaginally. However, the cesarean delivery does provide a few advantages in comparison to the normal vaginal delivery, some of which are listed in table 7.4.

However, cesarean section has been found to have no effect on the incidence of complications like hemorrhage, infection, genital tract injury, fecal incontinence, back pain, dyspareunia, postnatal depression, neonatal mortality rate, intracranial hemorrhage, brachial plexus injuries, cerebral palsy, etc.

Disadvantages of Cesarean Delivery

Cesarean delivery is associated with an increased risk of complications, enumerated in table 7.5.

Table 7.5: Complications associated with cesarean delivery

Abdominal pain
Injury to bladder, ureters, etc
Increased risk of rupture uterus and maternal death
Neonatal respiratory morbidity
Hysterectomy
Thromboembolic disease
Increased duration of hospital stay
Antepartum or intrapartum intrauterine deaths in future pregnancies
Patients with a previous history of cesarean delivery are more prone to develop complications like placenta previa and adherent placenta during future pregnancies.

Timing for Cesarean Delivery

In case of previous history of classical scar, the woman must preferably be hospitalized at 36 weeks and posted for an elective cesarean section at 38 weeks. In patients with previous history of lower segment uterine scar, the planned surgery should be preferably done after 39 weeks. This is so as the risk of respiratory morbidity considerably increases in babies born by cesarean section before 39 weeks of gestation. If the obstetrician is unsure about the exact period of gestation, it is best to wait for the onset of the uterine contractions or the rupture of membranes, which ever occurs earlier. However an emergency cesarean section may be required any time in cases of suspected or confirmed acute fetal compromise. In these cases, delivery should be accomplished as soon as possible, preferably within 30 minutes of the diagnosis of fetal distress.

Preparations for an Elective Cesarean Section

- Since cesarean delivery is associated with the risk of blood loss, women posted for ERCS must be offered hemoglobin assessment before the surgery to identify those who have anemia.
- Although blood loss of more than 1000 ml infrequently occurs after cesarean delivery, it may commonly occur in women having cesarean delivery for antepartum hemorrhage (both abruption and placenta previa) and uterine rupture. In such cases, the clinician should be prepared in anticipation of massive blood loss occurring at the time of surgery and should make arrangements for blood transfusion services, well in advance.
- Prophylactic single dose antibiotics in form of first generation cephalosporin or ampicillin should be prescribed.
- The risk for thromboembolism in these patients must be assessed as they may be confined to bed for long periods of time. Thromboprophylaxis in form of graduated stockings, hydration, early mobilization and low molecular weight heparin must be prescribed.
- Administration of anesthesia in woman with full stomach is associated with the risk of aspiration pneumonitis. While the risk for aspiration pnemonitis is minimal in cases of ERCS, in which the patient is usually kept on an overnight fast, this may not be the scenario with emergency cesarean delivery, where the patient may be full stomach. In these cases, in order to reduce the risk of aspiration pneumonitis, the patient must be administered premedication with an antacid (sodium citrate 0.3%, 30 mL, or magnesium

trisilicate 300 mg), H_2 receptor antagonists and/or proton pump inhibitors and antiemetics, all administered intravenously one hour before the surgery.

- A urinary catheter must be inserted in situ before the surgery in cases where regional anesthesia is planned, because anesthetic block may interfere with normal bladder function resulting in over-distension of the bladder. If bladder has not been previously catheterized, in all cases of cesarean section, bladder should be catheterized as a routine before the surgery in order to prevent inadvertent injuries to the bladder at the time of surgery.

Surgery for Cesarean Section

Anesthesia

Women who are having a cesarean delivery must preferably be offered regional anesthesia because it is safer and results in lower maternal and neonatal morbidity in comparison to general anesthesia. Women who are having a CS under regional anesthesia should be offered intravenous ephedrine or phenylephrine, and volume preloading with crystalloids or colloids to reduce the risk of hypotension occurring at the time of surgery.

Preparation of the skin

- The area around the proposed incision site must be washed with antiseptic soap solution (e.g. savlon) and water.
- The woman's pubic hair must not be shaved as this may increase the risk of wound infection. The hair may be trimmed, if necessary.
- Routine cleaning of the patient's skin at the site of surgery must be done with antiseptic solution (e.g. betadine) before surgery. Antiseptic skin cleansing before surgery is thought to reduce the risk of post-operative wound infections. The antiseptic solution must be applied three times to the incision site using a high-level disinfected ring forceps and cotton or gauze swab. The surgeon must begin at the proposed incision site and move outwards in a circular motion away from the site of incision site. In the end, the inner aspects of thighs and umbilicus must be swabbed.
- After reaching the edge of the sterile field, the previous swab must be discarded and new swab must be used.
- The surgeon must keep his/her arms and elbows high and surgical gown away from the surgical field.
- The woman must be draped immediately after the area of surgery has been adequately prepared, in order to avoid contamination.
- If the drape has a window, it should be placed directly over the incision site.

Type of Abdominal Skin Incision (Figure 7.2)

A vertical or transverse incision can be given over the skin. The vertical skin incision can be either in the midline or paramedian location, extending just above the pubic symphysis to just below the umbilicus. Previously vertical skin incision at the time of cesarean section was favored as it was supposed to provide far more superior access to the surgical field in comparison to the transverse incision. Also, the vertical incision showed potential for extension at the time of surgery. However, it was associated with poor cosmetic results, an increased risk of wound dehiscence and hernia formation. Therefore, now-a-days, transverse incision is mainly favored due to better cosmetic effect, reduced post-operative pain and improved patient recovery. Two types of transverse incisions are mainly used while performing cesarean section: The sharp (Pfannenstiel) type and the blunt (Joel Cohen) type.

Sharp Pfannenstiel transverse incision

In this type, a slightly curved, transverse skin incision, passing through the external sheath of the recti muscles is given,

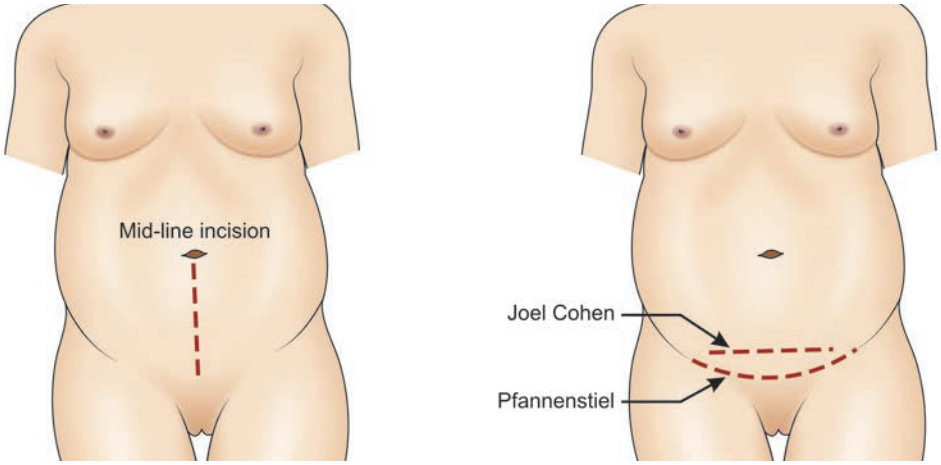


Fig. 7.2: Type of abdominal skin incision

about an inch above the pubic symphysis. The subsequent tissue layers are opened by using a sharp scalpel.

Joel Cohen blunt incision

In this type, a straight skin incision about three cm in size is given above the pubic symphysis and the subsequent tissue layers are opened bluntly, without using a sharp scalpel.

The initial cut is given only through the cutis. In the midline, which is free from large blood vessels, the cut is deepened to meet the fascia. A small transverse opening is made in the fascia with the scissors. The rest of the fascia is then opened transversely by pushing the slightly open tip of a pair of straight scissors, first in one direction and then in the other. The fascia is stretched caudally and cranially using the index fingers to make room for the next step. The muscle and fat tissue is separated by applying manual bilateral skin traction using the index and middle fingers of both the surgeon and his assistant. The use of surgical knife must be avoided as far as possible and if required the scissors can be used instead.

Sharp (Pfannenstiel) vs. Blunt (Joel Cohen)

Presently the use of Joel Cohen incision in preference to the sharp Pfannenstiel incision is associated with much controversy. The Joel Cohen method of opening the abdomen at cesarean delivery is supposed to be associated with shorter operative time, minimum tissue damage, minimal use of instruments, reduced pain, lower analgesic requirements; reduced blood loss and overall reduced rates of febrile morbidity in comparison to the Pfannenstiel incision. However, many other studies have shown absence of clear benefits to the mother and the fetus as a result of Joel Cohen incision. Therefore, presently there is no indication favoring the use of Joel Cohen incision.

Excision of previous scar

Excision of the existing previous scar must always be performed at the beginning of surgery by either giving an elliptical incision incorporating the scar or giving an incision over the previous scar, with the trimming of the fibrosed edges of the wound. Excision of the previous scar is usually difficult at the end of the surgery, but must be done if it has not been done previously.

Types of Uterine Incision

Lower segment uterine scar or the upper segment uterine scar

While in the past a vertical incision (classical) was commonly used, this was associated with high risk of scar rupture during future pregnancies. As a result, lower segment transverse scars are nowadays preferred. The lower segment uterine scar is considered to be more sound than the upper segment due to the following reasons:

- The lower uterine segment is thinned out at the time of labor. As a result, the thin margins of the lower segment can be easily apposed at the time of uterine repair without leaving any pocket. In case of the classical scar, it may be difficult to oppose the thick muscle layer of the upper segment. Blood filled pockets may be formed. This may be later replaced by fibrous tissues resulting in the weakening of the scar.
- The lower segment usually remains inert in the postpartum period. On the other hand, the upper segment undergoes rapid contractions and retractions resulting in the loosening of the uterine sutures. This can result in imperfect healing and further weakening of the uterine scar.
- When the uterus stretches in the future pregnancy, the stretch is along the line of the scar in the case of the lower segment scar, whereas in cases of vertical scar, the uterus stretches in the direction perpendicular to the scar, thereby resulting in the scar weakness.
- Chances of the placental implantation in the area of the scar at the time of the future pregnancy are highly unlikely in the case of the lower segment scar. Where as in case of the classical scar the placental tissue is quite likely to implant in the area of the scar at the time of future pregnancy. Penetration and the invasion of the scar by the placental trophoblasts are likely to produce further weakening of the scar.

As a result of the above mentioned reasons, the lower segment scar is much stronger as compared to the upper segment scar and is unlikely to give way during subsequent pregnancies. Lower segment scar may rupture occasionally at the time of labor. On the other hand, upper segment scar is weak and may rupture both during the antenatal period and at the time of labor.

Indications for a classical cesarean section

Though nowadays classical incisions are rarely performed, they might be rarely done in cases where the lower segment is not easily accessible, e.g. bladder densely adherent to the lower segment; carcinoma cervix; presence of an uterine myoma in the lower uterine segment; transverse lie of the fetus, with the shoulder impacted in the birth canal; cases of placenta previa in which the placenta penetrates through the lower uterine segment (placenta percreta) etc.

Variations in lower segment incision

Presently, rather than performing a classical cesarean section, the clinicians prefer to use some kind of variations in the

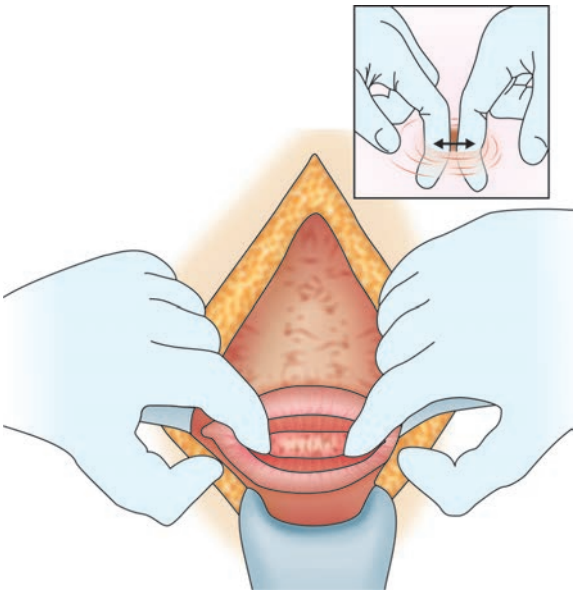


Fig. 7.3A: Extension of the uterine incision by manual stretching using the index fingers

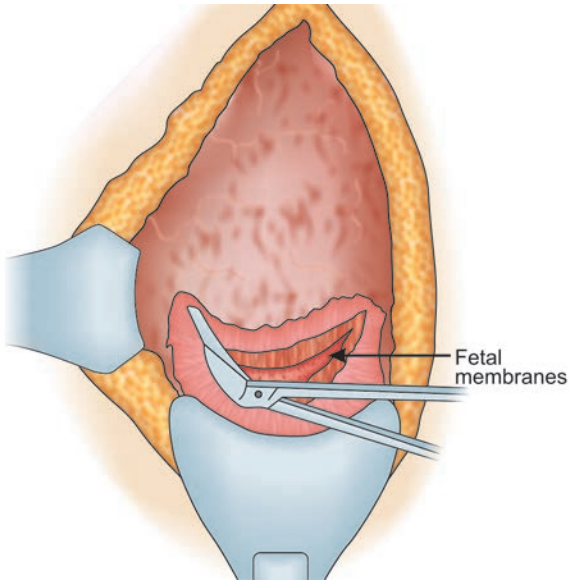


Fig. 7.3B: Extension of the uterine incision with help of scissors

lower segment uterine incision. Mostly, the surgeon is able to decide the exact incision only at the time of surgery.

Variations of the lower segment incision are commonly used in cases where there is requirement for an extended surgical field, in order to avoid scar extension e.g. transverse lie with hand prolapse and large baby, etc. Some of the variations include the following:

An inverted "T"-shaped incision: This incision involves cutting upwards from the middle of the transverse incision.

"J" shaped or hockey-stick incision: It involves extension of one end of the transverse incision upwards.

"U"- shaped or trap-door incision: This incision involves extension of both ends of the transverse scar upwards.

Of all these various choices, the "T" shaped scar is the worst choice due to its difficult repair, poor healing and chances of scar rupture during subsequent pregnancies.

Blunt vs. sharp uterine incision

While making an incision in the uterus, a curvilinear mark of about 10 cm length is made by the scalpel, cutting partially through the myometrium. A short (3cm) cut using the scalpel is made in the middle of this incision mark, reaching up to but not through the membranes. The rest of the incision can be completed either by stretching the incision using the two index fingers along both the sides of the incision mark (figure 7.3A) or using bandage scissors, to extend the incision on two sides (figure 7.3B). The bandage scissor is introduced into the uterus over the two fingers in order to protect the fetus. National Collaborating Center for Women's and Children's Health (NCCWCH, 2004) recommends that blunt rather than sharp extension of the uterine incision should be used because it is supposed to reduce amount of blood loss, incidence of postpartum hemorrhage and the requirement for transfusion at the time of cesarean section. If the lower uterine segment is very thin, injury to the fetus can be avoided by using the handle of the scalpel or a hemostat (an artery forceps) to open the uterus. Delivery of the fetal head should be in the same way as during the normal vaginal delivery. There is no need for routine use of forceps in order to deliver fetal head. Forceps should only be used at cesarean only if there is difficulty while delivering the baby's head.

Placental removal

At the time of cesarean, the placenta should be removed using controlled cord traction (figure 7.4) and not manual removal as this reduces the risk of endometritis.

Closure of the Uterine Incision

Single layered or double layered closure of uterine incision

Both single layered and double layered closure of uterine incision are being currently practiced. Though single layered closure is associated with reduced operative time and reduced blood loss in the short term, the risk of the uterine rupture during subsequent pregnancies is increased. The current recommendation by National Collaborating Center for Women's and Children's Health (NCCWCH, 2004) is to close the uterus in two layers as the safety and efficacy of closing uterus in a single layer is presently uncertain.

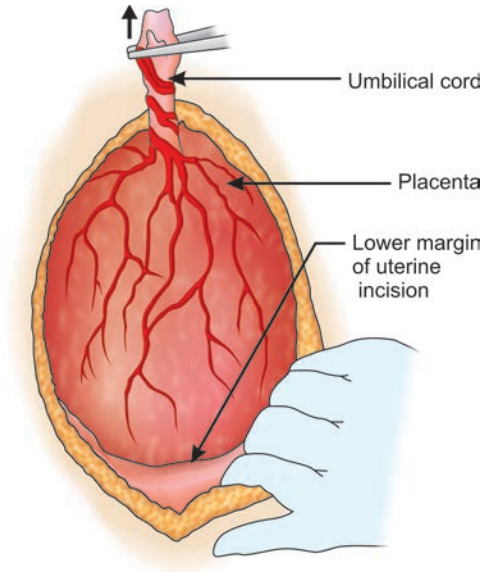


Fig. 7.4: Placental removal

Peritoneal Closure

The current recommendation by RCOG is that neither the visceral nor the parietal peritoneum should be sutured at the time of cesarean section as this reduces the operative time and the requirement for the postoperative analgesia.

Closure of Subcutaneous Space

There is no need for the routine closure of the subcutaneous tissue space, unless there is more than 2 cm of subcutaneous fat because this practice has not been shown to reduce the incidence of the wound infection.

Skin Closure

Obstetricians should be aware that presently the differences between the use of different suture materials or methods of skin closure at the time of cesarean section are not certain.

Prophylactic Antibiotics with Cesarean Section

A single dose intravenously of prophylactic antibiotics in the dose of ampicillin 2 g IV or cefazolin 1 g IV after the cord is clamped and cut helps in providing adequate prophylaxis. No additional benefit has been demonstrated with the use of multiple dose regimens. If the women shows signs of infection, e.g. fever, urinary tract infections, sepsis, etc, antibiotics must be continued until the woman becomes fever free for at least 48 hours.

Use of Uterotonics

Oxytocin 5 IU by slow intravenous injection should be used at the time of cesarean section in order to encourage uterine contractions and to reduce blood loss.

Table 7.6: Summary of the essential steps in a cesarean delivery

Use of a transverse lower abdominal incision (Joel Cohen incision)
Use of blunt extension of the uterine incision
Manual removal of the placenta at the time of cesarean delivery must not be done
Controlled cord traction for removal of the placenta must be done
Routine use of forceps to deliver baby's head must not be employed
The uterine incision must be closed with two suture layers
Neither the visceral nor the parietal peritoneum needs to be sutured
Routine closure of subcutaneous space is not required unless the thickness of fat > 2 cm
Regular use of superficial wound drains is not required
Early skin-to-skin contact between the mother and baby must be encouraged

The various essential steps to be undertaken at the time of cesarean delivery are summarized in table 7.6.

Immediate Postoperative Care

- After surgery is completed, the woman needs to be monitored in a recovery area.
- Monitoring of routine vital signs (blood pressure, temperature, breathing), urine output, vaginal bleeding and uterine tonicity (to check if the uterus remains adequately contracted), needs to be done at hourly intervals for the first four hours. Thereafter the monitoring needs to be done at every four hourly intervals for the first post-operative day at least. Adequate analgesia needs to be provided, initially through the IV line and later with oral medications.
- When the effects of anesthesia have worn off, about four to eight hours after surgery, the woman may be transferred to the postpartum room.

Pain management after CS

Adequate post-operative pain control is important. A woman who is in severe pain may not recover well. However excessive use of sedative drugs must be avoided as this may limit the patient's mobility, which is important to prevent thromboembolism. Patient-controlled analgesia using opioid analgesics should be offered after cesarean section as it is associated with higher rates of patient satisfaction. Women could be offered diamorphine (0.3–0.4 mg intrathecally) for intra and post-operative analgesia. Nonsteroidal antiinflammatory drugs may be used post-operatively as an adjunct to other analgesics, because they help in reducing the requirement for opioids. Adding acetaminophen also increases the effects of the other medications with very little additional adverse risk. Analgesic rectal suppositories can also be used for providing relief from pain in women following cesarean section.

Fluids and oral food after cesarean section

As a general rule, about 3 liters of fluids must be replaced by intravenous infusion during the first post-operative day, provided that the woman's urine output remains greater than 30 ml/ hour. If the urine output falls below 30 ml/hour the woman needs to be reassessed to evaluate the cause of oliguria. In uncomplicated cases, the urinary catheter can be removed by 12 hours post-operatively. IV fluids may need to be continued, until she starts taking liquids orally. The clinician needs to remember that prolonged infusion of IV fluids can alter electrolyte balance. If the woman receives IV fluids for more than 48 hours, her electrolyte levels need to be monitored every 48 hour. Balanced electrolyte solution (e.g. potassium chloride 1.5 g in 1 L IV fluids) may be administered.

If the surgery was uncomplicated, the woman may be given a light liquid diet in the evening after the surgery. If there were signs of infection, or if the cesarean section was for obstructed labor or uterine rupture, bowel sounds must be heard before prescribing oral liquids to the patient. In these cases, the woman can be given solid food when she starts passing gas. Women who are recovering well and who do not have complications after the surgery can be advised to eat and drink whenever they feel hungry or thirsty. The clinician must ensure the woman is eating a regular diet before she is discharged from the hospital.

Ambulation after cesarean section

The women must be encouraged to ambulate as soon as 6–8 hours following the surgery. In case she finds it difficult to get up from the bed and walk, she can be asked to remain in bed and do simple limb exercises (e.g. leg elevation, foot dorsiflexion and planter flexion, etc) and breathing exercises on the bed itself. Early ambulation enhances circulation, encourages early return of normal gastrointestinal function and facilitates general wellbeing. Even in cases where complications were encountered at the time of surgery, mobilization must be preferably begun within 24 hours after the surgery.

Dressing and wound care

- The dressing must be kept on the wound for the first day after surgery so as to provide a protective barrier against infection. Thereafter, dressing is usually not required.
- If blood or fluid is observed to be leaking through the initial dressing, the dressing must not be changed. The amount of blood/fluid lost must be monitored.
- If bleeding increases or the blood stain covers half the dressing or more, the dressing must be removed and replaced with ano- ther sterile dressing. The dressing must be changed while using a sterile technique. The surgical wound also needs to be carefully inspected.

Length of hospital stay

- Length of hospital stay is likely to be longer after a CS (an average of 3–4 days) in comparison to that after a vaginal birth (average 1–2 days). However, women who are recovering well and have not developed complications following cesarean may be offered early discharge.

The Hemostatic Cesarean Section

This is a new surgical technique used for managing pregnant women infected with HIV-1.

The surgeon must adorn double gloves while performing cesarean section in women who are HIV-positive. Hemostatic cesarean section is a type of elective cesarean section with technical modifications, which is used in all patients receiving antiretroviral treatment and in whom breast feeding has been prohibited. The patient is scheduled for surgery at 38 weeks of gestation, while the patient is not in labor and membranes are intact. The technique involves management of lower uterine segment while maintaining the integrity of membranes. This helps in avoiding massive contact between maternal blood and the fetus. Thus, this technique helps in reducing the rate of vertical transmission to less than 2%.

Complications

Uterine Rupture

Approximately 15% of all deliveries in the United State occur in women with previous cesarean sections. In a patient with a previous cesarean section, vaginal delivery may cause the previous uterine scar to separate. Disintegration of the scar, also known as scar rupture is one of the most disastrous complications associated with VBAC. The reported incidence of scar rupture for all pregnancies is 0.05%. Risk of scar rupture after vaginal delivery following one previous lower transverse segment cesarean section on an average is estimated to be about 0.8% – 1%. However the exact risk of scar rupture depends upon the type of uterine incision given at the time of previous cesarean (table 7.7). The weakest type of scar that may give way at the time of VBAC is the previous classical incision in the upper segment of the uterus, which

Table 7.7: Risk of scar rupture based on the type of uterine scar given at the time of previous cesarean delivery

Type of previous cesarean scar	*Estimated risk of rupture*
Classical cesarean	4–9%
T-shaped incision	4–9%
Low vertical	1–7%
Low-transverse incision	0.8–1%

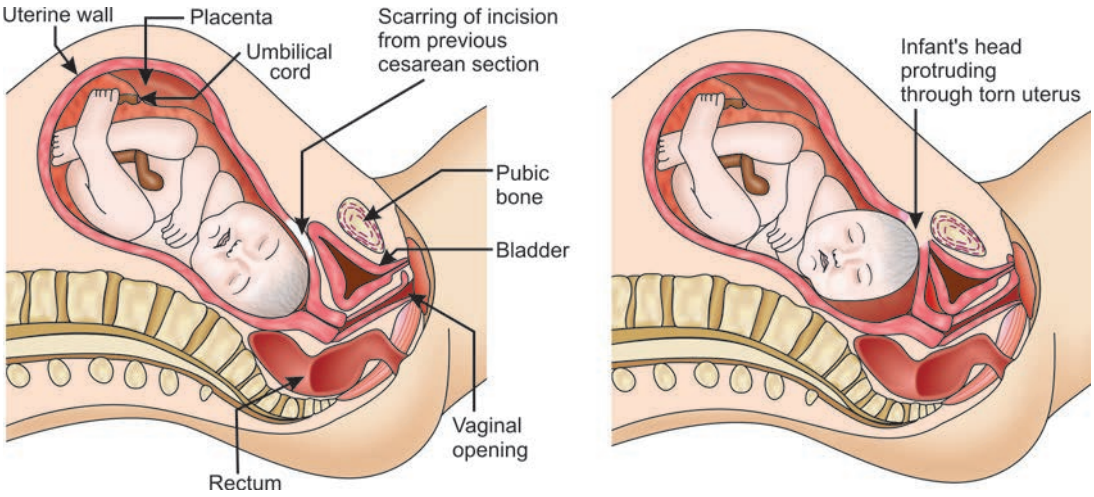


Fig. 7.5A: Attempted VBAC associated with subsequent rupture of previous lower segment uterine scar

is associated with almost 10% risk of development of scar rupture. Uterine rupture can result in complete extrusion of the fetus into the maternal abdominal cavity. In other cases, rupture is associated with fetal distress or severe hemorrhage from the rupture site. Though uterine rupture is often associated with fetal bradycardia, there is no one specific FHR pattern, which indicates the onset of uterine rupture. Variable and/or late decelerations often occur before the onset of fetal bradycardia. Another important clinical finding which is indicative of uterine rupture is the onset of unexpected antepartum or postpartum hemorrhage.

Types of uterine rupture

Uterine rupture is defined as a disruption of the uterine muscle extending to and involving the uterine serosa. At times, there may be disruption of the uterine muscle with extension to the bladder or broad ligament. The uterine rupture can be of two types: Complete rupture and Incomplete rupture.

Complete rupture

Complete rupture describes a full-thickness defect of the uterine wall and serosa resulting in direct communication between the uterine cavity and the peritoneal cavity (figures 7.5A and B).

Incomplete rupture

Incomplete rupture describes a defect of the uterine wall that is contained by the visceral peritoneum or broad ligament. Incomplete rupture is also known as uterine dehiscence and describes partial separation of the scar in association with minimal bleeding, with the peritoneum and fetal membranes remaining intact.

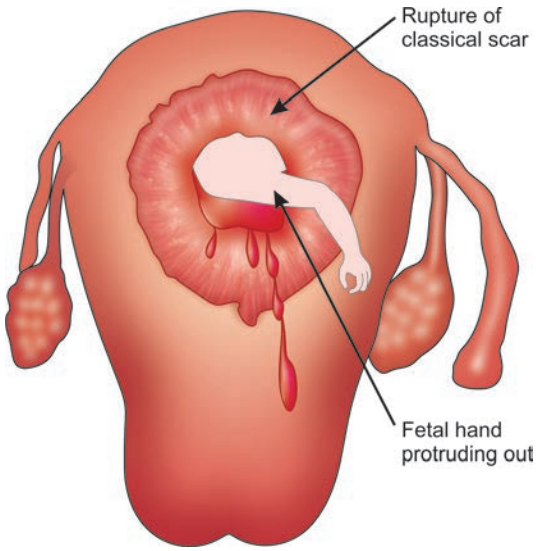


Fig. 7.5B: Rupture of a previous classical uterine scar

The identification or suspicion of uterine rupture is a medical emergency and must be followed by an immediate and urgent response from the obstetrician. An emergency laparotomy is usually required to save the patient's life.

Complete uterine rupture is very unlikely today. A complete rupture occurs in much less than 1% of women attempting VBAC. Incomplete rupture occurs in about 1% to 2% of the time. There is no clear cut predictive indicator for rupture uterus. However several factors which are indicative of a weak scar are mentioned in table 7.8.

Management of rupture uterus

When uterine rupture is diagnosed or strongly suspected, surgery is necessary. While in the previous days, most cases of

Table 7.8: Causes of a weak scar
Improper hemostasis at the time of surgery
Imperfect co-aptation of uterine margins at the time of surgery
Extension of the angles of the uterine incision
Infection during healing
Placental implantation at the site of incision
Overdistension of the uterus

Table 7.9: Steps to be taken to reduce the amount of PPH
Aortic compression can be applied to decrease bleeding
Administration of oxytocics (oxytocin, ergot alkaloids, carboprost, misoprostol, etc)
Surgical options like ligation of the hypogastric artery, uterine artery, or ovarian arteries.

uterine rupture were managed with hysterectomy, nowadays most cases are managed by controlling the bleeding surgically and repairing the defect.

A decision must be made regarding whether to perform hysterectomy or to repair the rupture site. If future fertility is desirable and the rent in the uterus appears to be repairable (straight-cut scar, rupture in the body of uterus; pelvic blood vessels are intact), repair of the rupture site must be performed. If future fertility is not desirable or the uterine rent appears to be unrepairable (multiple rents, with ragged margins, injury to the iliac vessels etc), hysterectomy should be performed. Typically, longitudinal tears, especially those in a lateral position, should be treated by hysterectomy, whereas low transverse tears may be repaired. A lower segment lateral rupture can cause transection of the uterine vessels. Therefore the obstetrician must make special efforts to localize the site of bleeding, before placing clamps at the time of hysterectomy in order to avoid injury to the ureter and iliac vessels. Bladder rupture must also be ruled out at the time of laparotomy by clearly mobilizing and inspecting the bladder to ensure that it is intact.

Though steps must be taken to resuscitate the patient, surgery should not be delayed owing to hypovolemic shock because it may not be easily reversible until the hemorrhage from uterine rupture is controlled. Uterine rupture may be associated with massive postpartum hemorrhage. Therefore upon laparotomy, steps mentioned in table 7.9 can be taken to reduce the amount of bleeding.

Due to the risk of rupture recurrence in a subsequent pregnancy, women with previously-repaired uterine ruptures are advised not to attempt labor in the future. Ideally, a repeat cesarean section should be performed prior to the onset of uterine contractions.

Assessment of scar integrity

In order to identify the previous cesarean scars which are likely to give way during VBAC, the following investigations can be done:

- *Hysterogram:* Radiographic imaging of the uterus which shows uterine defect in the lateral view.
- *Ultrasound imaging*: Ultrasound examination for visualization of scar defects and measurement of scar thickness.
- *Manual exploration*: Manual exploration of placenta to check scar integrity is especially useful in case of continuing postpartum hemorrhage and in case of other third stage problems.

Ultrasound Imaging for Visualization of Scar Defects and Measurement Scar Thickness

Ultrasound measurement of scar at 37 weeks of gestation is based on the fact that the risk of a defective scar is directly related to the degree of thinning of the lower uterine segment at around 37 weeks of pregnancy. According to the largest study by Rozenberg et al (1997), cut-off value of 3.5 mm on ultrasound measurement of scar thickness at 36 weeks was observed to show negative predictive value of 99.3% for scar rupture. The high negative predictive value of this method may encourage the obstetricians to offer a trial of labor to patients with a thickness value of 3.5 mm or greater. Different studies show different cut-off values for estimating the strength of the scar. Therefore, presently there is no clear cut value of scar thickness to indicate the strength of the scar. According to the latest study by Bujold et al (2009), done in Quebec, a cut-off of 2.3 mm helped in determining the women at high risk of scar rupture. However this study has yet not even been published yet, therefore it is difficult to evaluate the results. The first major problem with the use of ultrasound for measurement of scar thickness is the issue of interobserver variation. TVS seems to be more accurate than TAS, yet it is not commonly used.

Infection

Infection is a complication which can commonly develop after cesarean section. Endometritis or infection of the endometrial cavity must be suspected, if there is excessive vaginal bleeding/discharge following the surgery. Infection of the urinary tract can result in symptoms like dysuria, increased urinary frequency, pyuria, etc.

Trauma to the Urinary Tract

This complication can occur during the cesarean surgery and if not appropriately handled can result in development of urinary tract fistula.

Thromboembolism

Thromboembolism must be suspected if the patient develops cough, swollen calf muscles or positive Homan's sign. A positive Homan's sign is associated with deep vein thrombosis and is said to be present when passive dorsiflexion of the ankle by the examiner elicits sharp pain in the patient's calf.

Important Questions and Answers

Q.1. What further important information must be obtained about the previous cesarean section in the above mentioned case study?

Ans. The exact indication for the cesarean section is usually available from the patient's previous hospital notes. This would help the clinician in finding out, what type of uterine incision was given previously i.e. whether it was a transverse lower segment incision or a vertical incision? The clinician can also find out the exact reason for the previous surgery and if any complications were encountered during previous surgery. For e.g. if a T-shaped extension of the lower uterine segment scar was done at time of previous surgery, the woman would be at a high risk of scar rupture during future pregnancy. Such a patient should be posted for ERCS at the time of future pregnancies.

Q.2. Why is it important to obtain this additional information?

Ans. This extra information is very important as it would help in deciding the further course of management. Whether the patient with a history of previous cesarean section should be considered for VBAC or ERCS would largely be based on the type of previous cesarean section and its indication. If the patient had a cesarean section for a nonrecurring cause, if she had a transverse lower segment incision and if there is no indication to repeat the caesarean section in this pregnancy, then she may be allowed a trial of labor.

Q.3. What should be the management option in the above mentioned case?

Ans. The above mentioned cases had a previous cesarean section for breech presentation, which may or may not recur in this pregnancy. Also there is no obstetric indication for cesarean section during the present pregnancy. Such a patient may be considered for VBAC, provided that the patient has given informed consent for VBAC and other conditions mentioned in table 7.3 are fulfilled.

Q.4. What are the signs of impending scar rupture?

Ans. Signs of impending scar rupture are as follows:

- Pain over the scar
- Maternal tachycardia
- Fetal distress
- Poor progress of labor
- Vaginal bleeding

Q.5. What should be the maternal position during cesarean section?

Ans. All obstetric patients undergoing CS should be positioned with left lateral tilt to avoid aorto-caval compression. This can be accomplished by tilting the operating table to the left or placing a pillow or folded linen under the patient's right lower back.

Q.6. What should be the choice of anesthesia during the cesarean section?

Ans. The following types of anesthesia can be used:

- General anesthesia,
- Regional anesthesia (epidural block, spinal block).
- Infiltration of local anesthetic agents (used extremely rarely)

Regional anesthesia is regarded to be considerably safer than general anesthesia with respect to various complications resulting in maternal morbidity and mortality. Regional anesthesia is generally preferred because it allows the mother to remain awake, experience the baby's birth and to be able to have immediate contact with her infant following the birth.

Bibliography

1. Clark SL. Rupture of the scarred uterus. Obstet Gynecol Clin North Am. 1988;15(4):737-44.
2. Farmer RM, Kirschbaum T, Potter D, Strong TH, Medearis AL. Uterine rupture during trial of labor after previous cesarean section. Am J Obstet Gynecol. 1991;165(4 Pt 1):996-1001.
3. Franchi M, Ghezzi F, Raio L, Di Naro E, Miglierina M, Agosti M, Bolis P. Joel-Cohen or Pfannenstiel incision at cesarean delivery: does it make a difference? Acta Obstet Gynecol Scand. 2002;81(11):1040-6.
4. Khan KS, Rizvi A. The partograph in the management of labor following cesarean section. Int J Gynaecol Obstet. 1995;50(2): 151-7.
5. National Collaborating Centre for Women's and Children's Health guidelines. April 2004, RCOG Press: London.
6. Rozenberg P, Goffinet F, Phillippe HJ, Nisand I. Ultrasonographic measurement of lower uterine segment to assess risk of defects of scarred uterus. Lancet. 1996;347(8997):281-4.
7. The Royal College of Obstetricians and Gynecologists (2007). Birth after previous caesarean birth. Green top Guideline No 45.

Chapter

8

Hydatidiform Mole

Case Study

A 20-year-old primi patient presented with bleeding at nine weeks of gestation. She was diagnosed as a case of missed abortion after performing an ultrasound examination, following which a D&C was performed. However the patient continued to bleed even after the D&C. An ultrasound examination which was performed again was suggestive of hydatidiform mole. Serum and urine β hCG titers were performed and were found to be elevated. The case was diagnosed as molar pregnancy.

Introduction

Hydatidiform mole (H. mole) belongs to a spectrum of disease known as gestational trophoblastic disease (GTD), resulting from overproduction of the chorionic tissue, which is normally supposed to develop into the placenta. H. mole can be considered as a neoplasm of trophoblastic tissue and involves both syncitiotrophoblast and cytotrophoblast. Hydatidiform moles are nonviable and genetically abnormal conceptions, showing excessive expression of paternal genes. In this condition, the placental tissues develop into an abnormal mass. Often, there is no fetal mass at all; figures 8.1A and B shows gross clinical specimen of hyadatidiform mole. However sometimes, partial moles may show presence of fetal tissue. This disease can occur even during or after an intrauterine or ectopic pregnancy.

GTD represents a spectrum of premalignant and malignant diseases (table 8.1) including potentially benign entities

Table 8.1: Classification of gestational trophoblastic disease

Benign forms (90%)
Complete hydatidiform mole (CHM)
Partial hydatidiform mole (PHM)
Malignant forms (10%)
Invasive mole
Choriocarcinoma
Placental site trophoblastic tumor (PSTT)
Epithelioid trophoblastic tumor

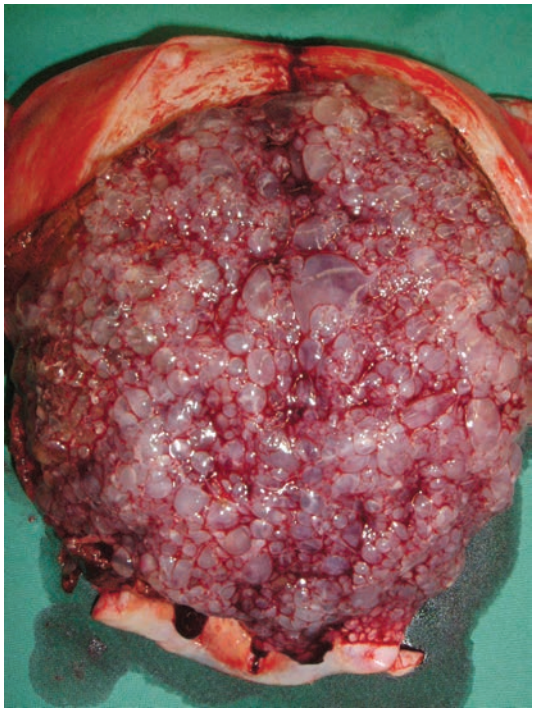


Fig. 8.1A: Clinical specimen of complete hydatidiform mole

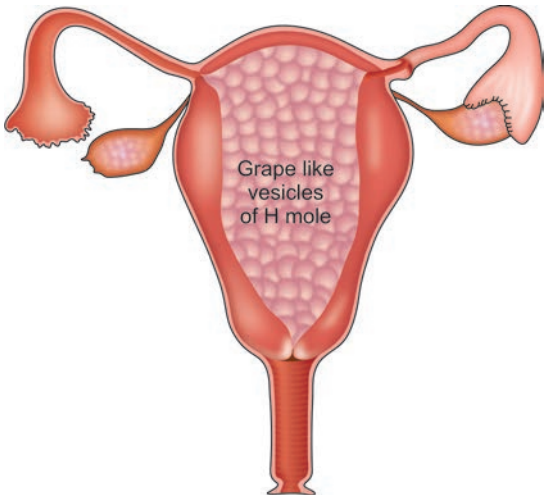


Fig. 8.1B: Grape like vesicles of hydatidiform mole

Table 8.2: Comparison between complete and partial mole

Parameter under consideration	*Complete mole*	*Partial mole*
Cytogenetic studies	46XX karyotype	Triploid karyotype 69XXY
Pathophysiology	Duplication of the haploid sperm following fertilisation of an "empty" ovum or dispermic fertilisation of an "empty" ovum	These contain two sets of paternal haploid genes and one set of maternal haploid genes. They usually occur following dispermic fertilisation of an ovum
Histopathological analysis	There is no evidence of fetal tissue.	There may be an evidence of fetal tissue or red blood vessels.
Invasive potential and propensity for malignant transformation	Persistent trophoblastic disease following uterine evacuation may develop in about 15% cases with a complete mole.	Persistent trophoblastic disease may develop in less than 5% of cases of partial mole.

like complete hydatidiform mole (CHM), and partial hydatidiform mole (PHM) and potentially malignant entities collectively known as gestational trophoblastic tumors (GTT). Gestational trophoblastic tumor includes conditions like invasive mole, choriocarcinoma and placental site trophoblastic tumor (PSTT). The difference between complete and partial hydatidiform mole is listed in table 8.2.

Pathophysiology of Complete and Partial Mole

Normal process of fertilization in which a sperm (containing 23 chromosomes) fertilizes an ovum (containing 23 chromosomes) resulting in formation of a diploid zygote (containing 46 chromosomes) is shown in figure 8.2A.

A hydatidiform mole is an abnormal pregnancy in which placental villi become edematous (hydropic) and start proliferating. During the formation of H. mole, firstly there is an edema of the whole central core, causing the villus to develop into a rounded cyst like structure filled with watery fluid. The entire embryonic chorionic tissue gets converted into grape like structures, in which each vesicle is connected to each other with help of fine stalk like structures.

Both complete and partial hydatidiform moles overexpress paternal genes. Complete hydatidiform moles are usually diploid, with all chromosomes being derived from the father by means of either monospermic or dispermic fertilization. Monospermic fertilization results from fertilization of a sperm with an anucleate oocyte (figure 8.2B). The genetic material is duplicated, resulting in a 46XX karyotype, because 46YY zygotes are incapable of developing independently. Rarely, complete hydatidiform mole can also be produced due to dispermic fertilization in which there is fertilization of two different sperms with an anucleate oocyte. Dispermic fertilization may result in either a 46XX or a 46XY karyotype. A 46XX karyotype is found in 90% of CHMs.

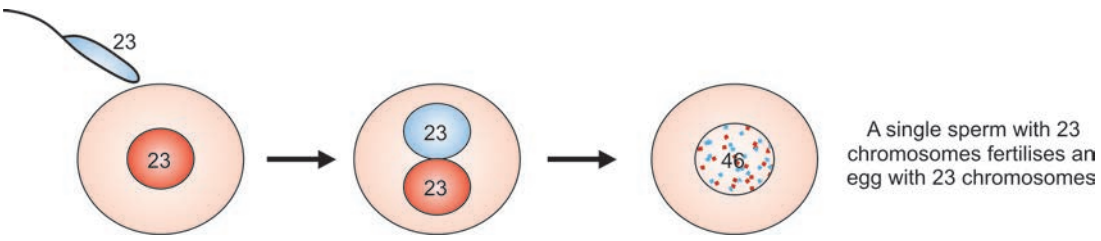


Fig. 8.2A: Normal process of fertilization

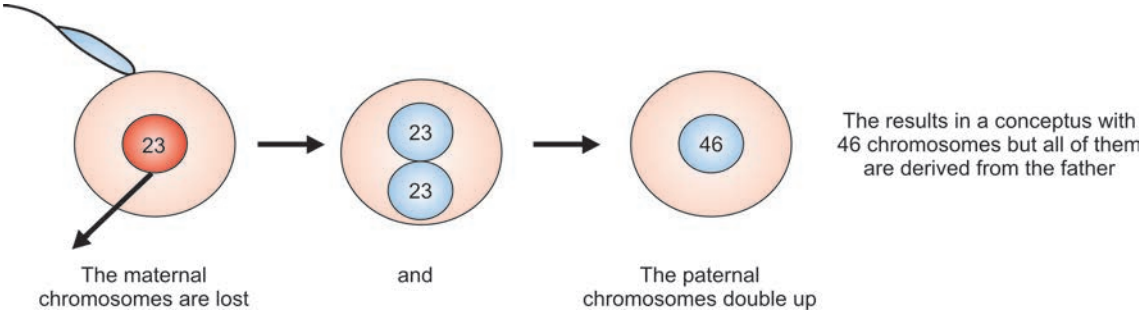


Fig. 8.2B: Complete hydatidiform mole

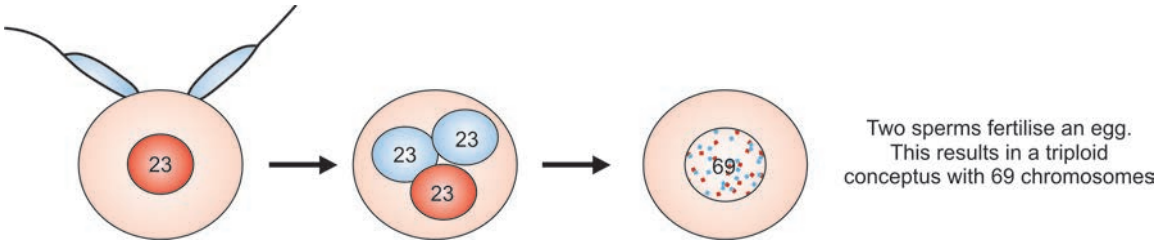


Fig. 8.2C: Partial hydatidiform mole

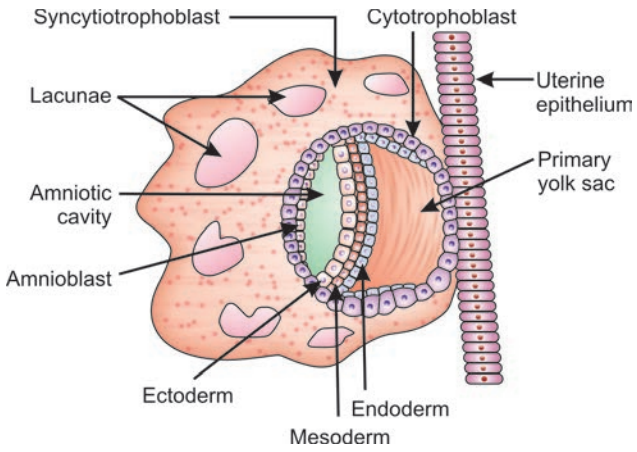


Fig. 8.3: Blastocyst and trophoblast at the time of implantation

Partial hydatidiform moles on the other hand are usually triploid, formed as a result of dispermic fertilization of two different sperms with an ovum (figure 8.2C). As a result, partial moles usually show a triploid karyotype having two sets of paternal chromosomes and one set of maternal chromosomes (69XXX, 69XXY or 69XYY). About 10% of PHMs have tetraploid or higher karyotypes consisting of multiple sets of paternal chromosomes combined with 1 set of maternal chromosomes.

Normal anatomy (figure 8.3)

As the blastocyst (early embryo) reaches 58-celled stage at about 4-5th day of fertilization, it gets transformed into two types of cells: Trophoectoderm which gives rise to trophoblast cells which serve as the precursor for placenta and an inner cell mass which forms the embryo proper. The early trophoblastic cells help in transferring nutrients between the maternal endometrium and the embryo. The trophoblast eventually develops into the functional part of the placenta and serves as a surface for the exchange of oxygen and nutrients. By the eight day following fertilization, the trophoblast gets divided into two layers: The syncitiotrophoblast and the cytotrophoblast (figure 8.3). Proliferation of syncitiotrophoblast accounts for the marked β hCG elevation seen in hydatidiform mole.

History

RISK FACTORS

Factors which may be associated with an increased risk for CHM and need to be elicited while taking history are described below:

Race and Ethnicity

Though the exact reasons are not known, Asian populations are affected more in comparison to other ethnic groups. In many Asian countries, the rates may be as high as 8–10 cases per 1,000 population. On the other hand, in the US, hydatidiform mole may occur in 1 per 1,000–2,000 pregnancies.

Maternal Age

Mothers in extremes of age groups, i.e. either too young (less than 20 years) or too old (older than 40 years) are usually affected. The risk of development of H. mole in women older than 40 years is about five times more than that in younger women.

Faulty Diet

Inadequate diet deficient in proteins, folic acid and vitamin A and containing excessive amounts of fats has also been found to be associated with H. mole. Therefore a detailed dietary history needs to be elicited in these patients. Since inadequate nutrition is often thought to be associated with pathogenesis of H. mole, intake of adequate nutrition and well balanced diet may reduce the risk of CHM.

On the other hand, partial mole is reported to be associated with the use of oral contraceptives, history of irregular menstruation and not with dietary factors.

Blood Group

H. mole has been typically found to be associated with individuals having AB blood group. On the other hand, a woman with blood group A, partnered with a man, also having blood A is at the lowest-risk.

CLINICAL PRESENTATION

- Initially, the symptoms may be suggestive of early pregnancy; however the uterus is often larger than the period of gestation. The fetal movements and heart tones are usually absent.
- There may be history suggestive of vaginal bleeding early in pregnancy. Vaginal bleeding is the most common clinical presentation of molar pregnancy.
- Passage of grape-like tissue is strongly suggestive of the diagnosis of H. mole.
- The second most common symptom of molar gestation is excessive uterine enlargement in relation to the gestational age.
- There may be excessive nausea and vomiting. Excessive nausea and vomiting in cases of H mole may be related to high serum levels of β hCG. Hyperemesis may commonly occur. Commonly the nausea and vomiting may be severe enough to require hospitalization.
- There may be symptoms suggestive of hyperthyroidism including tachycardia, restlessness, nervousness, heat intolerance, unexplained weight loss, diarrhea, tremors in hands, etc. Hyperthyoidism could be related to the production of TSH by the trophoblastic tissues or due to the similarity of alpha sub-units of hCG with that of TSH.
- H. mole may be associated with early appearance of preeclampsia (usually by the first or early 2nd trimester of pregnancy). This symptom is strongly suggestive of either H. mole or twin gestation, because occurrence of preeclampsia is extremely rare during this time period in normal pregnancies.
- Metastasis to the lungs (in cases of malignant moles) may result in symptoms like dyspnea, cough, hemoptysis, chest pain, etc.

General Physical Examination

Signs suggestive of preeclampsia: Signs including high blood pressure, proteinuria and swelling in ankles, feet and legs, may be observed.
Signs suggestive of hyperthyroidism: Signs including warm, moist skin, heat intolerance, restlessness, tremors in hands, etc, may be observed.
Signs suggestive of early pregnancy: These may include signs like amenorrhea, positive pregnancy test, etc.
Extreme pallor: The patient may appear extremely pale. The pallor may be disproportionate to the amount of blood loss due to concealed hemorrhage.

Specific Systemic Examination

ABDOMINAL EXAMINATION

On the abdominal examination the uterine size is usually abnormal in relation to the period of gestation. In most of the cases of CHM, the uterine size may be larger than the period of gestation where as in cases of partial mole the uterine size may be smaller in relation to the period of gestation. The uterus may appear doughy in consistency due to lack of fetal parts and amniotic fluid. Fetal movements and fetal heart sounds are absent. Fetal parts are usually not palpable. External ballottement is absent.

VAGINAL EXAMINATION

There may be some vaginal bleeding or passage of grape like vesicles. Internal ballottement cannot be elicited due to lack of fetus. Unilateral or bilateral enlargement of the ovaries in form of theca lutein cysts may be palpable.

Differential Diagnosis

Anembryonic Gestation

Anembryonic gestation, specifically the blighted ovum can present with clinical and sonographic findings similar to that of H. mole. Blighted ovum implies developmental arrest of the preembryonic cells or embryonic disk before the formation of a live embryo. As a result, the gestational sac is empty and does not contain the embryo. In most of the cases, blighted ova result from a chromosomal abnormality (trisomy 16 or 22). Although blighted ova may sonographically and pathologically mimic CHMs, they are genetically distinct from it. All blighted ova have maternal and paternal chromosomes, whereas all CHMs have only paternal chromosomes.

Threatened Abortion

H. mole may commonly mimic threatened abortion as both the conditions are associated with vaginal bleeding and similar sonographic findings.

Presence of Fibroid or an Ovarian Tumor with Pregnancy

These conditions are sometimes confused with H. mole as they may cause the uterine size to be larger in relation to the period of gestation.

Multiple Gestation

CHM may sometimes be confused with H. mole as both the conditions may be associated with early onset of preeclampsia before 20 weeks.

Management

The management plan for patients with H. mole is shown in flow chart 8.1.

Investigations

Complete Blood Count, Blood Grouping and Cross Matching

Determination of hematocrit and hemoglobin levels help in estimating the degree of anemia. Blood grouping and cross-matching is required as blood transfusion may be required in case of severe maternal anemia.

Serum β hCG Levels

β hCG levels in both serum and urine are raised. In cases of complete mole, β hCG levels may be more than 1,00,000 mIU/ml.

Ultrasound of the Pelvis

Sonography is the imaging investigation of choice to confirm the diagnosis of hydatidiform mole. Sonographic examination is not only helpful in establishing the initial diagnosis, it also helps in assessing the response to treatment regimes; determining the degree of invasion in malignant forms of GTN; determining the disease recurrence in malignant forms of GTN; and evaluation of liver metastasis.

Both transabdominal and transvaginal imaging must be performed using transducers with the highest ultrasound frequency possible. The specificity of ultrasound examination in the diagnosis of complete molar pregnancy may be increased if the sonographic findings are interpreted in correlation with the β hCG levels. While the sonographic picture of both H. mole and missed abortion may appear similar, a complete mole is usually associated with higher serum levels of β hCG in comparison with the cases of missed abortion.

Complete mole

On ultrasound examination, the following features are observed:

- Early complete molar pregnancies are commonly misdiagnosed as cases of missed miscarriage or anembryonic pregnancy (blighted ovum) on ultrasound examination. There may be presence of a gestational sac without an embryo. Additionally, second trimester CHM can be confused with retained products of conception. Therefore a high index of suspicion should be maintained for diagnosis of hydatidiform mole in the first trimester, even when it is not suspected on the basis of clinical findings.
- Characteristic vesicular pattern, also known as "snow storm appearance" may be present due to generalized swelling of the chorionic villi and presence of many small cystic spaces.
- The typical sonographic appearance of CHM in the second and third trimesters on modern ultrasound equipment is presence of an enlarged uterine endometrial cavity containing homogeneously hyperechoic endometrial mass with innumerable anechoic cysts sized 1–30 mm (figure 8.4).
- Ultrasound may also show the presence of theca lutein cysts in the ovaries (figures 8.5A and B). The presence of bilateral and/or large theca luteins usually occurs in association with high serum β hCG levels of greater than 1,00,000 mIU/mL. High circulating levels of β hCG associated with H. mole usually causes ovarian hyperstimulation resulting in formation of these cysts. In rare cases, theca lutein cysts may rupture, hemorrhage, or may even cause ovarian torsion. On sonograms, theca lutein cysts appear as large, septate, cystic ovarian lesions. They may be unilateral or bilateral and at times may be extremely large. If the lesions are large, tranasvaginal scanning may be of little use. In these cases, transabdominal scanning may be required for complete visualization of the enlarged

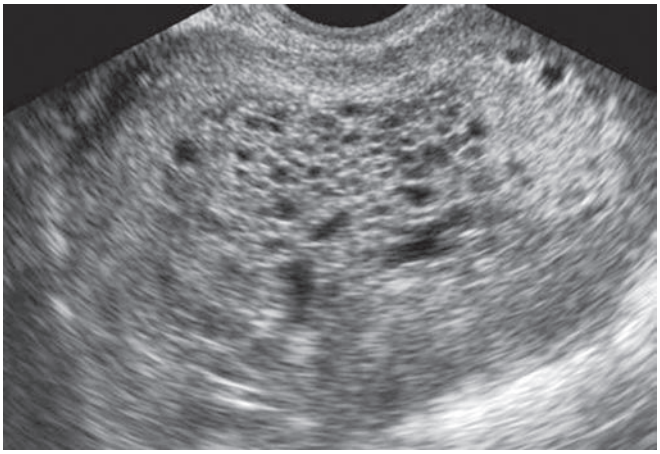
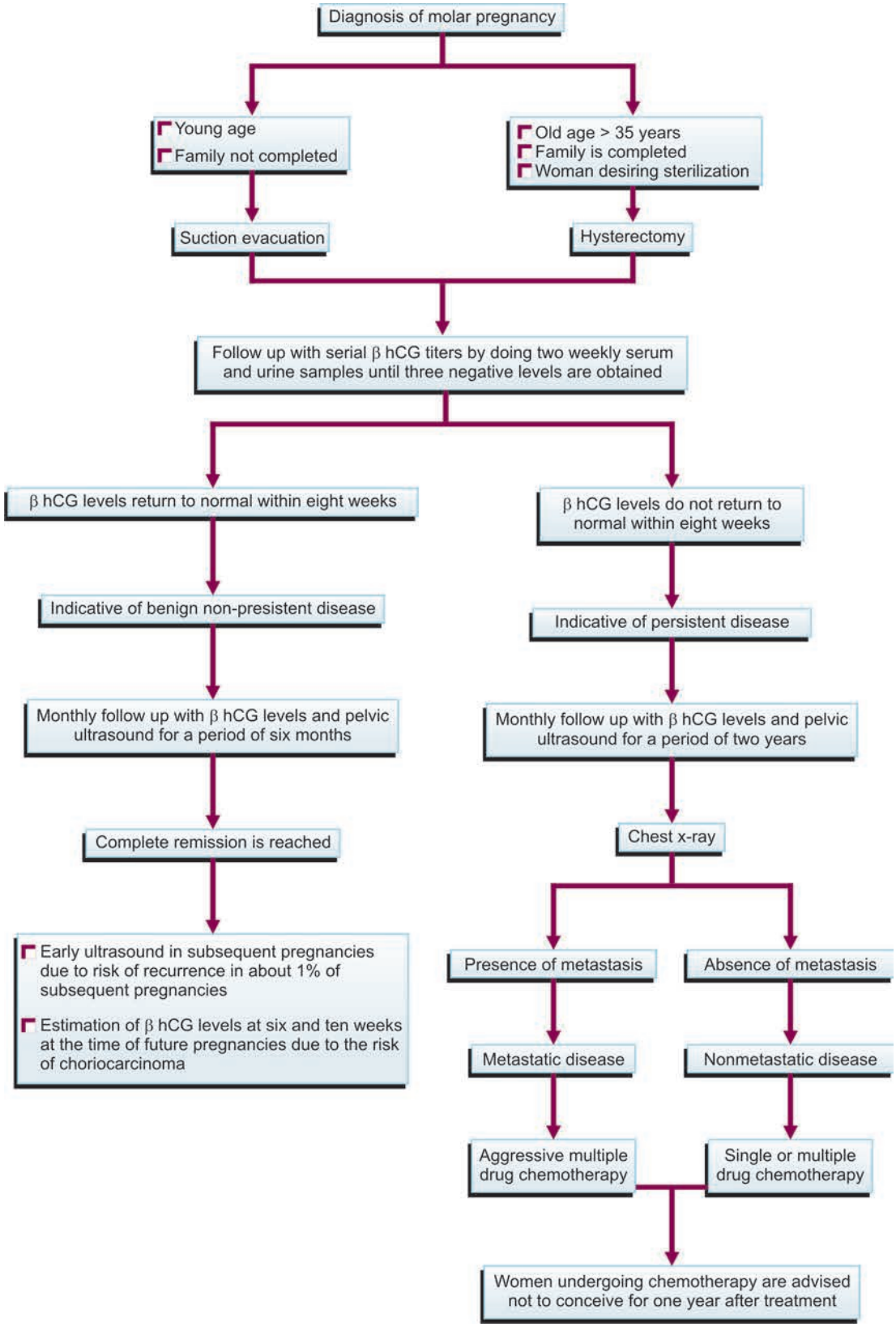


Fig. 8.4: Transvaginal sonogram of a second trimester complete hydatidiform mole (transverse section). There is presence of numerous anechoic cysts with intervening hyperechoic material

Flow chart 8.1: Management of molar pregnancy



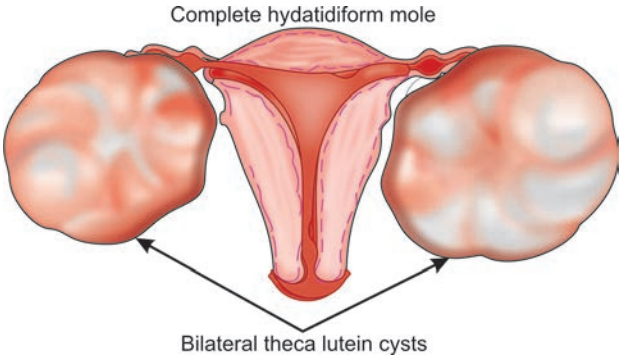


Fig. 8.5A: Diagrammatic representation of theca lutein cysts

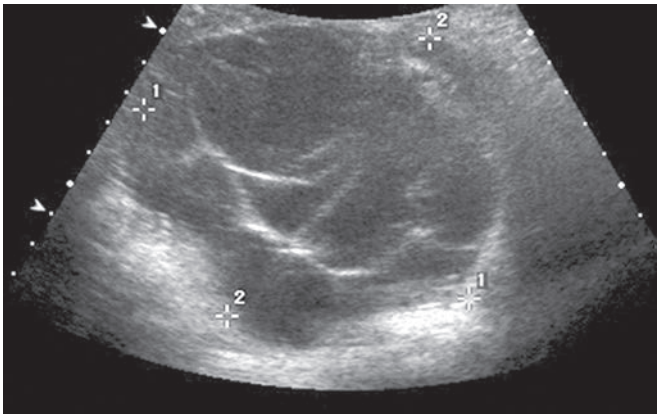


Fig. 8.5B: Transvaginal sonogram of left ovary (in the same case as fig 8.4) showing the presence of theca lutein cysts. Size of the enlarged left ovary is about 10.58 × 9.65 cm

ovaries. However before making the diagnosis of theca lutein cysts, the radiologist must exclude the possibility of a preexisting or concomitant cystic ovarian neoplasm. A repeat sonographic evaluation must be done following suction evacuation after serum β hCG levels have normalized. In most patients, theca lutein cysts regress within 8–12 weeks after the evacuation of hydatidiform mole.

Partial mole

- In cases of partial hydatidiform mole, the ultrasound findings include: A large placenta, cystic spaces within the placenta, an empty gestational sac, or the sac containing amorphous echoes or growth retarded fetus.
- Another sonographic finding which is significantly associated with the diagnosis of partial hydatidiform is the increase in ratio of transverse to anterior posterior dimension of the gestational sac to a value greater than 1.5.

Doppler Ultrasonography

Doppler ultrasound has no well defined role in the evaluation of hydatidiform mole. Presence of cystic vascular spaces showing high-velocity, low-impedance flow on Doppler ultrasound is characteristic of invasive disease. Doppler ultrasonography also has a role in monitoring the response of the disease following chemotherapy. Regression of cystic vascular masses following chemotherapy is indicative of successful treatment.

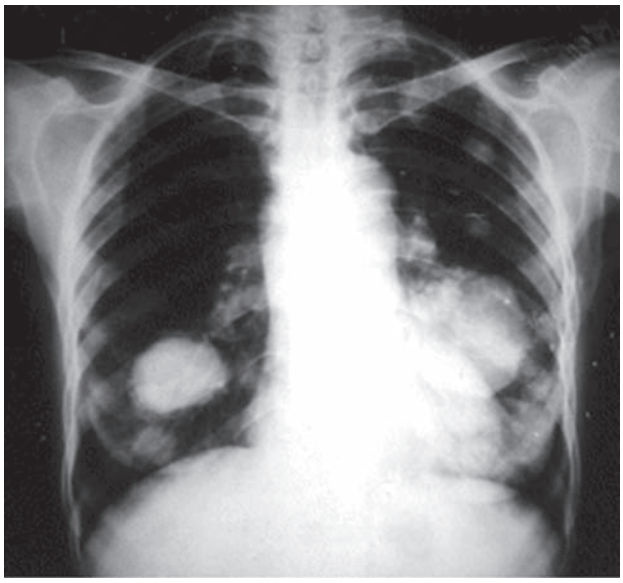


Fig. 8.6: Chest X-ray showing a cannon ball appearance, in which there are multiple, well defined, pulmonary nodules of varied sizes suggestive of pulmonary metastasis

Chest X-ray

The lungs are the most common site for metastasis in case of malignant gestational trophoblastic disease and may show the presence of distinct nodules or cannon ball appearance (figure 8.6). Other radiographic patterns which can be produced on the X-ray include an alveolar or snowstorm pattern, pleural effusion and an embolic pattern caused by pulmonary arterial occlusion. Metastasis to lungs is often associated with symptoms like dyspnea, cough, hemoptysis, chest pain, etc. A suspicion of pulmonary metastasis on chest X-ray must be followed by a CT or MRI examination of both head and abdomen. At present, MRI plays no role in the diagnosis of hydatidiform mole; however it is beneficial in diagnosing the metastatic disease. MRI is also used for characterizing the degree of myometrial and/or parametrial invasion and for assessing the response to chemotherapy.

If abdominal CT shows any evidence of metastatic disease, an ultrasound examination of the liver must be done in order to confirm the presence of hepatic metastatic disease. Pelvic ultrasonography is useful in detecting extensive uterine disease. Determination of cerebrospinal fluid/serum β hCG levels helps in detecting cerebral metastasis. Titers

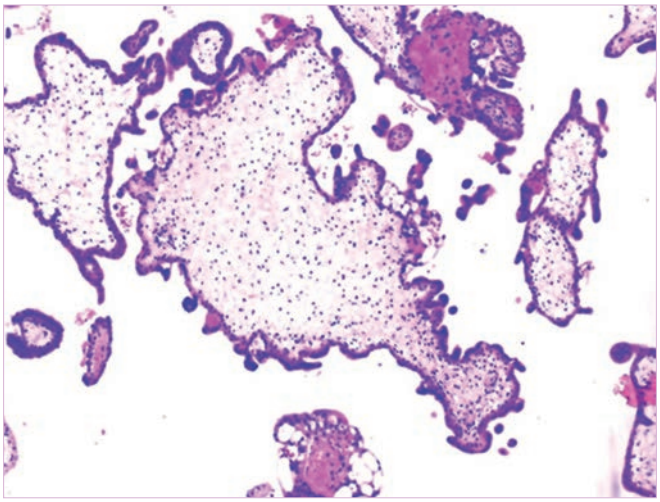


Fig. 8.7A: Histopathological slide of CHM showing diffuse trophoblastic hyperplasia

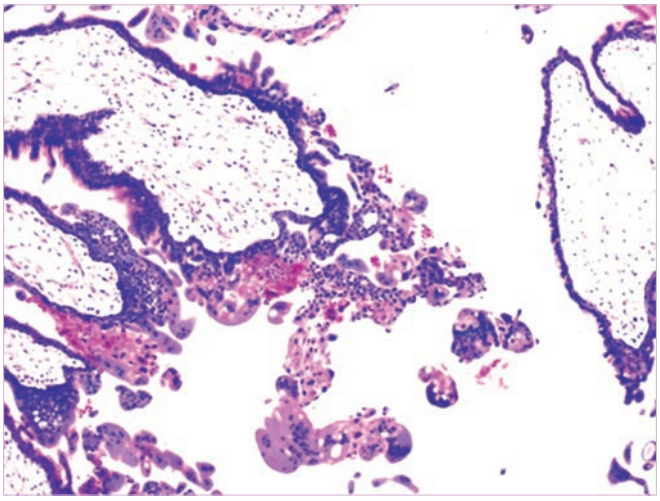


Fig. 8.7B: Histopathological slide of PHM showing focal trophoblastic hyperplasia and presence of fetal tissue

of greater than 1:60 are diagnostic of cerebral metastases. If gastrointestinal bleeding is present, upper and lower gastrointestinal tract endoscopy are indicated, whereas in presence of hematuria, an IVP and cystoscopy are indicated.

Histopathological Examination

The diagnosis of hydatidiform mole is confirmed by histological examination. Therefore all products of conception from nonviable pregnancies must be submitted for routine pathological evaluation. On pathologic evaluation, both CHMs and PHM demonstrate swollen chorionic villi having a grape-like appearance, along with presence of hyperplastic trophoblastic tissue (figures 8.7A and B). Though complete mole does not contain any fetal tissue, fetal tissue may sometimes be present in PHM. However this fetal tissue is usually nonviable. Even if fetal tissue is viable, fetus is often severely growth restricted, or may have multiple anomalies.

Rx *Treatment/Obstetric Management*

The two main treatment options in case of H. mole are suction evacuation and hysterectomy.

TREATMENT OF BENIGN DISEASE

Treatment by Suction Evacuation

Evacuation of the uterine contents is carried out by means of suction evacuation, irrespective of the uterine size. Due to the lack of fetal parts, a suction catheter, up to a maximum size of 12 mm, is usually sufficient to evacuate all complete molar pregnancies. A uterus of size up to 20 weeks can be readily evacuated. An intravenous line must be set up. Blood should be crossmatched and kept available. Cervical dilatation is usually not required as the cervix is soft and readily permits the entry of a suction canula. Passage of uterine sound prior to the evacuation is avoided as this may cause uterine perforation. The tip of the suction canula must be inserted just beyond the internal os. If the uterus is larger than 12 weeks in size, one hand must be placed on the fundus and the uterus should be massaged with the other in order to stimulate uterine contractions, thereby reducing the risk of uterine perforation. Routine curettage following suction evacuation is not recommended. Sharp curettage should be avoided due to the possible risk of uterine perforation. Usually repeat evacuation is not required as the initial evacuation is able to remove most of the molar material and cause the involution of residual tissues. Sometimes when large amount of molar material is left behind in the uterine cavity at the time of first evacuation, further evacuation within the next few days may help in reducing symptoms and prevent the need for future chemotherapy. However, if little residual material is left after the initial procedure, the RCOG (2004) recommends that no further evacuation for persistent disease is required. Anti-D immunoglobulins (50 μg) must be administered to Rh negative mothers.

There has been some debate regarding the use of oxytocin during and after the evacuation procedure. Some investigators have expressed concern that use of oxytocin may promote metastasis of trophoblastic tissue. However, presently there is no good evidence to show that uterine stimulation during evacuation increases the risk of persistent tumor. Administration of intravenous oxytocin helps in increasing myometrial tone and facilitating contraction, thereby reducing the total blood loss. RCOG (2004) has recommended that

where possible oxytocic infusions must only be commenced once evacuation has been completed. If the woman is experiencing significant hemorrhage prior to suction evacuation, use of oxytocin helps in controlling the amount of bleeding.

The medical termination of complete molar pregnancies, including cervical preparation with prostanoids (prostaglandin E2) prior to suction evacuation in cases with hydatidiform moles is discouraged. This is so as the prostaglandins may induce uterine contractions, thereby causing trophoblastic embolization to the pulmonary vasculature and disseminated disease. RCOG (2004) has recommended that prostaglandin analogues should be used in cases where oxytocin is ineffective in controlling uterine hemorrhage. In partial molar pregnancies where suction curettage cannot be used due to the presence of fetal parts, use of medical termination serves as a useful alternative.

Follow up with β hCG levels following suction evacuation

Patients with both complete and partial molar pregnancy should be monitored with serial β hCG measurements after evacuation to ensure that complete sustained remission has been achieved. Serial assays of serum and urine β hCG levels should be carried out on two weekly basis until three negative levels are obtained. In benign disease, human chorionic gonadotropin concentrations spontaneously return to normal by eight weeks following evacuation of molar pregnancy. In these cases, regular follow up in form of pelvic examination and urine β hCG titers at monthly interval needs to be done for a period of six months.

However women who have the malignant form of gestational trophoblastic disease (GTN) may show β hCG titers, which either plateau or rise and remain elevated beyond eight weeks. Such patients should have monthly follow up in form of pelvic examination and urine β hCG titers for at least two years. A chest X-ray is indicated to rule out the metastatic disease if the β hCG levels rise. If β hCG levels remain elevated, it is also important to rule out the occurrence of a new conception.

Since persistent GTN may develop after a molar pregnancy, non molar pregnancy or even following live birth, women with persistent abnormal vaginal bleeding after a non molar pregnancy should undergo serial determination of β hCG levels to exclude persistent GTN. Possibility of persistent GTN should also be considered in any woman developing acute respiratory or neurological symptoms after any pregnancy.

Contraceptive measures should be instituted and the patient advised to avoid pregnancy until hCG values have remained normal for six months. An early ultrasound should be performed in all subsequent pregnancies because hydatidiform mole may recur in about 1% of subsequent pregnancies. Estimations of β hCG levels must be done at six and ten weeks after any future pregnancy due to a small increase in the risk of development of choriocarcinoma in such patients.

Hysterectomy with Mole in Situ

Hysterectomy may serve as an option in the following cases:

- Elderly multiparous women (age > 40 years) who do not wish to become pregnant in the future.
- Those women with H. mole desiring sterilization.
- Those with severe infection or uncontrolled bleeding.
- Patients with nonmetastatic persistent disease who have completed childbearing or are not concerned about preserving fertility.

If theca lutein cysts are present, they must be left as it is at the time of surgery or at the most, they can be aspirated in order to reduce their size. The ovaries must be conserved. At the time of surgery, it is important to inform the patient that since hysterectomy does not prevent metastatic disease, therefore β hCG follow up is essential even after surgery. Hysterectomy however does eliminate the complications related to local invasion.

Chemotherapy Following Evacuation

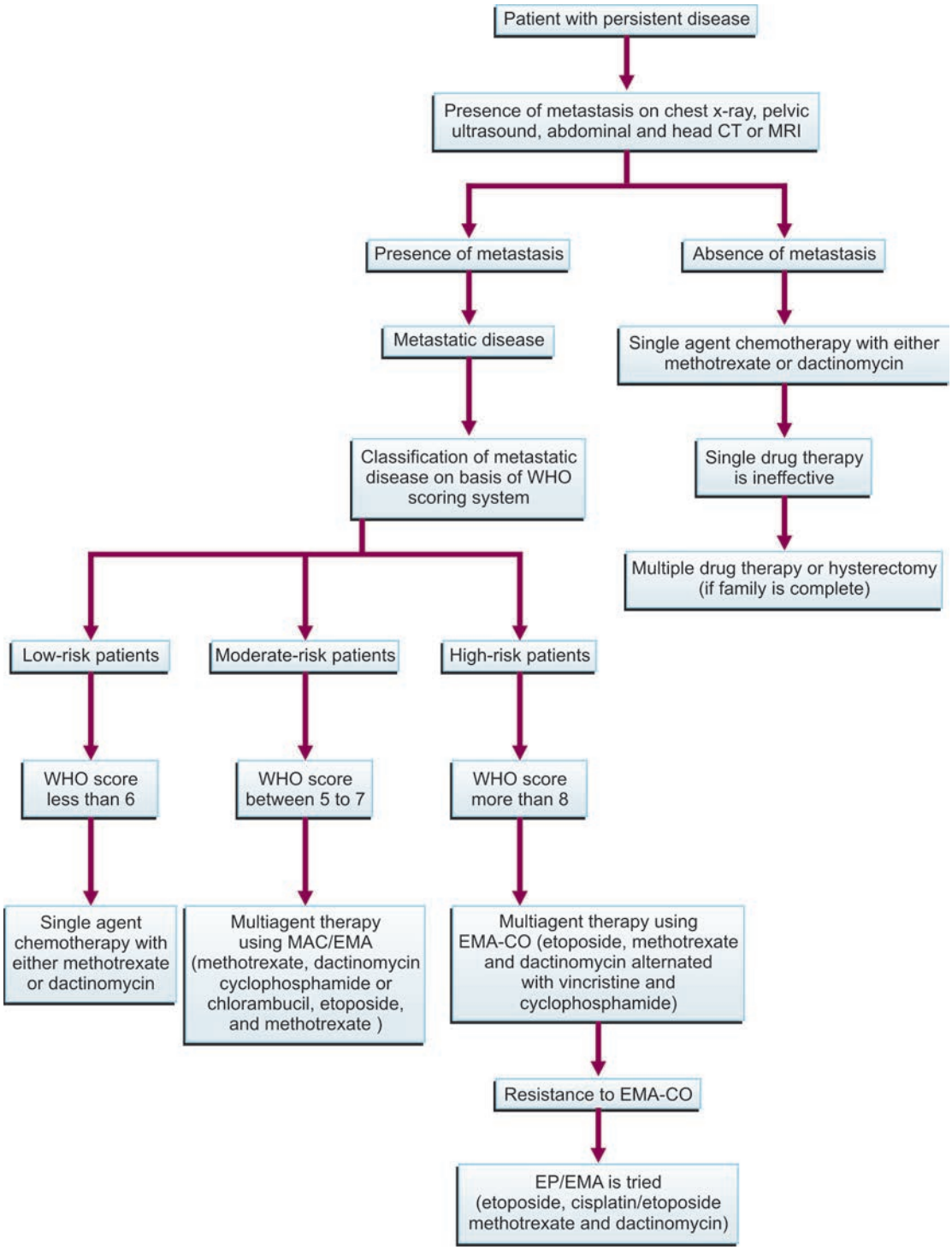
Women who undergo chemotherapy following evacuation are advised not to conceive for one year after completion of treatment. Oral contraceptive pills or any other acceptable method of contraception can be used. Some indications for chemotherapy [as recommended by SOGC, (2002)], following evacuation of molar gestation are as follows:

- An abnormal hCG regression pattern (a 10% or greater rise in hCG levels or plateauing hCG levels comprising of three stable values over two weeks).
- Histological diagnosis of choriocarcinoma or placental site trophoblastic tumor.
- The presence of metastases in brain, liver, gastrointestinal tact, lungs, vulvar or vaginal walls.
- High hCG levels (greater than 20,000 mIU/mL more than four weeks post-evacuation).
- Persistently elevated hCG levels six months post-evacuation.

TREATMENT OF PERSISTENT DISEASE

The management plan for the treatment of persistent disease is shown in flow chart 8.2. If the β hCG level does not normalize within 10 weeks, the disease is classified as persistent. In these cases, chest X-ray and CT scan of brain, chest, abdomen and pelvis needs to be done. If metastasis is detected on

Flow chart 8.2: Management of persistent disease



these investigations, the disease is classified as metastatic. The FIGO staging of malignant disease is shown in table 8.3.

If no metastasis is detected, the disease is classified as nonmetastatic. If the chest X-ray is clear, diagnosis of a nonmetastatic tumor is made. The metastatic disease can spread through the blood stream to lungs (80%); vagina (30%), pelvis (20%); brain (10%) and liver (10%). Metastasis to the vagina can occur in the fornices or suburethrally. If pulmonary metastases are present, CT scans of the brain and abdomen are indicated.

Table 8.3: FIGO Staging of GTN

Stage	*Description*
Stage I	Disease confined to the uterus
Stage II	GTN extends outside the uterus but is limited to the genital structures (adnexa, vagina, broad ligament)
Stage III	GTN extends to the lungs with or without genital tract involvement
Stage IV	All other metastatic sites

Persistent disease is usually treated with chemotherapy. Treatment is considered successful if at least 3 consecutive serum β hCG measurements at 1-week intervals are normal.

Treatment of Nonmetastatic Disease

- In most of the cases, nonmetastatic disease can be treated with a single chemotherapeutic drug (methotrexate or dactinomycin). Methotrexate is the drug which is most commonly used. Women who develop resistance to methotrexate are treated with a combination of intravenous dactinomycin and etoposide. If single drug chemotherapy is ineffective, hysterectomy or multidrug chemotherapy can be tried.

Methotrexate and folinic acid

Some commonly used regimens include:

- Methotrexate in the dosage of 0.4 mg/kg (maximum 25 mg) intravenously or intramuscularly daily for five days per treatment course.
- 50 mg intramuscularly, to be repeated every 48 hours for a total of four doses.
- Methotrexate in the dose of 1 mg/kg intramuscularly is given on days 1, 3, 5 and 7 along with calcium leucovorin rescue in dose of 0.1 mg/kg on days 2, 4, 6 and 8, 30 hours following injection of methotrexate. Courses are repeated every 14 days dependent on toxicity, i.e. first course on day 1; second course on day 15; third course on day 29 and so on. An adequate response to chemotherapy is defined as fall in the hCG levels by 1 log after a course of chemotherapy. If the response to 1mg/kg dose is inadequate, the dose is increased to 1.5 mg/kg for each of the four treatment days. If even then, the response after two consecutive courses of methotrexate-folic acid is inadequate, the patient is considered resistant to methotrexate. In these cases the patients may be administered the alternative drug dactinomycin. Methotrexate can produce side effects like mouth ulcers and soreness in the eyes. These can be treated using mouthwash, hypermellose eye drops and folinic acid.

Dactinomycin

Some commonly used regimens include:

- Dactinomycin in the dose of 9 – 13 μg/kg (maximum 500 μg/d) is administered intravenously daily for five days every two weeks.
- Pulsed dactinomycin 1.25 mg/m^2 intravenously every two weeks.

Dactinomycin is slightly more toxic than methotrexate and can cause side effects like hair loss, myelosupression, mouth ulcers, nausea, etc.

Treatment of Metastatic Disease

For purposes of treatment, patients with metastatic disease are classified into high-risk, moderate-risk and low-risk groups. The classification system adopted by the World Health Organization (WHO) and FIGO (federation international of gynecologists and obstetricians) for classifying gestational trophoblastic tumors and treatment protocols has become the most widely used prognostic scoring system. This classification system is shown in table 8.4. The low-risk group will

Table 8.4: The classification system by the WHO and FIGO for classifying gestational trophoblastic tumors and treatment protocols

Risk factor	*Risk score*			
	0	*1*	*2*	*4*
Age (years)	< 40	≥ 40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval (end of antecedent pregnancy to chemotherapy) in months	<4	4–6	7–13	> 13
Human chorionic gonadotropin (IU/L)	< 10^3	10^3–10^4	10^4–10^5	> 10^5
Number of metastasis	0	1–4	5–8	> 8
Site of metastasis	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
Largest tumor mass	-	3–5 cm	> 5 cm	-
Previous chemotherapy	-	-	Single drug	≥ 2 drugs

have a score of 0 to 6; the moderate-risk group has a score between 5 and 7; and the high-risk group will have a score of 7 or higher.

Low-risk metastatic disease is treated with single or multiple drug chemotherapy. Moderate-risk metastatic disease is usually treated with multiagent chemotherapy. High-risk metastatic disease requires aggressive multidrug chemotherapy. Low-risk disease has cure rates of 90% to 95%, whereas high-risk disease has cure rates of 60% to 80%.

Low-risk metastatic disease (WHO score: less than 6)

Women belonging to low-risk, i.e. scoring six or less on the classification system (table 8.4) must receive intramuscular methotrexate. Women who develop resistance to methotrexate are treated with a combination of intravenous dactinomycin and etoposide. The dosage and treatment schedule for methotrexate and dactinomycin is same as that for patients with nonmetastatic disease and has already been discussed. Chemotherapy is changed from methotrexate to dactinomycin if the hCG level plateaus (implying resistance to methotrexate) or if toxicity to methrotrexate precludes adequate chemotherapy. With the development of metastases or an elevation in β hCG titers, combination chemotherapy should be started. Treatment is continued for one to two courses past the first normal hCG levels.

Moderate-risk patients (WHO score: 5 to 7)

Traditionally, moderate-risk patients (WHO score of 5 to 7) have been treated with multiagent chemotherapy. The most commonly used combination chemotherapy include: MAC based combination (methotrexate, dactinomycin, cyclophosphamide or chlorambucil) or EMA (etoposide, methotrexate and dactinomycin). The Charing Cross group (U.K) has been recently treating moderate-risk patients with methotrexate and folinic acid, similar to low-risk patients.

High-risk patients (WHO score: 8 or greater)

Women with high-risk GTT usually require combination chemotherapy with selective use of surgery and radiotherapy. This group may include patients with metastases to the brain, liver and gastrointestinal tract. Complications such as massive bleeding may occur early in the disease. The standard chemotherapy regimen in high-risk group is EMA/CO (table 8.5) in which the drugs like etoposide, dactinomycin and methotrexate are alternated at weekly intervals with vincristine and cyclophosphamide. The commonly used regimen for resistant disease is EP/EMA (table 8.6), which includes drugs like etoposide, cisplatin, methotrexate and dactinomycin. There are few reports of treatment with the newer anticancer agents like paclitaxel, employment of G-CSF (granulocyte colony stimulating factor) and high-dose chemotherapy with autologous bone marrow support. Chemotherapy drugs like cisplatin, vinblastine and bleomycin may also prove to be effective as second-line therapeutic agents. Regimen 1 and 2 are alternated each week.

Table 8.5: EMA CO regimen for high-risk patients with gestational trophoblastic disease

Regimen 1 (EMA)
Week 1- Day 1
Actinomycin D 0.5 mg IV bolus
Etoposide 100 mg/m^2 IV in 500 ml N saline over 30 min
Methotrexate 300 mg/m^2 IV in 1 liter N saline over 12 h
Day 2
Actinomycin D 0.5 mg IV bolus
Etoposide 100 mg/m^2 IV in 500 ml N saline over 30 min
Folinic acid 15 mg IM 12-hourly x 4 doses starting 24 h after commencing methotrexate
Regimen 2 (CO)
Week 2 - Day 1
Vincristine (oncovin) 1.4mg/m^2 IV bolus (max. 2mg)
Cyclophosphamide 600 mg/m^2 IV in 500 ml N saline over 30 min

Table 8.6: EP/EMA regime for patients with disease resistant to EMA/CO

Regimen 1 (EP)
Week 1- Day 1
Etoposide 150 mg/m^2 IV in 500 ml N saline over 30 mins
Cisplatin 25 mg/m^2 IV over 4 h
Regimen 2 (EMA)
Week 2 - Day 1
Etoposide 100 mg/m^2 IV over 30 min
Methotrexate 300 mg/m^2 IV over 24 hours
Actinomycin D 0.5 mg IV bolus
Day 2
Folinic acid 15 mg PO 12 hrly for four doses to start 24 hours after starting methotrexate

Follow up After Chemotherapy

After chemotherapy treatment, human chorionic gonadotropin is measured weekly until hCG levels have become normal for three consecutive weeks, followed by monthly determination of hCG levels until they have become normal for 24 consecutive months (2 years). In the UK, follow up continues indefinitely because it is unclear when it is safe to stop. However in other countries, time varies from one center to the other. Women are therefore advised not to become pregnant for 12 months, following chemotherapy treatment because this may interfere with early detection of relapsed disease.

Complications

Benign forms of hydatidiform mole can result in complications like uterine infection, sepsis, hemorrhagic shock and preeclampsia, which may occur during early pregnancy. GTD does not impair fertility or predispose to prenatal or perinatal complications (e.g., congenital malformations, spontaneous abortions, etc). The most important complication related to GTD is the development of gestational trophoblastic tumors (GTT), which include conditions like invasive mole, choriocarcinoma and placental site trophoblastic tumor (PSTT). All of these may metastasize and are potentially fatal if left untreated.

Invasive Mole

Invasive mole (Chorioadenoma destruens) is a histologically benign condition resulting due to the invasion of abnormal trophoblasts into myometrium. It may also develop due to embolization of molar tissue through pelvic venous plexus. Approximately 15% of patients with invasive mole may develop metastases, lodging most commonly in the vagina and lungs.

Gestational Choriocarcinoma

Also known as chorioblastoma; trophoblastic tumor; chorioepithelioma or gestational trophoblastic neoplasia, gestational choriocarcinoma is a widely metastatic tumor composed of malignant trophoblastic cells, which arises from trophoblastic tissue of term pregnancies, as well as from ectopic gestation and spontaneous or induced abortions. Choriocarcinoma is a highly invasive tumor, which metastasizes early and is often widespread at the time of diagnosis. Lungs are the most common sites for metastases and are present in almost all patients with extrauterine disease. Other sites of metastasis include brain, liver, vagina, kidney and intestines.

Placental Site Trophoblastic Tumor

PSTT is a rare manifestation of gestational trophoblastic tumor which develops at placental implantation site. These tumors usually originate from the intermediate trophoblastic cell. They may present with a wide spectrum of clinical behavior, ranging from a self-limited state to persistent disease to a highly aggressive metastatic neoplasm, showing metastases to the lung, liver, peritoneal cavity, brain, etc. Due to the lack of syncytiotrophoblastic tissue, levels of serum human chorionic gonadotropin are only modestly elevated in PSTTs. They may complicate any type of pregnancy and may be diagnosed following a dilatation and evacuation procedure either for missed abortion or a hydatidiform mole. They have also been described following term pregnancies. PSTT is relatively resistant to chemotherapy, but responds well to surgery (hysterectomy) if the disease is localized. However in cases of advanced disease, chemotherapy with the EMA/CO protocol is usually used.

Important Questions and Answers

Q.1. What should be the next step of management in the patient described in the above case presentation?

Ans. Persistent vaginal bleeding after a miscarriage is a characteristic symptom associated with molar gestation. Though commonly, bleeding after a miscarriage is due to retained products of conception or incomplete miscarriage, the clinician must keep the possibility of molar gestation in his/her mind. In this case the following investigations need to be conducted: Complete blood count with a peripheral smear, serum and urine β hCG levels and an ultrasound examination.

Q.2. From the results of various investigations, diagnosis of CHM was reached. What should be the next step in management?

Ans. The patient now needs to be investigated to rule out the presence of persistent gestational trophoblastic disease. For this, serial determination of β hCG levels needs to be done. Measurement of three consecutive negative levels help in ensuring that complete sustained remission has been achieved. Serial assays of serum and urine β hCG levels should be carried out on two-weekly basis. In benign disease, β hCG concentrations spontaneously return to normal by eight weeks following evacuation of molar pregnancy. In these cases, regular follow up in form of pelvic examination and urine β hCG titers at monthly interval needs to be carried for a period of six months.

However, women who have the persistent form of gestational trophoblastic disease (GTN) may show plateauing or rising β hCG titers, which usually remain elevated beyond eight weeks. Such patients should have monthly follow up in form of pelvic examination and urine β hCG titers for at least two years.

Q.3. What are the treatment options in patients with persistent disease?

Ans. Persistent trophoblastic disease can be classified into two types: Nonmetastatic and metastatic based on the results of series of investigations, including chest X-ray (to detect pulmonary metastasis) and pelvic ultrasound (to detect vaginal metastasis). In case, the results of these investigations turn out to be positive, other investigations like CT/MRI of head and abdomen, etc need to be carried out. The

nonmetastatic disease and low-risk metastatic disease must be treated with single agent chemotherapy, either methotrexate or dactinomycin.

Moderate-risk patients are usually treated with multiagent chemotherapy, either MAC or EMA; single-agent chemotherapy may sometimes be also used. High-risk patients should be treated with multiagent chemotherapy EMA/CO, with selective use of surgery and radiotherapy. Salvage chemotherapy with EP/EMA and surgery should be employed in resistant disease.

Q.4. What advice regarding contraception should be given in the above patient?

Ans. Women should be advised to avoid pregnancy until hCG levels have been normal for six months following evacuation of a molar pregnancy and for one year following chemotherapy for gestational trophoblastic tumor.

There has been some controversy regarding the use of OCP's as a method of contraception following evacuation, until the serum β hCG levels have returned to normal. Some studies suggest that the use of combined oral contraceptive pill may increase the risk of malignancy in women whose β hCG titers remain high, whereas other studies have shown no risk. While some centers continue to prescribe oral contraceptive pills as a method of contraception, most centers from the UK recommend that these women must not take the pills until their hormone concentrations have returned to normal. The small potential risk of using emergency hormonal contraception (comprising of progesterone), in women with raised β hCG levels, is outweighed by the potential risk of pregnancy to the woman. An IUCD is inadvisable as it may cause bleeding which may be confused with the presence of persistent disease. Also insertion of IUCD before the normalization of hCG levels may be associated with the risk of uterine perforation. Surgical methods or barrier contraception proves useful in these cases.

Q.5. Can hormone replacement therapy be used in the patients who have been diagnosed with hydatidiform mole?

Ans. Hormone replacement therapy may be used safely once hCG levels have returned to normal. The RCOG recognizes that the COC and hormone replacement therapy is safe to use after hCG concentrations have returned to normal.

Q.6. What are the poor prognostic factors of the disease?

Ans. The poor prognostic factors for the disease include the following:

- Disease has spread to the liver or brain.
- Serum β hCG level is greater than 40,000 mIU/mL at the time the treatment begins.
- The patient had received chemotherapy in the past.
- Symptoms had been present for more than 4 months before starting chemotherapy treatment.
- Choriocarcinoma occurred after a pregnancy that resulted in the birth of a child.

Q.7. What should be the management plan in cases of twin gestation where one fetus is viable and other pregnancy is molar?

Ans. In cases of twin gestation, where there is one viable fetus and the other pregnancy is molar, the pregnancy should be allowed to proceed if the mother wishes, following appropriate counseling. The probability of achieving a viable baby is 40% and there is a risk of complications such as pulmonary embolism and preeclampsia. There is no increased risk of developing persistent GTN after such a twin pregnancy and outcome after chemotherapy is similar to that of singleton pregnancy.

Bibliography

1. Deng L, Yan X, Zhang J, Wu T. Combination chemotherapy for high-risk gestational trophoblastic tumor. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD005196. DOI: 10.1002/14651858.CD005196.pub2.
2. Gestational trophoblastic diseases: Report of a WHO scientific group. WHO Tech Rep Ser. 1983;692:51.
3. Newlands ES, Paradinas FJ, Fisher RA. Recent advances in gestational trophoblastic diseases. Hematol Oncol Clin North Am. 1999;13:225-42.
4. Sebire NJ, Seckl MJ. Gestational trophoblastic disease: Current management of hydatidiform mole. BMJ. 2008;337:453-58.
5. Sekharan PK. The management of gestational trophoblastic neoplasia FOGSI – ICOG consensus statement.
6. SOGC Practice Guidelines. Gestational Trophoblastic Disease. J Obstet Gynaecol Can. 2002;24(5):434-9.
7. The Royal College of Obstetricians and Gynecologists. The management of gestational trophoblastic neoplasia. Guideline No. 38, February 2004.

Chapter 9 Bad Obstetric History

Case Study

A 32-year-old woman G4P0A30 with previous history of three miscarriages all in the first trimester presented with 14 completed weeks of gestation for regular ANC check-up.

Introduction

These case symptoms are suggestive of bad obstetric history.

DEFINITION

Miscarriage can be defined as expulsion of fetus or embryo before a particular gestational age (usually taken as 24 weeks of gestation), when the fetus becomes capable of independent survival or before attaining a weight of 1000 grams. Definition of some commonly used terminology related with pregnancy loss is described in table 9.1.

Recurrent miscarriage is defined as the clinically recognized loss of three or more pregnancies with the same partner before 24 weeks of gestation. Bad obstetric history could be related to recurrent miscarriage or a history of previous unfavorable fetal outcome in terms of two or more consecutive spontaneous abortions, early neonatal deaths, stillbirths, intrauterine fetal deaths, congenital anomalies etc. Clinical investigations can be initiated after two consecutive spontaneous miscarriages, especially if the fetal heart activity had been previously present; when the woman is older than 35 years of age or when the couple has difficulty conceiving. Miscarriage can be considered as primary, when there is no previous history of live birth and considered as secondary when fetal loss occurs following a successful pregnancy.

ETIOLOGY

Some important causes of BOH include genetic causes, abnormal maternal immune response, abnormal hormonal response, maternal infection and anatomical factors. Bad obstetric history could also be because of environmental factors: Radiation exposure, occupational hazards, addictions and habits. Each of these would be discussed below in details. It is important to exclude each of these factors by taking the relevant history. The likelihood of a particular cause as the etiology of recurrent abortion is described in table 9.2.

Genetic Causes

Presence of chromosomal abnormality in either of the parents is responsible for a high proportion of early first trimester miscarriages. All couples with a history of recurrent miscarriage should have peripheral blood karyotyping performed. The most common types of parental chromosomal abnormalities are balanced reciprocal or Robertsonian translocations. Chromosomal abnormalities of the conceptus account for more than half of sporadic (pre)embryonic losses and in many cases, a visible embryo never forms. As the number

Table 9.1: Definition of some commonly used terminology related with pregnancy loss

Terminology	*Definition*
Early miscarriage	Pregnancy loss at ≤ 12 weeks.
Late miscarriage	Pregnancy loss between 12–24 weeks
Blighted ovum	Anembryonic pregnancy
Embryonic loss	Miscarriage at ≤ 8th gestational week
Fetal loss	Miscarriage between 9–24 weeks
Stillbirth	Pregnancy loss at ≥ 24th week

Table 9.2: Causes for recurrent miscarriage

Factor responsible for recurrent abortion	*Likelihood*
Genetic Factors	10% to 15%
Anatomic Abnormalities	10% to 15%
Endocrine Abnormalities	17% to 20%
Infectious causes	0.5% to 5%
Immunologic causes	20% to 50%
Environmental Factors	–
Unexplained/idiopathic causes	40% to 50%
Thrombophilia	–

of miscarriages increases, the possibility of the miscarriage due to the presence of chromosomal abnormality decreases and the chance of miscarriage due to the presence of recurring maternal cause increases. Genetic factors are the most important cause for sporadic miscarriage. If an abnormal parental karyotype is identified, the patient in any case must be referred to a clinical geneticist and offered genetic counseling, familial chromosomal studies and appropriate prenatal diagnosis in future pregnancies. In all couples with a previous history of recurrent miscarriage, cytogenetic analysis of the products of conception should be performed if the next pregnancy fails.

Factor V Leiden and Prothrombin G20210A mutations are common genetic mutations that predispose the carriers to develop venous thromboembolism. Factor V Leiden is the most common cause of primary and recurrent venous thromboembolism in pregnancy. Factor V Leiden carriage has also consistently been shown to increase the risk of early onset gestational hypertension, HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), severe placental abruption and fetal growth retardation.

Hormonal Causes

Hormonal factors have been proposed to contribute to recurrent miscarriage in 10% to 20% of patients. Hormonal aberrations may result from problems with certain endocrine glands, such as the pituitary, thyroid, adrenal gland or ovaries.

Luteal phase defect

Progesterone, a hormone produced by the ovary during the secretory stage, is necessary for maintenance of a healthy pregnancy. Low progesterone levels, often called luteal phase defect (LPD), has been thought to be a cause of spontaneous abortions. LPD has been found to be associated with poor follicular phase oocyte development, which may result in disordered estrogen secretion and subsequent dysfunction of the corpus luteum.

Polycystic ovary syndrome

Polycystic ovary syndrome has been considered as a cause of a variety of menstrual disorders ranging from amenorrhea to dysfunctional uterine bleeding, hirsutism and infertility. Hypersecretion of luteinizing hormone (LH) in PCOS, resulting in the elevation of LH: FSH ratio, is thought to be responsible for causing recurrent miscarriages.

Hypothyroidism

Maternal hypothyroidism may place the mother at an increased risk of adverse obstetrical outcomes. Thyroid disease may cause ovulatory dysfunction and luteal phase defects. Treated thyroid dysfunction, however, is not a risk factor for recurrent miscarriage. Untreated hypothyroidism, on the other hand can result in an increased risk for preeclampsia, placental abruption, miscarriage and perinatal mortality. Maternal hypothyroidism in the second trimester has been found to be associated with an increased rate of fetal death after 16 weeks of gestation.

Diabetes mellitus

Women with diabetes who have high hemoglobin A1c (glycosylated hemoglobin) levels in the first trimester are at an increased risk of miscarriage and fetal malformations. However, neither well controlled diabetes mellitus nor treated thyroid disease have been observed to be risk factors for recurrent miscarriage.

Hyperprolactinemia

Hyperprolactinemia may adversely affect corpus luteal function. However, presently there is insufficient evidence to assess the effect of hyperprolactinemia as a risk factor for recurrent miscarriage.

Infectious Causes

Any severe infection that leads to bacteremia or viremia can cause sporadic miscarriage. The role of infection in recurrent miscarriage is unclear. An infection can be implicated in the etiology of repeated pregnancy loss, only if it is capable of persisting in the genital tract, without being detected early or without causing sufficient symptoms, which could disturb the women. TORCH group of infections do not fulfill these criteria. Infections caused by TORCH complex (*Toxoplasma gondii*, *Rubella virus*, *Cytomegalovirus*, and *Herpes simplex virus*) are thought to be important causes for BOH, which is treatable, especially in the developing countries. The association between TORCH group of infections and recurrent miscarriage is not yet clear. The RCOG recommends that routine TORCH screening should be abandoned. TORCH infections are generally mild in the mother, but can prove disastrous to the fetus. The degree of severity is dependent on the gestational age of the fetus when infected, the virulence of the organism, the damage to the placenta and the severity of maternal disease. Infections by TORCH agents in women are usually asymptomatic and chronic. Other infectious organisms that have also been implicated include, *Bacterial vaginosis*, *Listeria monocytogenes*, *Mycoplasma hominis*, *Herpes virus*, *Chlamydia trachomatis*, *Cytomegalovirus*, *Group B streptococci*, *Ureaplasma*, etc. Role of infective agents as a cause of recurrent miscarriage is presently considered to be controversial in developed countries. However they can be considered as important causes of recurrent miscarriage in developing countries. The study by Devi et al (2002) has confirmed the significant association between infectious causes,

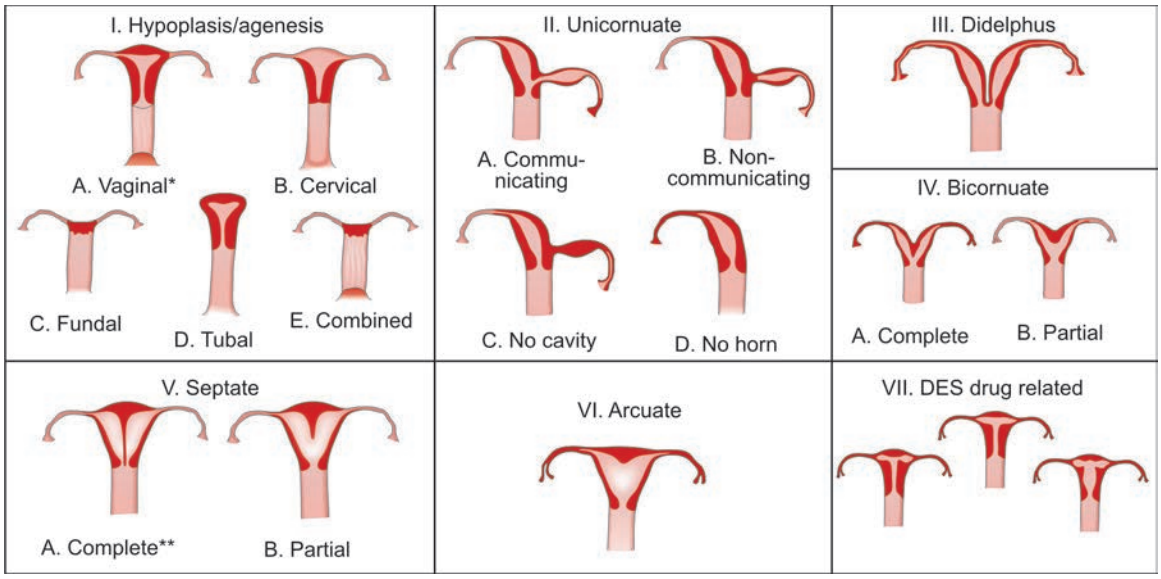


Fig. 9.1: Classification of the uterine anomalies by the American Society for Reproductive Medicine (1998)

*Uterus may be normal or take a variety of abnormal forms. **May have two distinct cervices.

Source: The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, müllerian anomalies and intrauterine adhesions. Fertil Steril 1988;49(6):944-55.

(especially TORCH infections) and BOH. The presence of bacterial vaginosis in the first trimester of pregnancy has also been reported as a risk factor for second trimester miscarriage and preterm delivery. Syphilis, a sexually transmitted disease, has been implicated as the cause for second trimester miscarriages, stillbirths, preterm labor, growth retardation, neonatal infections etc.

Anatomical Causes

Anatomical defects of the reproductive system could be one of the commonest causes of BOH. Uterine malformations, either congenital or acquired, could be responsible for approximately 12% to 15% cases of recurrent abortion. History of uterine malformations is often associated with late miscarriages. Congenital uterine anomalies include müllerian duct abnormalities, presence of uterine septum and uterine/cervical anomalies (figure 9.1). Acquired uterine anomalies leading to fetal loss include leiomyomas and endometriosis. Uterine abnormalities could result in impaired vascularization of pregnancy and limited space for the growing fetus due to distortion of the uterine cavity. Hysterosalpingography helps in diagnosing uterine anomalies. However the routine use of hysterosalpingography as a screening test for uterine anomalies in women with recurrent miscarriage is questionable.

Uterine malformations

Müllerian anomalies could result in an abnormal or irregularly shaped uterus, which could result in improper implantation and/or growth of the embryo, thereby resulting in recurrent miscarriages. The various müllerian anomalies, which can be implicated as a cause of recurrent miscarriage include septate uterus (50% to 60%), unicornuate uterus (34% to 44%), uterus didelphus, etc.

The classification of the müllerian anomalies by the American Fertility Society is shown in table 9.3 and

Table 9.3: American Fertility Society classification of müllerian anomalies

Classification	*Anomaly*
Class I	Segmental müllerian agenesis-hypoplasia
	A. Vaginal
	B. Cervical
	C. Fundal
	D. Tubal
	E. Combined anomalies
Class II	Unicornuate
	A. Communicating
	B. Noncommunicating
	C. No cavity
	D. No horn
Class III	Didelphus
Class IV	Bicornuate
	A. Complete (division down to internal os)
	B. Partial
Class V	Septate
	A. Complete (septum to the internal os)
	B. Partial
Class VI	Arcuate
Class VII	Diethylstilbesterol related

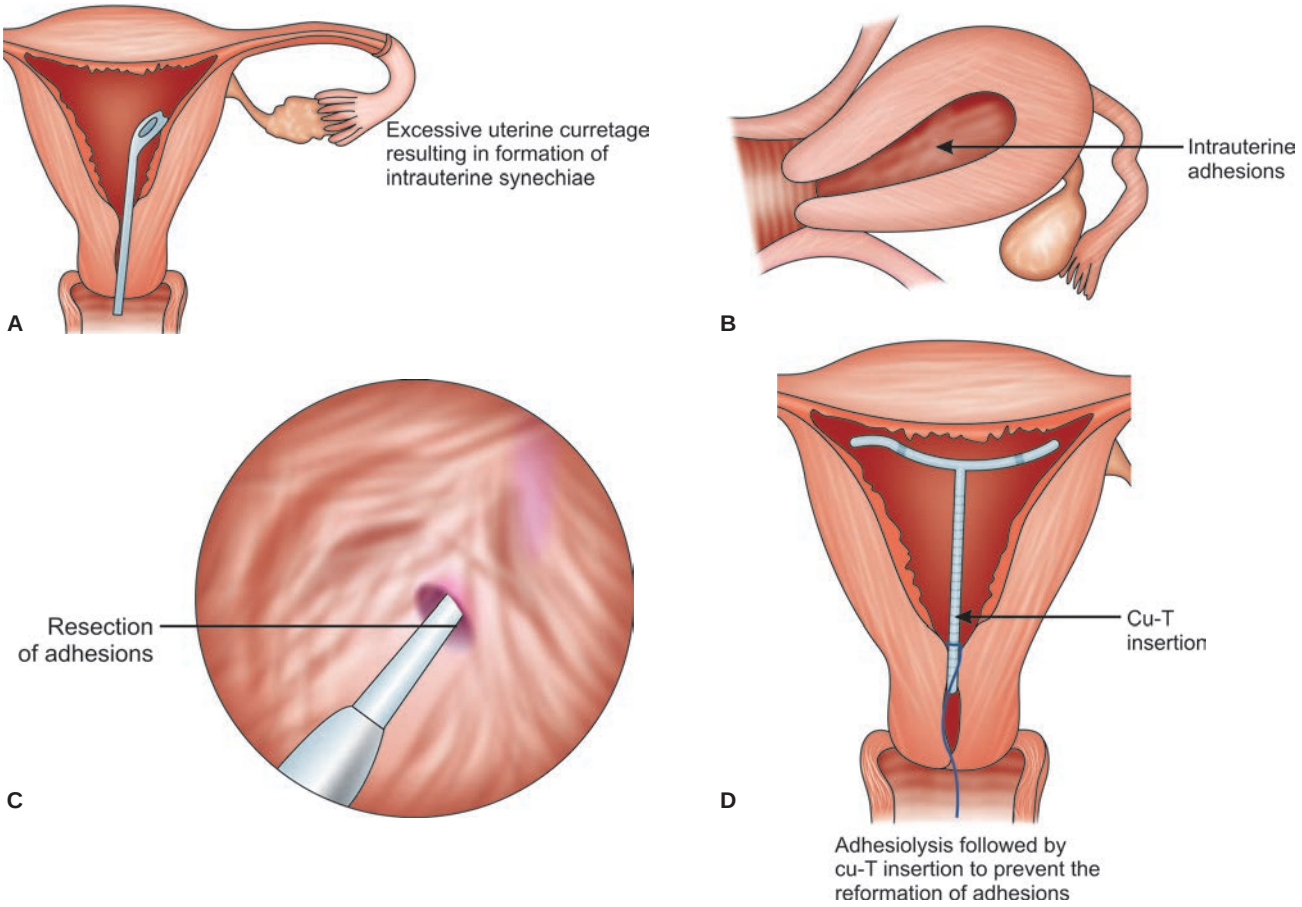


Fig. 9.2: Asherman's syndrome

figure 9.1. Presence of a uterine septum results in repeated pregnancy losses due to the following factors:

- Reduced intrauterine space for fetal growth.
- Placental implantation on a poorly vascularized uterine septum.
- Associated cervical incompetence, luteal phase insufficiency and distortion of the uterine milieu.

  However, not all patients with uterine anomalies experience repeated pregnancy losses. It is yet not explained, why some patients with uterine anomalies have normal reproductive function, while others experience recurrent miscarriages.

Asherman's syndrome

In addition to müllerian anomalies, an acquired anatomical cause of recurrent abortions is Asherman's syndrome, which is characterized by development of intrauterine adhesions, occurring in women who have had several dilatation and curettage procedures. These adhesions may cause amenorrhea, repeated miscarriages and infertility. Diagnosis of Asherman's syndrome can be reached by doing tests like hysteroscopy and transvaginal ultrasound examination. Treatment involves hysteroscopic surgery to cut and remove the adhesions or scar tissue (figures 9.2A to D). After the removal of scar tissue, the uterine cavity must be kept open, preferably by using a cu-T in order to facilitate healing and to prevent adhesions from returning. If an appropriate predisposing factor, such as uterine curettage or a severe uterine infection can be identified, then diagnostic hysterosalpingography or hysteroscopy could be performed.

Uterine fibroids

Uterine fibroids, most commonly those which are submucosal may distort the endometrial cavity, thereby resulting in recurrent pregnancy losses.

Cervical Incompetence

Cervical incompetence is a medical condition in which the pregnant woman's cervix starts dilating and effacing before her pregnancy has reached term, usually between 16–28 weeks of gestation, without any associated pain or uterine contractions. As a result, cervical incompetence may cause

Table 9.4: Risk factors for development of cervical incompetence

Diagnosis of cervical incompetence in a previous pregnancy
Previous history of preterm premature rupture of membranes
History of diethylstilbestrol exposure, which can cause anatomical defects in uterus and cervix
History of previously having received trauma to the cervix

the second and third trimester miscarriages and preterm births. Cervical incompetence is probably responsible for causing 20% to 25% of miscarriages in the second trimester. The woman gives history of recurrent second trimester pregnancy losses, occurring earlier in gestation in successive pregnancies and usually present with a significant cervical dilatation of 2 cm or more in the early pregnancy. However, usually there is absence of any other symptoms. In the second trimester, cervix may dilate up to 4 cm in association with active uterine contractions. This may be associated with rupture of the membranes resulting in the spontaneous expulsion of the fetus.

Cervical incompetence could be due to congenital or acquired causes. The most common acquired cause of cervical incompetence is a history of cervical trauma or the previous history of cervical lacerations. Therefore, history of any cervical procedure including cervical conization, LEEP, instrumental vaginal delivery or forceful cervical dilatation during previous miscarriage needs to be elicited. History of any cervical cerclage performed at the time of previous pregnancy also needs to be elicited. Some of the risk factors for development of cervical incompetence are listed in table 9.4.

Diagnosis

On clinical examination, the cervical canal may be dilated and effaced. Fetal membranes may be visible through the cervical os. Sonographic serial evaluation (every two weeks) of the cervix for funneling and shortening in response to transfundal pressure has been found to be useful in the evaluation of incompetent cervix.

Other findings observed on ultrasound examination include the following:

- Cervical length < 25mm. However finding of the short cervical length on TVS is not a confirmed diagnostic test for incompetent cervix. It could also be due to early preterm labor.
- Protrusion of the membranes.
- Presence of the fetal parts in the cervix or vagina.
- Cervical dilation and effacement with the changes in form of T, Y, V, U (can be remembered using the mnemonic "**T**rust **Y**our **V**aginal **U**ltrasound") (figures 9.3A and B). T-shaped cervix on ultrasound examination points towards a normal cervix. As the internal cervical os opens and the membrane start herniating into the upper part of endocervical canal, the cervical shape on ultrasound changes into a Y. With the further progression of above mentioned cervical changes, Y shape changes into U.
- Another important finding on TVS examination suggestive of cervical incompetence is funneling. Funneling implies herniation of fetal membranes into the upper part of endocervical canal. However this too is not diagnostic of incompetent os.

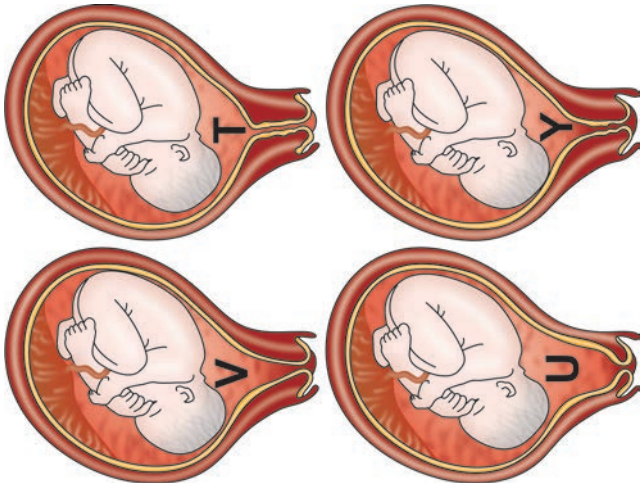


Fig. 9.3A: Anatomical changes in the endocervical canal associated with cervical incompetence

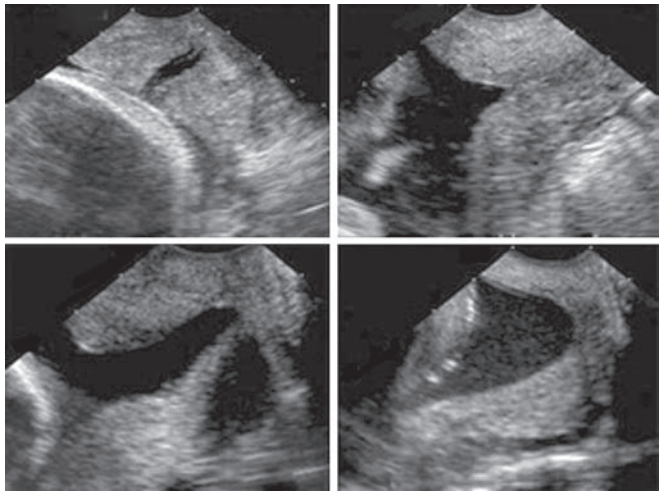


Fig. 9.3B: Ultrasound changes in endocervical canal with cervical incompetence

Some of the tests for diagnosing cervical incompetence, which were previously used and are still used at some places, include the following:

Passage of a No. 8 (8 mm) Hegar dilator, traction using an intrauterine Foley catheter, etc.

Treatment

No treatment for cervical incompetence is generally required, except when it appears to threaten a pregnancy. Cervical incompetence can be treated using surgery involving placement of a cervical cerclage suture which reinforces the cervical muscle. Surgical repair of the cervix is done using a vaginal or abdominal approach. Other alternatives which are sometimes considered include the following:

- Bed rest for which no trial has been conducted and there is little evidence regarding its effectiveness.
- The use of vaginal pessaries to elevate and close the cervix.

At present, the surgical approaches form the treatment of choice. Surgery involves placement of a cervical cerclage suture, either transabdominally or transvaginally. Different types of surgical procedures that can be performed include the following:

- Mc Donald procedure
- Shirodkar operation
- Wurms procedure (Hefner cerclage)
- Transabdominal cerclage
- Lash procedure

Out of the above mentioned surgical procedures, Mc Donald's procedure and Shirodkar's procedure are most commonly performed. Cerclage could be either emergency or prophylactic.

Prophylactic cerclage: Prophylactic cerclage is placed at 12–16 weeks of gestation, but antibiotics are given perioperatively. Sexual intercourse, prolonged standing (> 90 minutes) and heavy lifting are to be avoided following cerclage. These patients should be followed up with periodic vaginal sonography to assess stitch locations and funneling. No additional restrictions are recommended as long as the stitches remain within the middle or upper third of the cervix without the development of a funnel and the length of the cervix is greater than 25 mm.

If vaginal surgery does not prove to be successful despite aggressive care, transabdominal cerclage can be tried.

Emergency/rescue cerclage: Emergency or rescue cerclage is used in cases of patients with acute presentation of incompetent cervix. Placement of emergency cerclage is both difficult and controversial. This surgery must be undertaken when there is still 10–15mm or more of cervical canal left. Patient must be admitted for at least 24 hours prior to the surgery. Perioperative treatment with indomethacin and antibiotics must be administered before placing the cerclage. Patient must be observed for 2–4 days post-operatively. The cerclage is rarely performed after 24–25 weeks of pregnancy. The cerclage is normally removed at 37 weeks or at the onset of the labor.

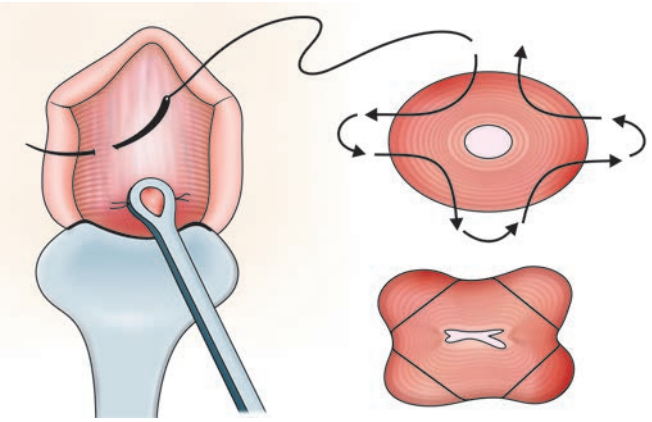


Fig. 9.4: Mc Donald's procedure

Surgical Procedures

Mc Donald procedure

In Mc Donald procedure, a 5 mm band of permanent purse string secure using 4–5 bites is placed high on the cervix (figure 9.4). It is usually removed at 37 weeks, unless there is a reason (e.g. infection, preterm labor, preterm rupture of membrane etc) for an earlier removal.

In Mc Donald procedure, no bladder dissection is required. The advantages of Mc Donald procedure over Shirodkar procedure include the following:

- Simplicity of the procedure (does not involve bladder dissection or complete burial of the sutures).
- Ease of removal at the time of delivery.
- The stitch can also be applied when the cervix is effaced or the fetal membranes are bulging.

The disadvantage of the procedure is the occurrence of excessive vaginal discharge with the exposed suture material.

Shirodkar technique (figures 9.5 A to G)

In Shirodkar procedure, a permanent purse string suture which would remain intact for life is applied. Therefore the patient is delivered by a cesarean section. The suture is placed submucosally as close to the internal os as possible by giving incisions both over the mucosa on the anterior and posterior aspects of the cervix. This is followed by dissection and separation of the bladder and the rectum from both anterior and posterior surface of the cervix respectively. Though the original Shirodkar procedure involved the dissection of both bladder and rectal mucosa, the Shirodkar procedure performed nowadays mainly involves the opening of the anterior fornix and dissection of the adjacent bladder. The knot is tied anteriorly and buried by suturing the mucosal opening in the anterior fornix. Some obstetricians prefer tying a posterior knot in order to prevent erosion into the bladder. This procedure is usually performed under spinal or epidural anesthesia.

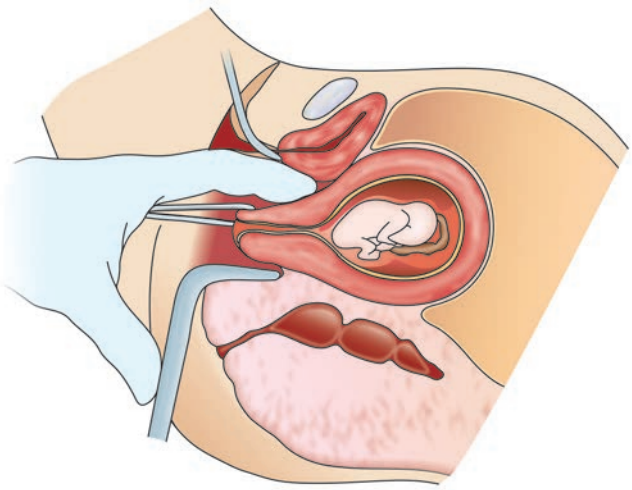


Fig. 9.5A: Pulling the anterior lip of cervix

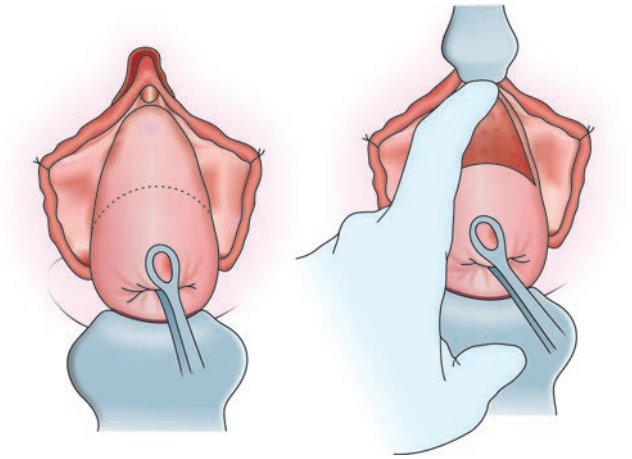


Fig. 9.5B: Incision and dissection of anterior vaginal mucosa

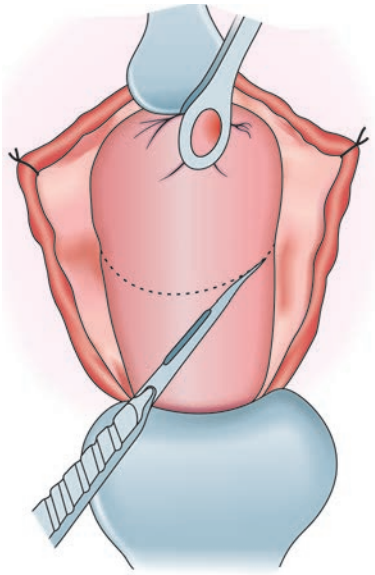


Fig. 9.5C: Incision of posterior vaginal wall mucosa

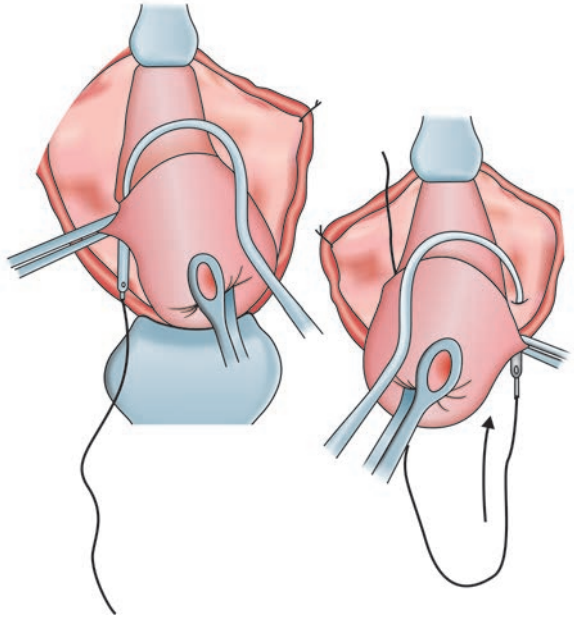


Fig. 9.5D: Application of the suture as close to the internal cervical os as possible

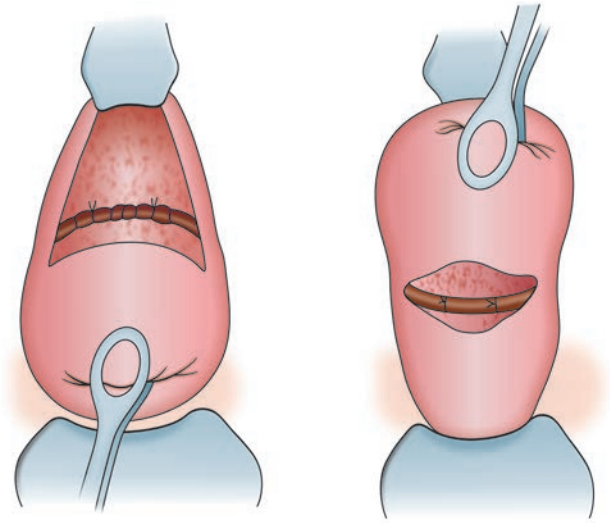


Fig. 9.5E: Sutures have been tied both anteriorly and posteriorly

Initially, both Shirodkar and the Mc Donald started suturing with the catgut, but eventually Shirodkar turned to fascia lata and Mc Donald turned to silk. Presently, mersilene tape is used as an appropriate suture material. Both the procedures have been found to be equally effective. However, it is generally easier to perform Mc Donald suture as no bladder dissection is involved.

Wurm's procedure

Also known as Hefner's cerclage, it is done by application of U or mattress sutures (figure 9.6) and is of benefit when minimal amount of length of cervical canal is left.

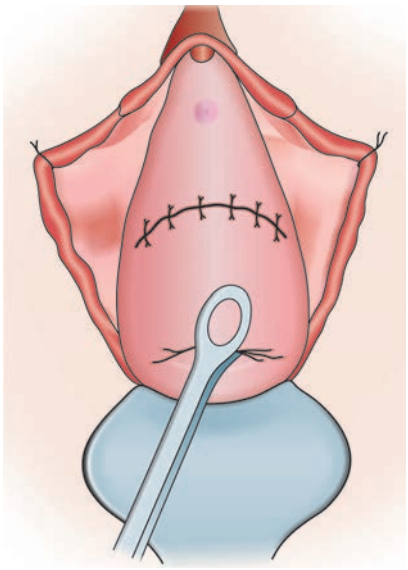


Fig. 9.5F: Closure of the vaginal mucosa

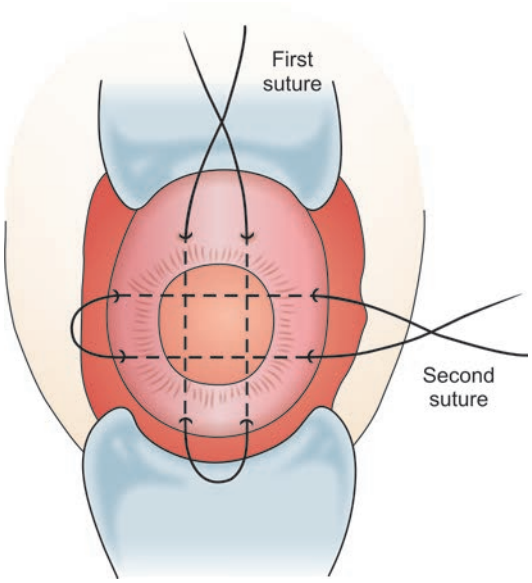


Fig. 9.6: Application of Wurm's stich

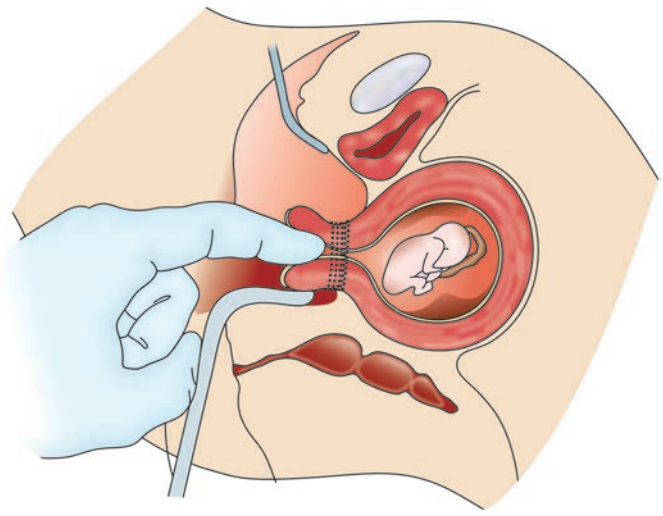


Fig. 9.5G: Appearance of cervix after application of Shirodkar's stitch

Transabdominal cerclage

If either of the cervical procedures fails, transabdominal cerclage is used. The indications for transabdominal cerclage include the following: Traumatic cervical lacerations, congenital shortening of the cervix, previous failed vaginal cerclage and advanced cervical effacement. The original intention with transabdominal approach was that the suture was inserted between pregnancies or in the early pregnancy and left in situ for the rest of the life. The delivery was undertaken by cesarean section during each pregnancy. As a result, the major disadvantage associated with transabdominal cerclage is the requirement of two abdominal procedures: One to place the suture and other for cesarean delivery. Also, since the surgery is performed in a highly vascular area of the cervix, which is adjacent to the uterus, it is associated with a high rate of complications. The procedure of transabdominal cerclage comprises of the following steps:

- A midline or Pfannenstiel incision is given over the abdominal wall.
- The vesicouterine fold of the peritoneum is divided.
- Bladder is reflected caudally.
- Uterine vessels are identified and a mersilene tape suture is passed through the broad ligament below the uterine vessels in the potential free space between the uterine vessels and the ureter.
- The suture is tied either anteriorly or posteriorly and the bladder is replaced.

Lash procedure

This surgical procedure is usually performed in nonpregnant woman. It is usually performed for an anatomical defect in cervix resulting from cervical trauma. In this surgery, the cervical mucosa is opened anteriorly, bladder reflected and the cervical defect repaired with interrupted transverse sutures before closing the vaginal mucosa.

Indications for cerclage

Indications for cerclage are as follows:

- History compatible with incompetent cervix.
- Sonogram demonstrating funneling
- Clinical evidence of extensive obstetric trauma to the cervix.

Contraindications for cerclage

- Uterine contractions/bleeding.
- Chorioamnionitis.
- Premature rupture of membranes.
- Cervical dilatation of more than 4 cm
- Polyhydramnios
- Fetal anomaly incompatible with life.

Risks of cerclage

- Premature rupture of the membranes
- Chorioamnionitis
- Preterm labor
- Cervical laceration or amputation resulting in the formation of scar tissue over the cervix
- Bladder injury
- Maternal hemorrhage
- Cervical dystocia
- Uterine rupture, vesicovaginal fistula

Inherited Thrombophilias

This can cause both early and late miscarriages, resulting due to intravascular thrombosis. A number of conditions that predispose to vascular thrombosis include antithrombin III deficiency, protein C deficiency, protein S deficiency, factor V Leiden gene mutation, prothrombin G20210A mutation and hyperhomocysteinemia. Protein C & S are the natural inhibitors of coagulation. Systemic thrombosis has been implicated as a cause of recurrent miscarriage and numerous pregnancy related complications including preeclampsia, abrubtion placenta, placental infarction, intrauterine growth retardation, intrauterine death, etc. The ACOG recommends inherited thrombophilia screening only for unexplained second trimester or third trimester losses. Treatment of these thrombophilias usually requires continuation of heparin therapy throughout pregnancy. The presumed mechanism of late pregnancy losses due to these inherited thrombophilias is the thrombosis of uteroplacental circulation. Presently, there is absence of a randomized trial to justify routine screening for factor V Leiden (FVL) mutation. Currently, there is no test that can reliably discriminate those women with recurrent miscarriage and FVL mutation who are destined to miscarry from those who are destined to have a successful pregnancy. However due to the fact that this mutation is associated with poor pregnancy outcome and maternal risks during pregnancy, the practice of routine screening for FVL and offering thromboprophylaxis to those with FVL mutation and evidence of placental thrombosis, is completely justified.

Immune Causes

The immune factors associated with pregnancy loss can be classified as autoimmune and alloimmune factors.

Autoimmune factors

The autoimmune factors include the synthesis of autoantibodies e.g. antiphospholipid antibodies (antiphospholipid syndrome), antinuclear antibodies, antithyroid antibodies, etc.

Antiphospholipid antibodies: The main types of antiphospholipid antibodies are lupus anticoagulant (LA) and anticardiolipin (aCL) antibodies (IgG & IgM). The association between antiphospholipid antibodies and recurrent miscarriage is referred to as antiphospholipid syndrome (APS). Presence of antiphospholipid antibodies in the blood may result in an increase in the blood viscosity. This may result in the development of thrombosis inside the placental blood vessels, which may be responsible for producing placental insufficiency and/or miscarriage.

Alloimmune factors

Under normal circumstances, the maternal immune system recognizes implanting embryo as foreign body and produces "blocking antibodies", thereby protecting embryo from rejection. These blocking antibodies coat the placental cells, thereby preventing their destruction by maternal lymphocytes. In recurrent miscarriages, there is absence of these blocking antibodies due to failure of recognition of cross-reactive antigens of trophoblast lymphocyte by the mother. Alloimmune traits such as immunologic differences between reproductive partners have been proposed as the factor responsible for this. However, tests for HLA type and antipaternal cytotoxic antibody are not routinely recommended in cases with recurrent miscarriages.

Antiphospholipid Antibody Syndrome

Antiphospholipid antibody syndrome (APAS), also known as Hughes Syndrome is an autoimmune condition that may manifest with recurrent fetal loss, thrombosis (both arterial and venous) and/or autoimmune thrombocytopenia. APAS has emerged as the most important treatable cause of recurrent miscarriage, early onset preeclampsia, preterm labor, low birth weight babies and intrauterine growth restriction. There are three primary classes of antibodies associated with the antiphospholipid antibody syndrome:

- Anticardiolipin antibodies (directed against membrane anionic phospholipids),
- The lupus anticoagulant and
- Antibodies directed against specific molecules including a molecule known as beta-2 glycoprotein I.

Based on the presence or absence of an underlying autoimmune disorder, such as systemic lupus erythematosus, antiphospholipid antibody syndrome may be classified into two: Primary and secondary. If the patient has an underlying autoimmune disorder, the patient is said to have secondary antiphospholipid antibody syndrome. If the patient has

no known underlying autoimmune disorder, it is termed as primary antiphospholipid antibody syndrome.

Pathophysiology of the antiphospholipid antibody syndrome

The antiphospholipid antibody syndrome is an autoimmune phenomenon. The exact mechanism by which the antiphospholipid and anticardiolipin antibodies induce thrombophilic state is not known. In APAS, the homeostatic regulation of blood coagulation is altered. However, the mechanisms of thrombosis have yet not been defined. For women with known antiphospholipid antibody syndrome, it is recommended that prepregnancy counseling is given to the woman and that she be monitored closely from the beginning of the pregnancy.

Defect in cellular apoptosis has been postulated as an important hypothesis behind the pathogenesis of APAS. This exposes the membrane phospholipids so that they can bind with various plasma proteins, such as beta-2 glycoprotein I. Once bound, a phospholipid-protein complex is formed, which subsequently becomes the target of autoantibodies. There may be production of antibodies against coagulation factors, including prothrombin, protein C, protein S and annexins.

Activation of platelets further enhances adherence capacity of endothelial surface. Activation of vascular endothelium, in turn, facilitates the binding of platelets and monocytes resulting in the damage related to APAS. Complement activation has been increasingly recognized to play a significant role in the pathogenesis of APAS.

Clinical features

Clinically, the series of events in APAS, which can lead to hypercoagulability and recurrent thrombosis can affect virtually any organ system, as shown in the table 9.5.

Thus, history of any of the following should raise the suspicion for APAS in obstetrician's mind:

- Thrombosis (e.g., deep vein thrombosis, myocardial infarction, transient ischemic attack, cerebrovascular accident, etc.) This is especially important if the episodes are recurrent, occur at an earlier age, or in the absence of other known risk factors.
- History of recurrent miscarriages (especially late trimester or recurrent) or premature birth.
- History of heart murmur or cardiac valvular vegetations.
- History of hematologic abnormalities, such as thrombocytopenia or hemolytic anemia.
- History of nephropathy.
- Nonthrombotic neurologic symptoms, such as migraine, headaches, chorea, seizures, transverse myelitis, Guillain-Barré syndrome, etc.
- Unexplained adrenal insufficiency.
- Avascular necrosis of bone in the absence of other risk factors.
- Pulmonary hypertension.

Table 9.5: Clinical features of APAS depending on the organ system affected

Organ system affected	*Symptom*
Peripheral venous system	Deep venous thrombosis
Central nervous system	Cerebrovascular accident, stroke, etc
Hematologic system	Thrombocytopenia, hemolytic anemia
Effect on pregnancy	Recurrent pregnancy losses, IUGR, preeclampsia, etc
Pulmonary system	Pulmonary embolism, pulmonary hypertension
Dermatologic effect	Livedo reticularis, purpura, infarcts, ulceration
Cardiovascular system	Libman-Sacks valvulopathy, myocardial infarction
Ocular effects	Amaurosis, retinal thrombosis
Adrenal system	Infarction, hemorrhage, etc
Musculoskeletal	Avascular necrosis of bone

Physical examination

On physical examination, the features enumerated in table 9.6 can be observed:

Table 9.6: Features observed on general physical and systemic examination in cases of APAS

Cutaneous lesions	*Venous thrombosis*	*Arterial thrombosis*
Livedo reticularis	Leg swelling (deep vein thrombosis)	Abnormal results on neurological examination
Superficial thrombophlebitis	Ascites (Budd-Chiari syndrome)	Digital ulcers, gangrene of distal extremities
Leg ulcers	Tachypnea (pulmonary embolism)	Signs of Myocardial Infarction
Painful purpura	Peripheral edema (renal vein thrombosis)	Heart murmurs (frequently indicative of aortic or mitral insufficiency and Libman Sacks endocarditis
Splinter hemorrhages	Abnormal funduscopic examination results indicate thrombosis of retinal vein	Abnormal funduscopic examination results indicating retinal artery occlusion.

Table 9.7: Revised classification criteria for the antiphospholipid syndrome

Clinical criteria	
Vascular thrombosis	One or more clinical episodes of arterial, venous, or small vessel thrombosis in any tissue or organ confirmed by findings from imaging studies, Doppler studies, or histopathology (for histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall) or presence of pregnancy morbidity.
Pregnancy morbidity (Poor Obstetric History)	Unexplained death of a morphologically normal fetus at or beyond 10 weeks. One or more premature deliveries before 34 week of gestation because of severe preeclampsia/ eclampsia or severe IUGR. Three or more unexplained consecutive abortions before 10 weeks of gestation (this is controversial, if no fetal heart has been seen, as some believe that very early abortion is not caused by APAS).
Paraclinical/laboratory Criteria:	The presence of lupus anticoagulant in plasma on two or more occasions at least 12 weeks apart. Presence of moderate to high levels of anticardiolipin (IgG or IgM) in serum or plasma (i.e., >40 IgG phospholipid units (GPL)/mL or IgM phospholipid units (MPL)/mL or >99th percentile) on two or more occasions at least 12 weeks apart. Presence of moderate to high levels of antibeta-2 glycoprotein I antibodies (IgG or IgM) in serum or plasma (>99th percentile) on two or more occasions at least 12 weeks apart.

Source: Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). Journal of Thrombosis and Haemostasis, 2006;4:295–306.

Diagnosis of APAS

In 2006, revised criteria for the diagnosis of APS were published in an international consensus statement. This is described in table 9.7. In order to reach the diagnosis of APAS, at least one clinical criterion and one laboratory criterion must be present.

Investigations

The following laboratory tests should be considered in a patient suspected of having APS:

- aCL antibodies (IgG, IgM)
- Anti-beta-2 glycoprotein I antibodies (IgG, IgM)
- Prolongation of the following clotting assays due to the presence of lupus anticoagulant:
  - kaolin clotting time,
  - Dilute Russell viper venom time (DRVVT)
  - Activated partial thromboplastin time (aPTT)
- Serologic test for syphilis (false positive result)
- CBC count (thrombocytopenia, hemolytic anemia): Thrombocytopenia is fairly common in persons with APS.

Lupus anticoagulant (LA): LA is directed against plasma coagulation molecules, thereby prolonging the in vitro clotting times of plasma by interfering with assembly of components of the coagulation cascade on a phospholipid template. In vitro, presence of this antibody therefore results in the prolongation of clotting assays, such as activated partial thromboplastin time (aPTT), kaolin clotting time and dilute Russell viper venom time (DRVVT). The presence of LA is confirmed by mixing normal platelet poor plasma with the patient's plasma. If a clotting factor is deficient, the addition of normal plasma corrects the prolonged clotting time.

Anticardiolipin antibodies: aCL antibodies react primarily with membrane phospholipids, such as cardiolipin and phosphatidylserine. There are three known isotypes of aCL, i.e., IgG, IgM, and IgA. Of these three isotypes of aCL, the values of IgG most strongly correlate with the occurrence of thrombotic events. Cardiolipin is the dominant antigen used in most serologic tests for syphilis; consequently, these patients may have a false positive test result for syphilis.

Cutoff levels for IgG aCL [in IgG phospholipid (GPL) units] and IgM aCL [in IgM phospholipids (MPL) units] have been presented in guidelines issued by the Association of Clinical Pathologists, with negative results defined as < 5 GPL units and < 3 MPL units, low positive results defined as values <15 GPL units and <6 MPL units, medium levels defined as 15–80 GPL units and 6–50 MPL units and high levels defined as <80 GPL units or <50 MPL units.

In detection of lupus anticoagulant, the dilute Russell's viper venom time (DRVVT) test is more sensitive and specific than either the activated partial thromboplastin time (aPTT) or the kaolin clotting time (KCT) tests. Anticardiolipin antibodies are detected using a standardized enzyme linked immunosorbent assay (ELISA).

Imaging Studies:

- Imaging studies are helpful for confirming a thrombotic event, for e.g. the use of CT scanning or MRI of the brain (cerebrovascular attack), chest (pulmonary embolism), or abdomen (Budd-Chiari syndrome).
- Doppler ultrasound studies are recommended for possible detection of DVT.
- Two dimensional echocardiography may help demonstrate an asymptomatic valve thickening, vegetations or valvular insufficiency. Aortic or mitral insufficiency is

the most common valvular defect found in persons with Libman Sacks endocarditis.

Treatment

The prophylactic measures comprise of elimination of various risk factors, such as oral contraceptives, smoking, hypertension or hyperlipidemia. The following treatment options can be considered:

- Patients with recurrent pregnancy loss must be administered a prophylactic dose of subcutaneous heparin [preferably low-molecular-weight heparin (LMWH)] and low-dose aspirin. Since long term use of heparin can cause osteoporosis, patients who require heparin administration throughout pregnancy should also receive calcium and vitamin D supplementation. Therapy is usually withheld at the time of delivery and is restarted after delivery, continuing for 6–12 weeks postpartum. Most obstetricians prefer to avoid the use of warfarin (coumadin) during pregnancy as it can cross the placental barrier and produce teratogenic changes in the fetus.
- Breastfeeding women may be administered the combination of heparin and warfarin. If warfarin therapy is instituted, the patient must be instructed to avoid excessive consumption of foods that contain vitamin K.
- Some researchers have examined the use of combination comprising of aspirin and prednisone during pregnancy. Most of the studies suggest that complications associated with prednisone use usually outweigh the benefits associated. Thus prednisone must not be used in addition to aspirin. In patients for whom the treatment with aspirin and heparin is not successful, use of intravenous immunoglobulins (IVIG) can be used. At this time, the studies suggest this may be helpful in refractory cases, but is not recommended for use on a routine basis.
- In patients with SLE, hydroxychloroquine, which may have intrinsic antithrombotic properties, can be considered.
- Consultations with specialists like rheumatologist, hematologist, neurologist, cardiologist, pulmonologist, hepatologist, ophthalmologist, etc may be required depending on clinical presentation.
  - Women with aPL antibodies who experience recurrent miscarriages may have favorable prognoses in subsequent pregnancies, if treated with aspirin and heparin.
  - The patient must be educated about anticoagulation therapy and explained the importance of planned pregnancies so that long term warfarin can be switched to aspirin and heparin before pregnancy is attempted.

Environmental Factors

Exposure to noxious or toxic substances is supposed to result in miscarriages. Various environmental factors, exposure to which is supposed to result in spontaneous miscarriages include the following:

- Cigarettes
- Alcohol and caffeine
- Antiprogestogens
- Antineoplastic agents
- Anesthetic gases
- Petroleum products
- Ionizing radiation
- Exposure to organic solvents, environmental toxins (heavy metals), etc.
- Exposure to DES: Exposure to diethylstilbestrol (DES) can cause complex congenital anomalies, including uterine hypoplasia, or T-shaped uterus, cervical weakness and vaginal changes. DES is a synthetic estrogen compound which was administered to some pregnant women during the 1950's and 1960's. Exposure of a pregnant woman to DES is supposed to cause uterine malformations in the developing female fetus.

Unexplained Cases of Recurrent Miscarriage

In nearly 50% of the cases with recurrent miscarriage, no cause can be identified, despite careful investigations.

History

RISK FACTORS

Detailed history from both the partners needs to be taken. The different risk factors for recurrent miscarriages need to be elicited as follows:

Maternal age: Maternal age is an important risk factor for a further miscarriage. Advanced maternal age adversely affects ovarian function, giving rise to a decline in the number of good quality oocytes.

History of specific medical illness: It is important to elicit the history of specific medical illnesses like diabetes, thyroid disease (table 9.8 and 9.9), etc.

Table 9.8: Symptoms suggestive of hyperthyroidism

Palpitations, nervousness, breathlessness
Heat intolerance
Insomnia
Increased bowel movements
Light or absent menstrual periods
Tachycardia
Tremors in hands
Weight loss
Muscle weakness
Warm moist skin
Hair loss

Table 9.9: Symptoms suggestive of hypothyroidism

Weight gain or increased difficulty in losing weight
Fatigue, weakness
Hair loss; coarse, dry hair; dry, rough, pale skin
Reduced thermogenesis resulting in cold intolerance
Muscle cramps and frequent muscle aches
Constipation
Memory loss
Husky, low-pitched and coarse voice
Abnormal menstrual cycles, decreased libido
Depression, irritability
Pitting edema in the lower extremities

History suggestive of infectious disease: TORCH infections and infections by other microorganisms (*Neisseria gonorrheae, Chlamydia, mycoplasma*, etc) have been implicated as a cause of recurrent miscarriages. It is important to take the history of an infective illness in the past, especially that associated with fever and rashes.

History of exposure to environmental toxins: The obstetrician needs to elicit history of exposure to environmental toxins (e.g. history of smoking, drinking alcohol, exposure to radiations, DES, etc).

History suggestive of previous episodes of thrombosis: Symptoms suggestive of deep vein thrombosis include sudden unilateral swelling of an extremity; presence of pain or aching of an extremity, etc. This would help in ruling out thrombophilia as the cause for recurrent miscarriage.

History suggestive of antiphospholipid antibody syndrome: Signs and symptoms suggestive of APAS have been enumerated in table 9.5.

History of previous miscarriages: This is an independent risk factor for further miscarriages.

Timing for previous miscarriage is also important. Since the causes for early and late pregnancy losses are different, it is important for the clinician to ask the time of previous pregnancy losses. Early miscarriage can be defined as pregnancy loss at ≤ 12 weeks.

General Physical Examination

General physical examination should be done with the aim of detecting the causes for recurrent miscarriage, including PCOS (hirsuitism and hyperandrogenism), diabetes, prolactin disorders (galactorrhea), hyperandrogenism and thyroid disorders (thyroid enlargement). Pedal edema, though a feature of hypothyroidism, is a common finding in normal pregnancy; therefore if thyroid disorder is suspected, investigations for thyroid function test must be carried out.

Specific Systemic Examination

EXAMINATION OF EXTERNAL GENITALIA

Examination of external genitalia is important to detect the presence of blisters, sores, chancres etc, which could be associated with genital tract infection. Infections of the genital tract could be associated with the presence of abnormal vaginal discharge.

Herpes viral infection: This is associated with presence of multiple ulcers in the external genitalia.

Syphilis: Primary syphilis infection is associated with the presence of a painless sore on external genitalia, which are usually painless, firm, oval and round. Swelling of the glands in the groin may occur, but is usually nontender.

ABDOMINAL EXAMINATION

Abdominal examination as described in chapter 1 needs to be carried out.

PELVIC EXAMINATION

Pelvic examination should be done to look for signs of infection, cervical anatomy, uterine size and shape (uterine leiomyomas, uterine malformations like bicornuate uterus, septate uterus etc).

Management

Management comprising of investigations and definitive obstetric management is discussed below.

Investigations

Various investigations required for a case of bad obstetric history need to be decided based on the patient's history and examination.

Parental Karyotype

All couples with a history of recurrent miscarriages should have peripheral blood karyotyping and cytogenetic analysis of the products of conception.

Thyroid Function Test

Tests for thyroid function include tests for thyroid hormones (T_3, T_4 and TSH) and detection of antibodies (antithyroid antibodies). Measurement of TSH levels in the second trimester is a sensitive indicator of thyroid function.

Serum Prolactin Levels

Normal serum prolactin levels in nonpregnant women vary from 2–29 ng/mL. During pregnancy, the prolactin levels normally increase and may lie in the range of 10–209 ng/ml. Hyperprolactinemia has been reported as an important cause for recurrent miscarriage. Treatment with bromocriptine has been found to significantly reduce the rate of miscarriage.

Blood Glucose Levels

Blood sugar levels (both fasting and postprandial) need to be carried out. For ruling out diabetes mellitus and gestational diabetes, tests like oral glucose tolerance test (OGTT) and GCT (Glucose Challenge Test) also need to be carried out respectively (see chapter 13).

Blood Grouping

ABO and Rh typing of both the parents must be done as Rh isoimmunization is an important cause for repeated pregnancy losses (chapter 6).

Venereal Disease Research Laboratory (VDRL)

The most common tests for detection of syphilis using nonspecific antibodies are RPR (rapid plasma reagin) and VDRL tests.

TORCH Test

Confirmation of maternal infection by TORCH screening is recommended.

High Vaginal Swab

High vaginal swab helps in detection of infections like chlamydia, bacterial vaginosis, etc.

Testing for APAS

Testing for lupus anticoagulant or anticardiolipin (aCL) antibodies

For the diagnosis of APAS, it is mandatory that the patient should have two positive tests at least 6 weeks apart for either lupus anticoagulant or anticardiolipin (aCL) antibodies of IgG and/or IgM class (present in medium or high titer, see table 9.7).

Sonohysterography is a new technique (figure 9.7) which helps in imaging of the uterine cavity in order to better diagnose the uterine anomalies. In this technique, sterile saline solution is infused inside the uterine cavity with help of a plastic catheter in conjunction with transvaginal ultrasound. The saline infusion distends the uterine cavity and provides an excellent contrast to the endometrial lining, providing improved visualization of uterine and endometrial pathology. Hysterosonography, therefore acts as a sensitive and specific

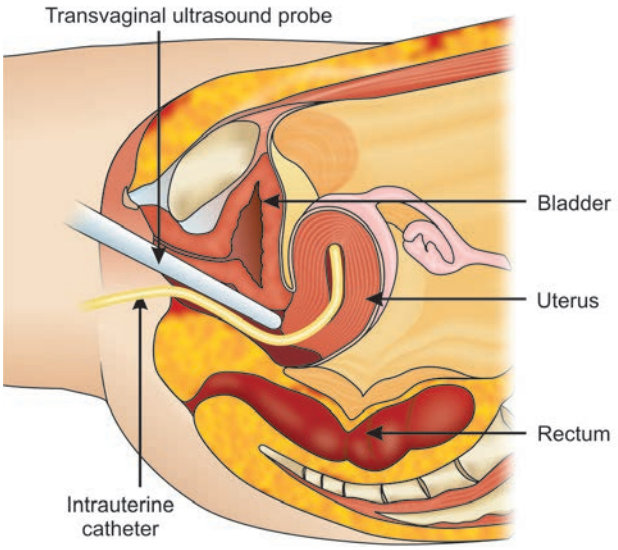


Fig. 9.7: Technique of sonohysterography

screening tool for evaluating the uterine cavity and it could be an accurate alternative to HSG in screening for uterine abnormalities.

Hysterosalpingography is a procedure which involves taking X-ray of the pelvis following the instillation of radiopaque contrast agent. This technique is not more sensitive than either ultrasound examination or sonohysterography. Hysterosalpingography (HSG) helps in delineating the shape of the uterine cavity and in confirming the patency of the fallopian tubes (figure 9.8A). HSG also helps in diagnosing causes of recurrent miscarriage including uterine malformations (figure 9.9), cervical incompetence, Asherman's

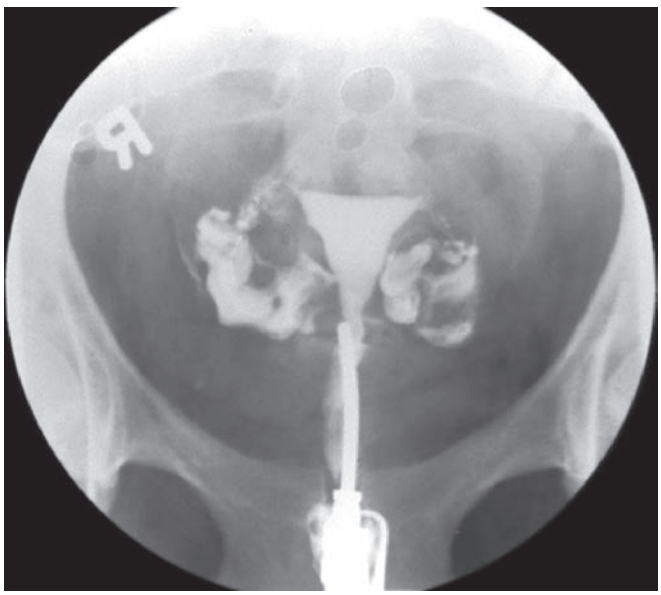


Fig. 9.8A: Normal hysterosalpingogram showing smooth triangular uterine cavity, with the dye spilling from the ends of both tubes.

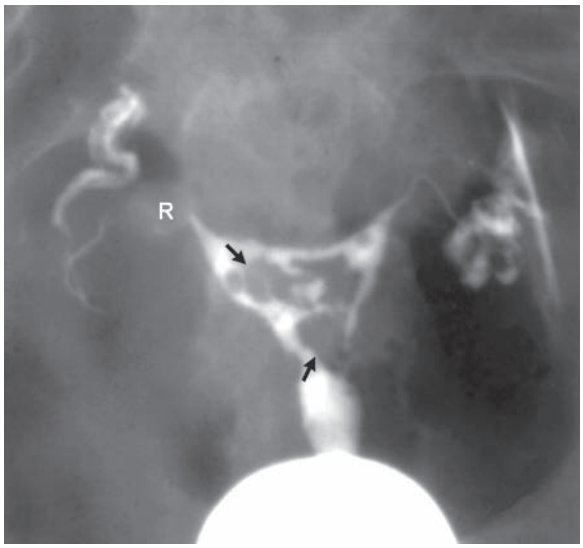


Fig. 9.8B: Hysterosalpingogram revealing irregular filling defects in the endometrium suggestive of endometrial adhesions. (Arrows represent adhesions). The patient was diagnosed to be suffering from Asherman's syndrome on hysteroscopy on which resection of the intrauterine adhesions was done

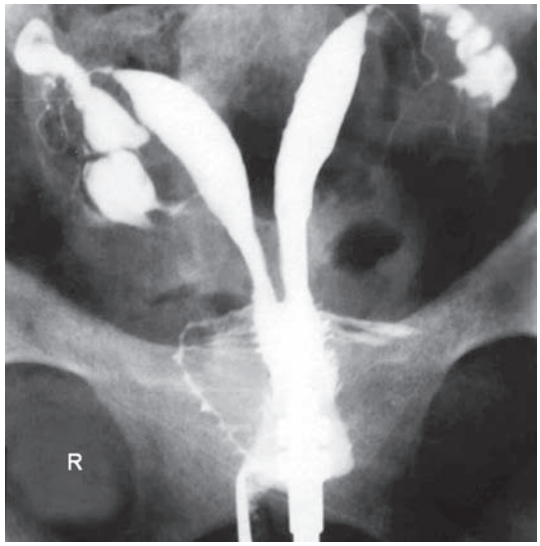


Fig. 9.8C: HSG showing presence of uterine septum, which was confirmed on hysteroscopy

syndrome (figure 9.8B) etc. For the true assessment of the deformity, HSG must be taken at right angles to the axis of uterus. Sometimes, it may not be possible to differentiate a septate uterus (figure 9.8C) from a bircornuate uterus (figure 9.8D) by HSG alone. Septate uterus may be differentiated from bicornuate uterus on the basis of the angle between the uterine cavities. In case of septate uterus, this angle is usually less than 75°. If this angle is equal to or greater than 105°, diagnosis of a bicornuate uterus is usually made. Angles between 75° and 105° are more likely to be due to septate

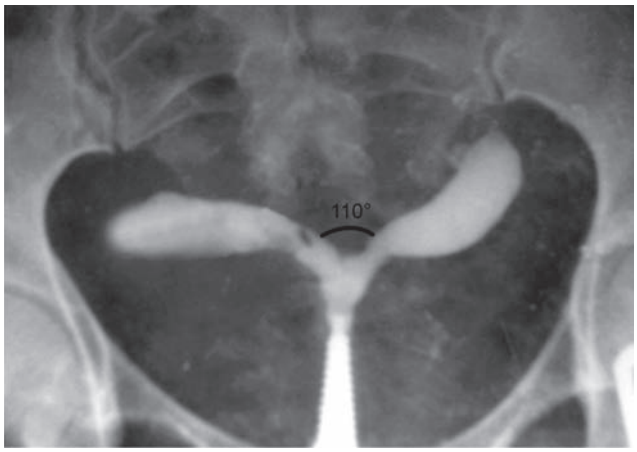


Fig. 9.8D: Hysterosalpingogram showing a single cervical canal and a possible duplication of the uterine horns. It was difficult to differentiate between bicornuate uterus and septate uterus on ultrasound alone. Since an angle of greater than 105° was found to be separating the two uterine horns, the diagnosis of bicornuate uterus was made

uterus, but an ultrasound examination or a laparoscopy may be required to confirm the diagnosis. The external uterine configuration is better assessed with help of laparoscopy. If the uterine fundal contour can be visualized, the diagnosis of septate uterus can be made. Uterus didelphys, another müllerian duct anomaly, which closely resembles bicornuate uterus can be differentiated from it on the basis of the number of cervical canals present (figure 9.9). In cases of uterus didelphys, two cervical canals are present but only one is seen in cases of bicornuate uterus.

Ultrasound Examination

All women with recurrent miscarriage should undergo an ultrasound examination for assessment of uterine anatomy and morphology (figure 9.10). Ultrasound, especially a vaginal scan helps in detection of abnormalities inside the uterus (uterine septa, intrauterine adhesions, submucousal adhesions, leiomyomas), testing the ovarian reserve and making diagnosis of polycystic ovaries. With the advent of three dimensional ultrasound examination, the requirement for diagnostic hysteroscopy and laparoscopy has considerably reduced.

Hysteroscopy

Hysteroscopic examination helps in visualization of the interior of the uterine cavity [presence of structural uterine anomalies, e.g. adhesions, uterine septa (figure 9.11), etc], the endometrial lining and shape of the uterus.

Laparoscopic examination helps in the visualization of external surface of the uterus (e.g. presence of bicornuate uterus, unicornuate uterus, etc).

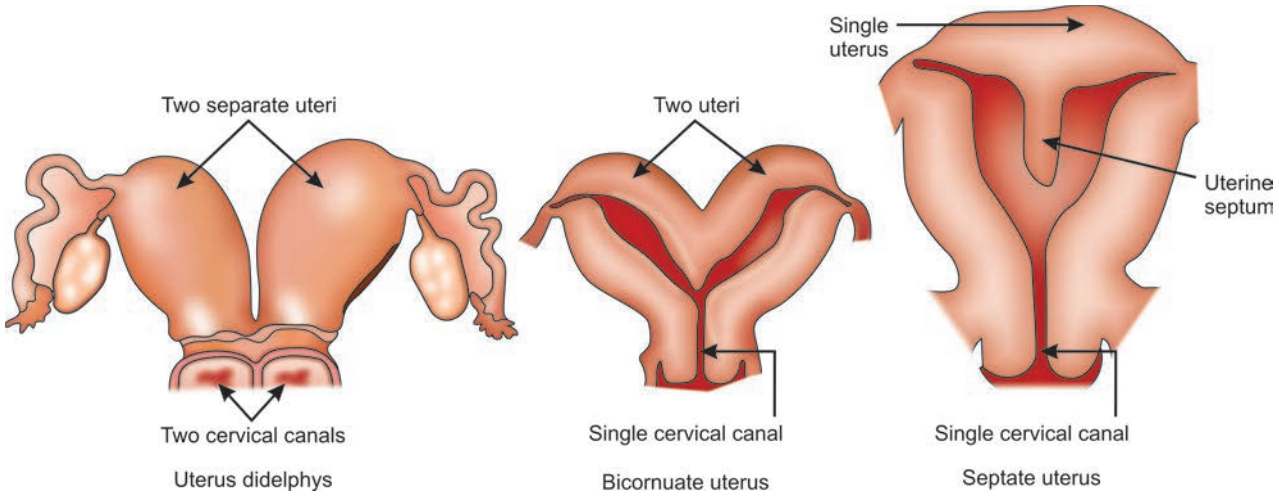


Fig. 9.9: Various müllerian duct anomalies

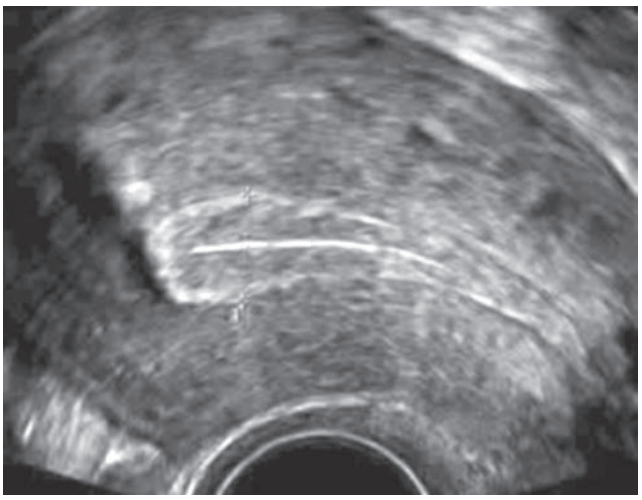


Fig. 9.10: Transvaginal ultrasound images of a uterus in a 32 years old woman, with a normal endometrial lining that is 11.2 mm showing the normal "triple stripe" appearance

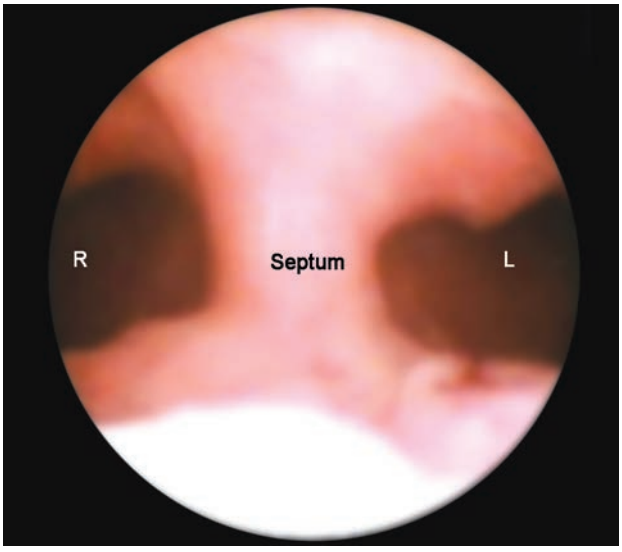


Fig. 9.11: Hysteroscopic visualization of uterine septum at the time of laparoscopy

Thrombophilia Screening

This includes screening for factor V Leiden, Prothrombin G20210A mutation and thrombophilia screening.

Test for Cervical Incompetence

Ultrasonography

Ultrasound examination for diagnosing the cases of cervical incompetence has been described in the text.

Passage of No. 6-8 Hegars dilator

If the clinician is able to pass No 6–8 Hegar's dilator through the internal os without any pain or resistance especially in the premenstrual period, this test is indicative of cervical incompetence. Also, there is absence of a snapping sound as the Hegar's dilator is suddenly withdrawn out of cervical canal in cases of cervical incompetence.

Rx *Treatment/Obstetric Management*

Psychological Support

It is important to alleviate patient's anxiety and to provide psychological support. About 40% to 50% of the total cases of recurrent abortion remain unexplained. For these cases, tender loving care (TLC) especially by the family and the

partner, reassurance and supportive care are all that are usually required. However, presently there are no randomized controlled trials in support of TLC. All obstetricians should be aware of the psychological sequel associated with miscarriage and should provide adequate psychological support and follow up, as well as access to formal counseling when required.

Genetic Counseling

Genetic abnormalities require referral to a clinical geneticist. In case of detection of a chromosomal anomaly, genetic counseling, familial chromosomal studies, counseling and appropriate prenatal diagnosis in future pregnancies offer the couple a good prognosis for future pregnancies.

Preimplantation genetic diagnosis

Preimplantation genetic diagnosis or prenatal diagnosis (amniocentesis and chorionic villus sampling) helps in identifying embryos having or not having chromosomal abnormalities.

Control of Diabetes and Thyroid Dysfunction

Prepregnancy glycemic control is particularly important for women with overt diabetes mellitus. Replacement with thyroid hormone analogues may be required in hypothyroid women.

Operative Hysteroscopy

Operative hysteroscopy can help in treatment of the following anomalies:

- Removal of submucous leiomyomas,
- Resection of intrauterine adhesions,
- Resection of intrauterine septa.

Treatment of Luteal Phase Defects

Treatment of luteal phase defects is done using micronized progesterone in the dosage of 100 mg daily. Progesterone supplementation must continue until 10–12 weeks following gestation.

APLA Syndrome

Treatment of APLA syndrome has been described in the text above.

Cervical Incompetence

Surgery for cervical incompetence has been described in the text above.

Inherited Thrombophilias

Antithrombotic therapy with heparin (5,000 IU subcutaneously) or low molecular weight heparin (subcutaneously) once daily has been found to be effective. Antithrombotic therapy is usually administered up to 34 weeks of gestation.

PCOS

Treatment of PCOS involves weight reduction, use of insulin sensitizing agents (metformin) and ovulation induction with clomiphene citrate.

Infections

For cases in which an infectious organism has been identified, appropriate antibiotics should be administered, e.g. penicillin (syphilis); ganicyclovir (cytomegalovirus); acyclovir (genital herpes); pyramethamine and sulphadiazine (toxoplasmosis). Posttreatment cultures must be done in order to verify eradication of the infectious agent before the patient is advised to attempt conception.

Important Questions and Answers

Q.1. In the above mentioned case study, there was no history suggestive of any cause pertaining to recurrent miscarriage. What investigations need to be performed in this case?

Ans. Some of the investigations which need to be done include the following: ABO/Rh, blood glucose levels (fasting/postprandial; GCT, TFT, VDRL, TORCH, lupus anticoagulant and anticardiolipin antibodies, and a transvaginal ultrasound scan. Abnormalities on ultrasound examination, should be followed by hysteroscopy, laparoscopy, sonohysterography and/or HSG depending on the type of abnormalities detected.

Q.2. In this case, all investigations were within normal limits and a diagnosis of unexplained recurrent miscarriage was made. What should be the next line of management in women with unexplained recurrent miscarriage?

Ans. In significant proportion of cases of recurrent miscarriage, cause remains unexplained, despite detailed investigations. These women can be reassured that the prognosis for a successful future pregnancy with supportive care alone is in the region of 75%. Women with unexplained recurrent miscarriage have an excellent prognosis for future pregnancy outcome without pharmacological intervention, if offered supportive care (TLC) alone. The prognosis in cases with recurrent pregnancy losses worsens with increasing maternal age and the number of previous miscarriages.

Q.3. When should the clinician start investigating the women presenting with a history of recurrent abortions?

Ans. The clinician should start investigating the woman presenting with a history of recurrent abortions in the following cases:

- More than or equal to three abortions,
- Unexpected fetal death after 16 weeks,
- Severe IUGR,
- Severe preeclampsia/eclampsia before 34 weeks.

Q.4. Should routine progesterone supplementation or supplementation with human chorionic gonadotrophin (hCG) be given during pregnancy to prevent a miscarriage?

Ans. There is presently insufficient evidence to evaluate the effect of progesterone or human chorionic gonadotrophin (hCG) supplementation in pregnancy to prevent a miscarriage. The present evidence regarding the use of both progesterone and hCG for treatment of recurrent pregnancy losses has presented with conflicting results. Furthermore, the presence of low progesterone levels may indicate a pregnancy that has already failed. Use of exogenous supplementation with progesterone or hCG can be recommended only if well designed randomised controlled trials in future are able to prove the efficacy of these strategies. However despite of lack of good quality evidence, supplementation with progesterone and hCG is commonly being used in clinical practice.

Q.5. Does polycystic ovarian morphology itself predict an increased risk of future pregnancy loss among ovulatory women with a history of recurrent miscarriage when they conceive spontaneously?

Ans. All women with PCOS may not be necessarily at a high risk of recurrent miscarriage. Polycystic ovarian morphology is a classical feature of PCOS. Though the prevalence of polycystic ovarian syndrome is significantly higher among women with recurrent miscarriage in comparison with the general population, polycystic ovarian morphology by itself is not a predictor for an increased risk of future pregnancy loss among ovulatory women with a history of recurrent miscarriage who conceive spontaneously.

Q.6. When is APAS considered as a cause for adverse pregnancy outcome?

Ans. Adverse pregnancy outcomes in association with APAS include the following:

- Three or more consecutive miscarriages before ten weeks of gestation,
- one or more morphologically normal fetal deaths after the tenth week of gestation and
- one or more preterm births before the 34th week of gestation due to severe preeclampsia, eclampsia or placental insufficiency.

Women with recurrent miscarriage associated with high levels of antiphospholipid antibodies are at a high risk of complications during the three trimesters including repeated miscarriage, preeclampsia, fetal growth restriction and preterm birth.

Bibliography

1. de Braekeleer M, Dao TN. Cytogenetic studies in couples experiencing repeated pregnancy losses. Hum Reprod. 1990;5: 519-28.
2. Hirahara F, Andoh N, Sawai K, et al. Hyperprolactinemic recurrent miscarriage and results of randomized bromocriptine treatment trials. Fertil Steril. 1998;70(2):246-52.
3. Khamashta MA, Hughes GR. ACP Broadsheet no 136: February 1993. Detection and importance of anticardiolipin antibodies. J Clin Pathol. 1993;46:104-7.
4. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. N Engl J Med. 2002;346:752-63.
5. Management of Early Pregnancy Loss. ACOG Practice Bulletin (American College of Obstetricians and Gynecologists) 24 (February). 2001.
6. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). Journal of Thrombosis and Haemostasis. 2006;4:295-306.
7. Regan L, Braude PR, Trembath PL. Influence of past reproductive performance on risk of spontaneous abortion. BMJ. 1989; 299:541-5.
8. Rema Devi, N. Sreenivas, Sayee Rajangam. Bad Obstetric History and Infectious Causes. Int J Hum Genet. 2002;2(4): 269-71.
9. Stirrat GM. Recurrent miscarriage. Lancet. 1990;336:673-5.
10. Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: Remanagement of obstetric APS 1037 report of an international workshop. Arthritis Rheum. 1999;42:1309-11.

Chapter

10 Postpartum Hemorrhage

Case Study

A thirty-year-old G4 P3 L3 patient had a normal vaginal delivery in the morning at the hospital. A live health baby weighing 4.5 kg was delivered. The woman was transferred to the postpartum ward after 3–4 hours of delivery. At the time of transfer the patient was stable, her uterus was well contracted on per abdominal examination and slight amount of vaginal bleeding was present. However she had to be shifted to the emergency ward in evening in the state of shock due to excessive breeding.

Introduction

The above mentioned case scenario is suggestive of PPH. PPH can be considered as a major obstetric emergency and a leading cause of maternal mortality and morbidity. Some amount of blood loss can occur normally during the process of child birth. Approximate blood loss at the time of normal vaginal delivery is considered to be 500 ml; 1000 ml at the time of cesarean section and 1500 ml during postpartum hysterectomy.

According to WHO, postpartum hemorrhage can be defined as blood loss of 500 ml or more per vaginum during the first 24 hours after the vaginal delivery of the baby or blood loss of more than 1000 ml at the time of cesarean delivery. ACOG has defined PPH as a decrease in hematocrit by 10% or requirement of blood transfusion 24 hours after the delivery. The WHO has classified PPH into two: Primary PPH and Secondary PPH.

Primary PPH

Primary postpartum hemorrhage can be defined as blood loss, estimated to be greater than 500 ml, occurring from the genital tract, within 24 hours of delivery. Primary PPH can be considered as the commonest cause for obstetric hemorrhage.

Secondary PPH

Secondary PPH can be defined as abnormal bleeding from the genital tract, occurring 24 hours after delivery until 6 weeks postpartum.

This definition of PPH is however based on subjective observations because it may be difficult to accurately assess the amount of blood loss. Some of the parameters, which can help assess the blood loss, include the following:

- Hemodynamic stability of the patient: Is the patient stable or unstable based on hemodynamic parameters (pulse, blood pressure, etc)?
- Change in the patient's hematocrit: A rapid decline in the patient's hematocrit of ≥10% between the time of admission and the postpartum period.
- Does the patient require a transfusion of red blood cells?

Some methods for estimating the blood loss are as follows:

- Collection of blood into blood pans and plastic bags.
- Use of calibrated drapes and receptacles at the time of delivery to estimate the blood loss.
- Weighing the sponges soaked in blood and calculating the change in weight of the dry and soaked sponges.
- Acid/alkali hematin method: The collected blood is converted into hematin and the amount is determined by calorimetric readings.

Causes of PPH

The mnemonic "4 T's" (tone, trauma, tissue and thrombin) helps in describing the four important causes of PPH, which are enumerated in table 10.1:

Atonic Uterus

Uterine atony is one of the most important causes for PPH, responsible for nearly 90% cases. Uterine atony refers to the failure of the uterine muscle to contract normally following delivery of the baby and placenta (figure 10.1). Separation

Table 10.1: Causes of PPH

Tone: Atonic uterus
Trauma: Cervical, vaginal and perineal lacerations, pelvic hematomas, uterine inversion, ruptured uterus
Tissue: Retained tissue (placental fragments), invasive placenta
Thrombin: Coagulopathies

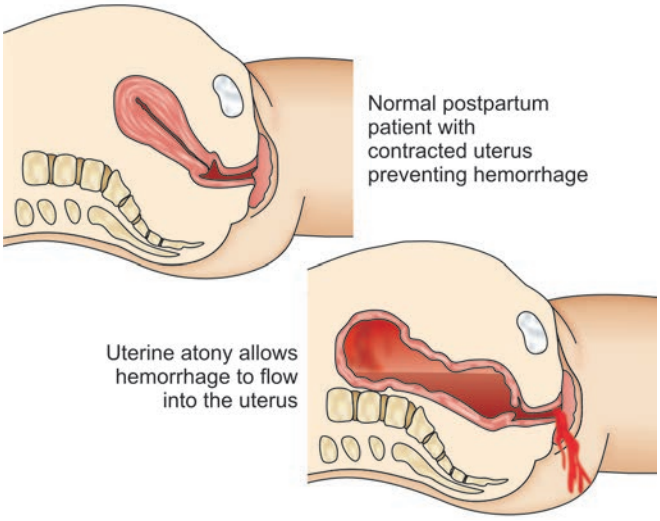


Fig. 10.1: Mechanism of bleeding in an atonic uterus

of the placenta from the wall of the uterus results in shearing off of the maternal blood vessels, which supply blood to the placenta. Under normal circumstances, the contraction of the uterine musculature causes compression of these blood vessels. However the bleeding would continue to occur if the uterine musculature does not effectively contract.

Causes of atonic uterus

Risk factors for development of uterine atony are as follows:

- Overdistension of uterus
- Induction of labor
- Prolonged/precipitate labor
- Anesthesia (halogenated drugs like halothane) and analgesia
- Tocolytics
- Grand multiparity
- Mismanagement of 3rd stage of labor
- Full bladder
- Antepartum hemorrhage (placenta previa, abruption placenta, couvelaire uterus, etc)
- Prolonged labor
- Chorioamnionitis
- Polyhydramnios
- Fetal macrosomia
- Dystocia

Traumatic Causes for PPH

The various traumatic causes for PPH are as follows:

- Large episiotomy and extensions
- Tears and lacerations of perineum, vagina or cervix
- Pelvic hematomas
- Uterine inversion
- Ruptured uterus

Tissue – Retained Tissue (Placental Fragments), Invasive Placenta

PPH can commonly occur if retained bits of placental tissue or blood clot remain inside the uterine cavity and are not expelled out. Invasive placenta refers to abnormal adherence of the placenta to the uterine wall due to invasion of the uterine wall by the placental trophoblasts. Adherent placenta can be of three types: Placenta accreta; placenta increta and placenta percreta. These would be described later in the chapter.

Thrombin – Coagulopathies

Abnormalities of the coagulation pathway (both intrinsic and extrinsic) can also commonly result in PPH.

History

RISK FACTORS

Risk factors for development of postpartum hemorrhage, which need to be elicited while taking the history, include the following:

- Overdistended uterus (multifetal gestation, large fetus, polyhydramnios)
- Grand multiparity (para 4 or more)
- Past history of PPH or retained placenta or manual removal of placenta
- Prolonged labor
- Operative delivery (use of forceps, ventouse etc)
- Delivery of a large placenta (e.g. due to multifetal gestation)
- Episiotomy, fetal macrosomia,
- History of antepartum hemorrhage (both placenta previa and abruption) in the present pregnancy
- History of infection (e.g. chorioamnionitis)
- Previous history of cesarean sections
- Preexisting maternal hemorrhagic conditions (e.g. hemophilia A, hemophilia B, Von Willebrands disease). The obstetrician needs to enquire about the woman's personal or family history of bleeding, including bleeding with minor trauma, medications, postsurgical bleeding and tooth extractions. History of excessive bleeding from various sites including menorrhagia, epistaxis, hematuria, etc also needs to be taken.

Risk Factors During Labor

The presence of following risk factors at the time of labor must prompt extra vigilance among clinical staff regarding

Table 10.2: Changes in vital signs with increasing amount of blood loss

Blood loss (% Blood Volume)	*Pulse rate*	*Systolic Blood Pressure (mm of Hg)*	*Degree of shock*	*Symptoms*
10%–15% (500–1000 ml)	Normal	Normal	Compensated	Postural hypotension, palpitations, dizziness
15%–25% (1000–1500 ml)	Slight increase (80–100 beats/minute)	Slight fall (80–100)	Mild	Thirst, weakness
25%–35% (1500–2000 ml)	Marked increase (100–120 beats/minute)	Moderate fall (60–80)	Moderate	Pallor, oliguria, confusion
> 40% (2000–3000 ml)	Highly marked tachycardia	Marked fall (40–60)	Severe	Anuria, air hunger, coma, death

the early detection and management of PPH in these cases. Some of these factors include:

- Delivery by emergency cesarean section
- Delivery by elective cesarean section
- Retained placenta
- Mediolateral episiotomy
- Prolonged labor (>12 hours)
- Delivery of a big baby (>4 kg)
- Operative vaginal delivery
- Pyrexia in the intrapartum period

General Physical Examination

Though a case of postpartum hemorrhage is unlikely to be given as a clinical case during exams, it is been discussed in details because it is an obstetrical emergency which is commonly encountered in obstetric practice. Therefore every obstetrician must be well prepared to deal with this potentially life threatening emergency.

Signs and Symptoms

Vital signs are highly unreliable indicators of the severity of bleeding. Mild to moderate degree of blood loss of 500–1000 ml (10% to 15%) is unlikely to affect the vital signs like pulse, blood pressure, etc. However, severe degrees of blood loss are likely to produce signs and symptoms as described in table 10.2. Blood loss exceeding 30% of blood volume or more may be associated with a positive tilt test.

Tilt test

An increase in heart rate of more than 10 beats per minute and/or decrease in diastolic blood pressure of more than 10 mm of Hg when the patient is tilted from supine to a semirecumbent body position (45° from the horizontal) can be described as a positive tilt test.

Specific Systemic Examination

ABDOMINAL EXAMINATION

The uterus must be palpated per abdominally to assess if it well contracted or not. If the uterus appears to be well contracted and hardened, PPH due to uterine atonicity can be ruled out. In these cases the most important cause of PPH could be trauma to the genital tract or retained tissue fragments inside the uterine cavity.

PER SPECULUM EXAMINATION

Vagina must be inspected in good light to visualize any tears or lacerations, which could be responsible for bleeding. If the patient is not cooperative and vaginal injury is been suspected as a cause of PPH, a thorough examination of the lower genital tract under general anesthesia may be required. A per speculum examination of the cervix (figure 10.2) may also be carried out to rule out the presence of cervical and vaginal tears.

Differential Diagnosis

As described in table 10.1 various reasons for PPH could be uterine atonicity, trauma, retained tissue or coagulation abnormalities. The obstetrician needs to find out the exact cause of PPH through history, clinical examination and diagnosis. Various coagulation abnormalities which could be responsible for producing PPH are enumerated in table 10.3.

Management

Management comprising of investigations and definitive obstetric management is discussed next.

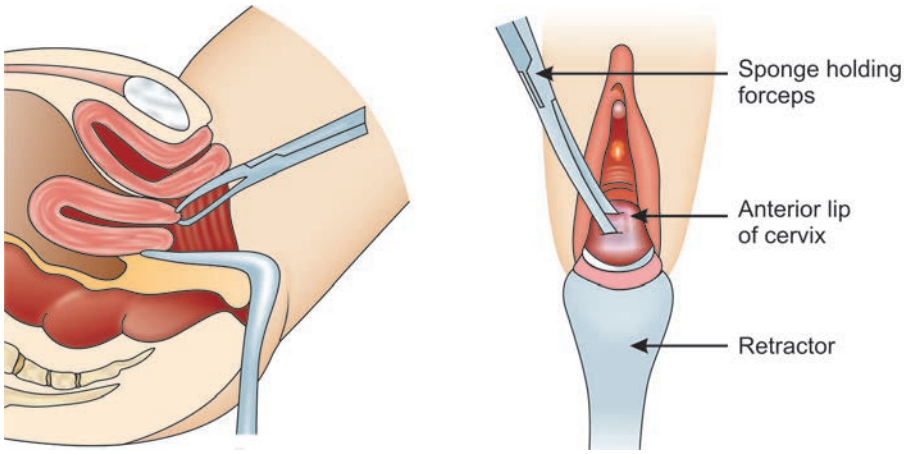


Fig. 10.2: Per speculum examination of the cervix

Table 10.3: Coagulation abnormalities resulting in PPH

Drugs (e.g., aspirin, heparin, warfarin, alcohol, chemotherapy)
Liver disease
Severe vitamin K deficiency
DIC
Von Willebrand's disease
Hemophilia
Idiopathic thrombocytopenic purpura
Heparin induced thrombocytopenia

Investigations

The following investigations need to be done in cases of PPH:

- *Complete Blood Count with peripheral smear.*
- *Coagulation profile:* Platelet count, prothrombin time (evaluates extrinsic pathway—factors X, VII, V, II, I); activated partial thromboplastin time (evaluates intrinsic pathway—XII, XI, IX, VIII, V, II, I); thrombin time (measures ability of thrombin to transform fibrinogen in fibrin), bleeding time (evaluates platelet function and capillary integrity).
- *Urinalysis* (for hematuria)
- *High vaginal swab,* to rule out infection (especially gonorrhea, Chlamydia, etc)
- *Transabdominal or transvaginal ultrasound:* Ultrasound examination may especially be required if retained products of conception are suspected. Presence of a normal endometrial stripe on TVS almost always helps in ruling out the presence of retained placental fragments.

Treatment/Obstetric Management

Since PPH can present as a major obstetrical emergency, more important than managing PPH is preventing PPH from occurring in the first place.

PREVENTION OF PPH

Some of the steps for preventing PPH are described below:

- Identification of cases at high risk of developing PPH. Such cases should be carefully assessed during regular ANC checkups. All women with significant risk of PPH should be managed at a hospital equipped with intensive care facilities and access to specialist services. Facilities for rapid transportation of the patient to the nearest such hospital at the earliest must be available.
- Since anemia is an important risk factor contributing to the mortality and morbidity related to PPH, it should be diagnosed and treated as soon as possible in the antenatal period itself.
- The most important step which must be routinely used in the third stage for prevention of PPH is the active management of third stage of labor. Active management of labor comprises of the following steps:
- Administering a uterotonic drug, usually 0.25 mg of methargin or ergometrine 0.2 mg soon after the delivery of the anterior shoulder and/or oxytocin 10 IU within one minute of the birth of the baby.
- Clamping the cord as soon as it stops pulsating.
- Uterine massage (would be described later).
- Controlled cord traction or Brandt-Andrews maneuver. The procedure of controlled cord traction is shown in figure 10.3 and comprises of the following steps:
- The cord must be clamped as close to the perineum as possible.
- The clinician must look for the signs of placental separation. Some of the signs of placental separation are as follows:
  - Appearance of a supra-pubic bulge due to hardening and contracting of uterus. This is usually the first sign to appear.
  - Sudden gush of blood.

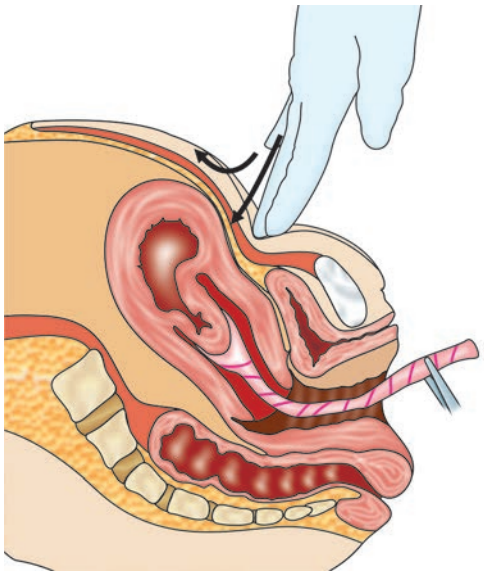


Fig. 10.3: Controlled cord traction

- A rise in the height of the uterus (as observed over the abdomen) due to the passage of placenta to the lower uterine segment.
- Irreversible cord lengthening.

- Once these above mentioned signs occur, the clinician must hold the cord with the right hand and place the left hand over the mother's abdomen just above the pubic bone.
- The clinician must apply slight tension on the cord with right hand in downward and backward direction. At the same time the uterus must be stabilized by applying counter pressure in upward and backward direction during the controlled traction with the left hand.
- The mother should be encouraged to push with the uterine contractions.
- The cord should never be pulled without applying counter traction above the pubic bone.
- As the placenta delivers, it should be held in two hands and gently turned, until the membranes are twisted and stripped off intact from the uterine wall.
- If the membranes tear, gentle examination of the upper vagina and cervix must be carried out to look for torn bits of membrane. These if present, can be removed with the help of a sponge forceps.
- The entire placenta and membranes must be examined carefully to look for any missing lobe/membrane bit.

MANAGEMENT OF PPH

Management of a patient with PPH is shown in flow chart 10.1. According to the guidelines by the Scottish Executive Committee of the RCOG the immediate management in case with PPH comprises of the steps enumerated in table 10.4 and are described below. All of these steps are required to be undertaken simultaneously.

Table 10.4: Steps involved in the immediate management of patients with PPH

Communicate (call for help)
Resuscitation of the patient (ABC: Airway, Breathing and Circulation)
Monitoring the patient and carrying out certain investigations
Treating the underlying cause of bleeding

Communication

If the perceived blood loss is 500–1000ml and there are no signs of clinical shock, basic measures, like typing and cross matching 2 units of blood, carrying out a coagulation profile, establishing intravenous access and monitoring clinical parameters should suffice.

However loss of greater than 1000 mLs or any signs of shock should fully alert the clinical team. Since severe PPH can often develop into a life threatening emergency, the following people must be urgently called and alerted: Experienced midwife and other nursing staff; senior obstetrician and/or consultant; senior anesthetic and/or consultant; blood bank staff; hematologist; blood transfusion services, OT staff, etc.

Resuscitation

Patient resuscitation must be done to assess ABC: Airway, Breathing and Circulation. Since excessive bleeding can result in the development of hypovolemic shock, immediate intravenous access using two wide bore cannula (14–16 gauge) must be established. The foot end of the patient's bed must be elevated or the head can be tilted down in order to facilitate circulation. Oxygen must be administered with the help of a face mask. The patient must be kept warm and dry.

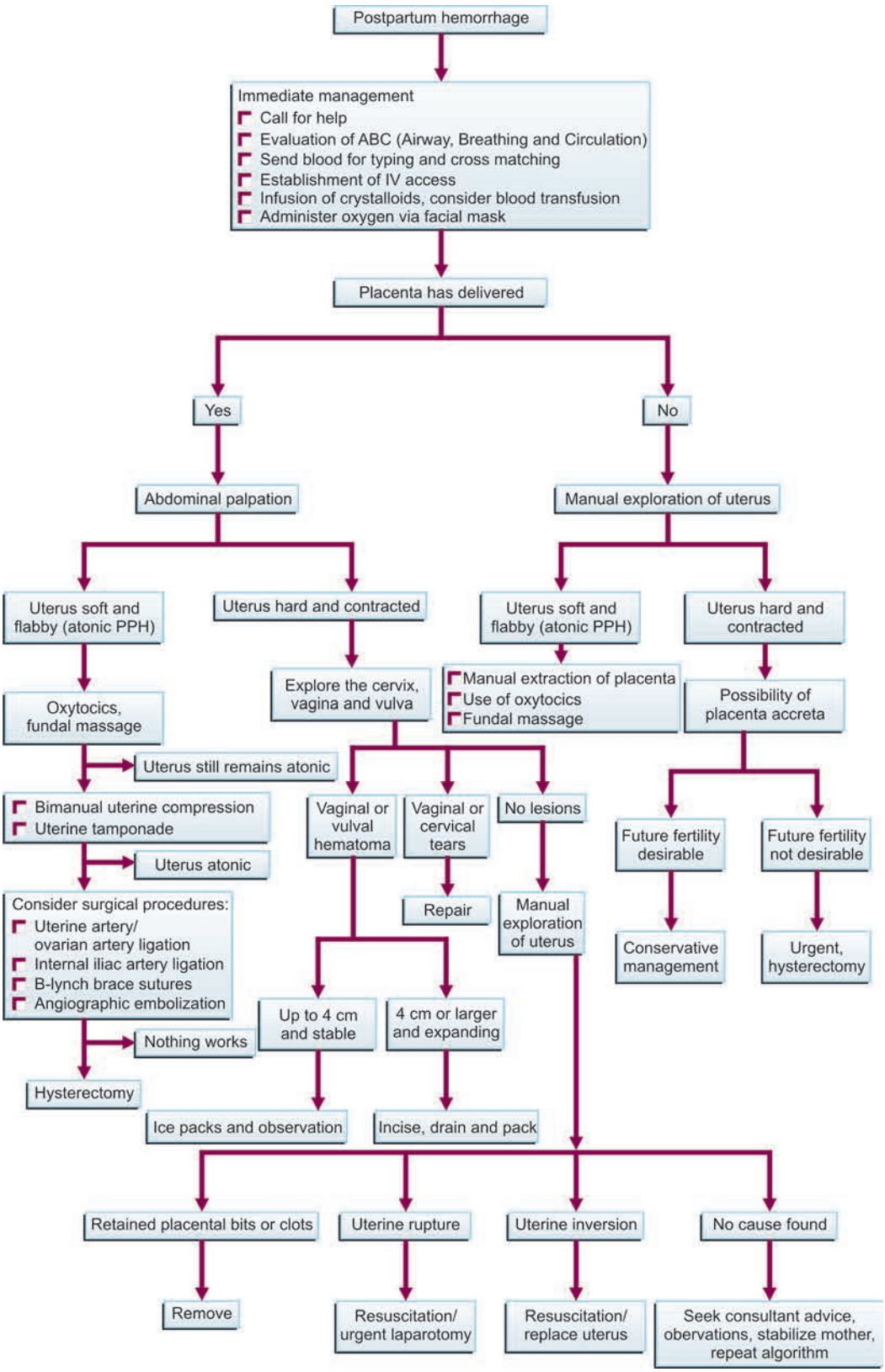
Hemodynamic resuscitation must involve the following in the order to priority:

- Restoration of blood volume
- Restoration of hemoglobin concentration
- Restoration of coagulation.

Restoration of blood volume

Crystalloids (e.g. Hartmann's solution, normal saline, etc) must be intravenously transfused. If urine output is not maintained to at least 30 ml/hr, CVP line must be placed. If despite of adequate CVP, urine output remains inadequate or the left ventricular function appears compromised, a Swan-Gnaz catheter must be placed.

Flow chart 10.1: Management of PPH



Restoration of hemoglobin concentration

If patient is suffering from excessive blood loss or severe hypovolemic shock, blood transfusion may be required. In emergency, if the patient's own blood group is not available, O negative blood may be used. Whole blood frequently is used for rapid correction of volume loss because of its ready availability, but component therapy is ideal. A general practice has been to transfuse 1 unit of fresh frozen plasma for every 3 to 4 units of red cells given to patients who are bleeding profusely.

Restoration of coagulation

Transfusion of fresh frozen plasma may be considered if PT/APTT> 1.5 times normal. Cryoprecipitate may be administered if fibrinogen levels are less than 1 g/l. Platelet concentrates may be administered in case of low platelet count. If clinically indicated (in presence of coagulation abnormalities), up to 1 liter of fresh frozen plasma and 10 units of cryoprecipitate can be transfused.

Patient Monitoring and Investigations

The investigations that need to be carried out have already been described before, whereas the parameters that need to be monitored are described below in table 10.5.

Treating the cause of bleeding

Once the maternal condition has stabilized the cause of PPH must be identified and treated. The further management must be decided based on the fact whether placenta has delivered on not. If the placenta has delivered, PPH could be due to uterine atonicity, uterine trauma, retained placental tissue, coagulation disorder, etc. Both these conditions are described below:

Placenta has Delivered

If the placenta has delivered, the main thing the clinician needs to see is whether the uterus has contracted or not.

Table 10.5: Parameters to be monitored in patients with PPH

Continuous pulse/BP monitoring in cases of severe PPH with shock. In moderate cases of PPH, monitoring can be done at 15–30 minutes intervals depending upon the patient's condition
ECG/pulse oximetry, especially in cases of severe PPH
Amount of vaginal bleeding (to be assessed at every 15–30 minute intervals)
Uterine tone to be assessed at 15–30 minutes intervals depending upon the patient's condition
Hourly monitoring of urine output (must be at least 30 ml/hr)
CVP monitoring (if urine output is inadequate)
Swan Gnaz catheter (if urine output remains inadequate despite of adequate CVP)

Uterus well contracted

If the uterus contracts but the bleeding continues despite a well contracted uterus, the clinician must look for other causes including traumatic causes and coagulation abnormalities. The following steps need to be taken:

- Inspection of the placenta and lower genital tract needs to be carried out to ascertain the origin of bleeding. This is especially important in cases in which the uterus appears to be firm and well contracted. There could be a missing placental cotyledon on inspection of placenta, which suggests that PPH could probably due to retained placental bits inside the uterine cavity. If inspection of the lower genital tract reveals laceration, tear or injury on the cervix, vagina, it needs to be repaired as soon as possible in order to stop the bleeding. The woman must be positioned in lithotomy with adequate anesthesia/analgesia so as to ensure the proper examination of lower genital tract.
- The obstetrician must ensure that adequate lighting, assistance and instruments are available in order to provide adequate exposure of the genital tract.
- It may be necessary to take the woman to theater to examine under anesthesia, if proper visualization of lower genital tract does not appear to be possible.
- The vulva, vagina, cervix and perineum must be inspected for trauma. In patients with previous history of LSCS, the possibility of uterine scar rupture must be kept in mind and manual exploration of the scar must be done. Speculum examination will allow visualization of cervix and lower genital tract to exclude lacerations. If clot is visible within the cervical os, it may be removed with a sponge holding forceps.
- Any injury if found, must be adequately sutured and repaired.
- If infection is suspected, combinations of broad spectrum antibiotics e.g. amoxicillin, gentamicin and metronidazole, can be given.
- In case no trauma to the lower genital tract is found, the obstetrician must suspect the presence of coagulation abnormalities. In such cases the obstetrician must send a complete coagulation profile, if it had not been sent earlier. The following investigations need to be done: PT, APPT, levels of D-dimer, fibrinogen and FDPs. Possibility of DIC should be kept in mind, especially if the woman has a history of abruption placenta, intrauterine death, etc. A consultation with a hematologist may be required if DIC is suspected.

Uterus is atonic

If the placenta has delivered, but the uterus is not hard and contracted; instead appears to be atonic and flabby, the PPH

Table 10.6: Various oxytocics used for controlling PPH

Drug	*Dosage*	*Side-effects*	*Contraindications*
Oxytocin	20 IU in 1 L of saline may be infused intravenously at a rate of 125 mL per hour	Water intoxication and nausea at high dosage	Nil
Methylergometrine (methargin)	0.25 mg intramuscularly or intravenously	Nausea, vomiting, hypertension, retained placenta, if given before placental separation, occurs	Hypertension, heart disease
Carboprost (15-methyl PGF2α)	250 µg given as intramuscular injection every 15 minutes for a maximum of eight doses.	Diarrhea, vomiting, flushing, pyrexia, hypertension, bronchoconstriction, etc.	Significant pulmonary, cardiac, hepatic or renal disease
Misoprostol	600-1000 µg perectally or orally. Dose and frequency has yet not been standardized	Diarrhea, pyrexia (> 40°)	Significant pulmonary, cardiac, hepatic or renal disease

is of atonic type. In this case the following steps need to be carried out:

- The urinary bladder must be emptied.
- The uterine cavity must be explored for any retained placental bits.
- The vagina and cervix must be still inspected for presence of lacerations and tears (traumatic PPH is commonly present in association with atonic PPH).
- Repeat administration of uterotonics.
- Bimanual uterine massage.

Medical Management of Atonic Uterus

Administration of uterotonics

Uterotonic agents used for controlling PPH include oxytocin, ergot alkaloids and prostaglandins (table 10.6).

Oxytocin

Oxytocin stimulates the upper segment of the myometrium to contract rhythmically. This causes constriction of spiral vessels which helps in reducing the blood flow through the uterus. Oxytocin is an effective firstline treatment for postpartum hemorrhage. It is used in the dose of 10 international units (IU) intramuscularly, or 20–50 IU in 1 L of saline may be infused at a rate of 125 mL per hour. As much as 500 mL can be infused over 10 minutes without complications. Intravenous route is favored over the intramuscular route, which is very painful. Oxytocin is also more stable, when exposed to heat and light in comparison to ergot preparations.

Ergot alkaloids

Methylergonovine (Methergin) and ergometrine are ergot alkaloids that cause generalized smooth muscle contraction. As a result, the upper and lower segments of the uterus contract tetanically and pass into a state of spasm without any relaxation in between. A typical dose of methylergonovine, 0.2 mg administered intramuscularly, may be repeated as required at intervals of two to four hours. The total dose of ergometrine in 24 hours must not exceed 1000 micrograms. Since ergot alkaloid agents raise blood pressure, they are contraindicated in women with preclampsia or hypertension. Other adverse effects include nausea and vomiting.

Syntometrine

Syntometrine is a combination of ergometrine 0.5 mg and oxytocin 5 IU. It is the agent of choice for prophylaxis in the third stage of labor. In comparison to oxytocin, syntometrine is associated with statistically significant increase in the risk of sideeffects (especially vomiting) and a small, but statistically significant reduction in the rate of PPH. In case of atonic PPH, syntometrine one ampoule may be administered intramuscularly if it had not been previously given. Caution should be observed in hypertensive women. In these women, it is more suitable to use prostaglandins.

Prostaglandin F2α

Prostaglandins F2α enhance uterine contractility and cause vasoconstriction. The prostaglandin most commonly used for controlling PPH is 15-methyl prostaglandin F2α, or carboprost (Hemabate). Carboprost is usually administered intramuscularly in a dose of 0.25 mg; this dose can be repeated every 15-90 minutes for a total dose of 2 mg or a maximum of eight doses. In severe cases of PPH, carboprost can also be administered intramyometrially. Carboprost has been proven to control hemorrhage in up to 87% of patients. While high dose carboprost (250 µg) has been found to be useful in controlling PPH, low dose carboprost (125 µg) can also be used for the active management of third stage of labor. Carboprost

should be used with caution in patients with asthma, hypertension, hepatic or renal diseases. Side effects include nausea, vomiting, diarrhea, hypertension, headache, flushing, bronchoconstriction and pyrexia.

Misoprostol

Misoprostol is another prostaglandin that increases uterine tone and decreases postpartum bleeding. Misoprostol is effective in the treatment of postpartum hemorrhage, but side effects, such as diarrhea, fever, shivering, etc may limit its use. It can be administered sublingually, orally, vaginally and rectally. Doses range from 600 to 1,000 μg. The dose recommended by FIGO is 1,000 μg to be administered per rectally. Although misoprostol is widely used in the treatment of postpartum hemorrhage, it is presently not approved by the U.S. Food and Drug Administration (FDA) for this indication. Misoprostol, however, is safe, inexpensive and easily storable. Therefore it has a high potential of usefulness in developing countries.

Bimanual uterine massage

If the clinician finds the uterus to be soft upon bimanual examination, a bimanual uterine massage must be performed to contract the myometrial muscles. The maneuver involves the massage of the posterior aspect of the uterus with the abdominal hand and that of the anterior aspect of the uterus with the vaginal hand and comprises of the following steps (figure 10.4):

- One of the clinician's hands is formed into a fist and placed inside the vagina, with the back of the hand directed posteriorly and knuckles in the anterior fornix so as to push against the body of the uterus (figure 10.4).
- The other hand compresses the fundus from above through the abdominal wall. The fundus of the uterus must be immediately massaged, until uterus is well contracted.
- Uterus must be massaged every 15 minutes during the first two hours. If this maneuver controls the bleeding, the clinician must maintain this compression for at least 30 minutes.

Uterine tamponade

This method aims at increasing intrauterine pressure in order to control uterine bleeding. However it carries the potential risk of infection and trauma. It may also conceal the bleeding and give a false sense of security. Uterine tamponade can be achieved in two ways:

- *Intrauterine packing*: Intrauterine packing using ribbon gauze soaked in povidine-iodine solution helps in stopping bleeding. This is usually removed 24 hours later.
- *Balloon tamponade*: This can be achieved using a large bulb Foleys catheter, Sengstaken-Blakemore tube or an SOS Bakri tamponade balloon. A Foleys catheter with a balloon of 30 ml (which may be inflated up to 100 ml) is quite effective in controlling postpartum bleeding. However, the shape of the balloon may not correspond to that of elongated uterine cavity. Despite of this, insertion of a Foley catheter is especially useful in cases where cervical lacerations that have been repaired, but continue to bleed. When a Sengstaken Blakemore tube is used, it must be left inflated for 24 hours and then deflated. However, the Sengstaken Blakemore tube was originally designed to control bleeding from the esophageal varices and not that from the uterine cavity. The recently available SOS Bakri tamponade balloon (figure 10.5) has been specifically

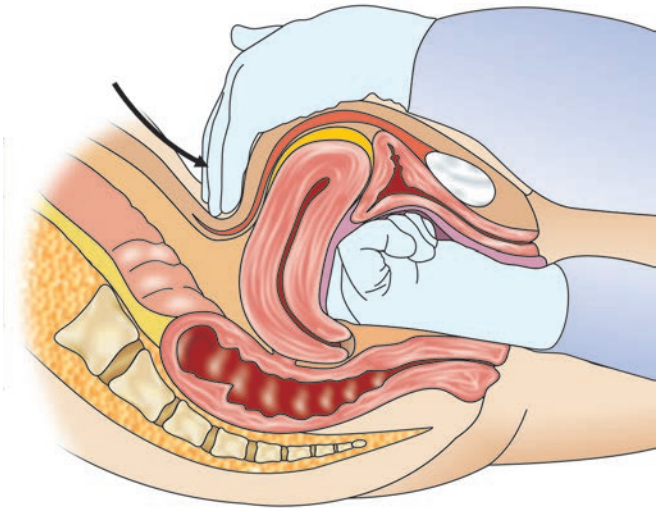


Fig. 10.4: Bimanual uterine compression

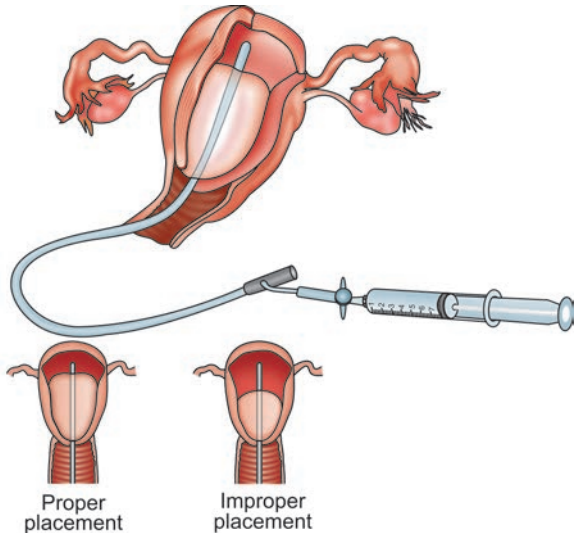


Fig. 10.5: Bakri tamponade balloon

designed to deal with PPH. The Bakri balloon catheter helps in temporary control of postpartum hemorrhage, potentially avoiding a hysterectomy. The balloon portion of the catheter is inserted past the cervical canal and internal ostium into the uterine cavity under ultrasound guidance.

Surgical options for treatment of atonic uterus

If all the above described conservative measures fail to control PPH, laparotomy may be required to save the mother's life. Surgical hemostasis must be initiated as soon as possible in order to save the patient's life. Though there are different surgical options available, the surgical option of choice to be used in a particular patient depends upon the following factors:

- Extent and cause of hemorrhage
- General condition of patient
- Desirability for future reproduction
- Experience and skill of the obstetrician in charge

Available Surgical Options

If the above described conservative and medical therapeutic options are unable to control the bleeding, the obstetrician may have to resort to surgery as the last therapeutic option. Application of aortal compression at the time of surgery must be considered. Various surgical options that can be used in a patient to control PPH are described below:

- Brace sutures of uterus: B lynch suture
- Uterine artery or utero-ovarian artery ligation
- Bilateral ligation of internal iliac (hypogastric arteries)
- Hysterectomy
- Angiographic embolization
- Hysterectomy

Blood Supply to the Female Pelvis

Discussion of the blood vessels supplying the pelvis and the uterus is important because the surgical methods for controlling PPH aim at controlling the blood supply to the uterus by ligation of some of these vessels. Blood supply to the pelvis and uterus are shown in figures 10.6A and B respectively. The blood supply to the pelvic structures is mainly by the common iliac vessels, which give rise to internal iliac and external iliac arteries. The internal iliac artery (formerly known as the hypogastric artery) has an anterior division and a posterior division. Anterior division gives rise to five visceral branches and three parietal branches. The visceral branches are: Uterine; superior vesical; middle hemorrhoidal; inferior hemorrhoidal and vaginal arteries, whereas the parietal branches are: Obturator artery, inferior gluteal and internal pudendal arteries. The posterior division on the other hand, gives rise to the following branches: Collateral branches to the pelvis, iliolumbar, lateral sacral and superior gluteal arteries.

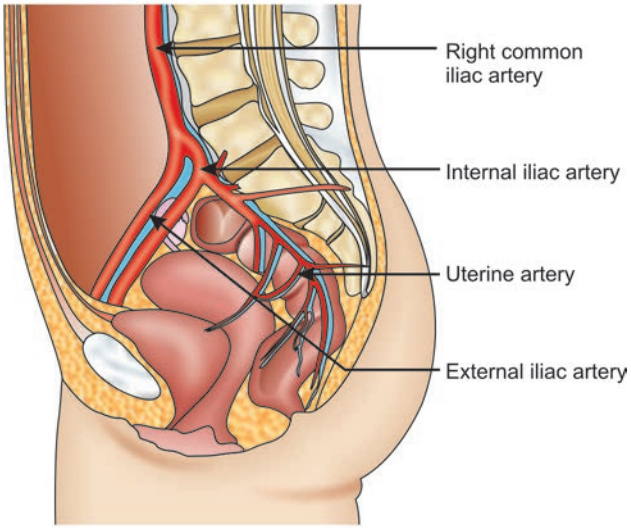


Fig. 10.6A: Anatomical view of pelvic blood vessels

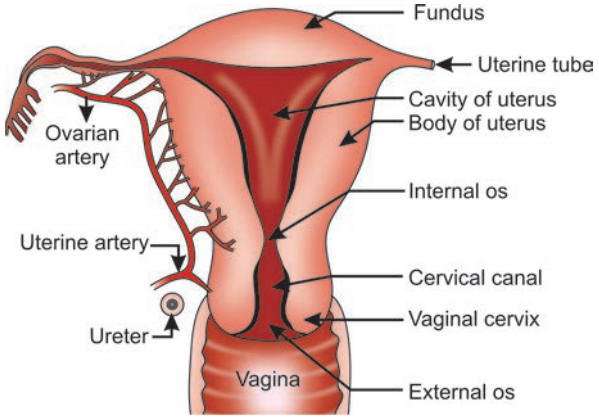


Fig. 10.6B: Blood supply to the uterus

The blood supply to the uterus is mainly via the uterine and ovarian vessels. The ovarian arteries are direct branches of the aorta beneath the renal arteries. The uterine artery is the branch of internal iliac vessel. Uterine artery assumes important role at the time of pregnancy because it supplies maternal circulation to the placenta during this time. The uterine artery passes inferiorly from its origin into the pelvic fascia. It runs medially in the base of broad ligament to reach the uterus. It then reaches the junction of the body and cervix of the uterus (internal os) by passing superiorly. While taking such a course, the uterine artery passes above the ureter at right angles. It then ascends along the lateral margin of the uterus within the broad ligament. It continues to move along the lower border of the fallopian tubes where it ends by

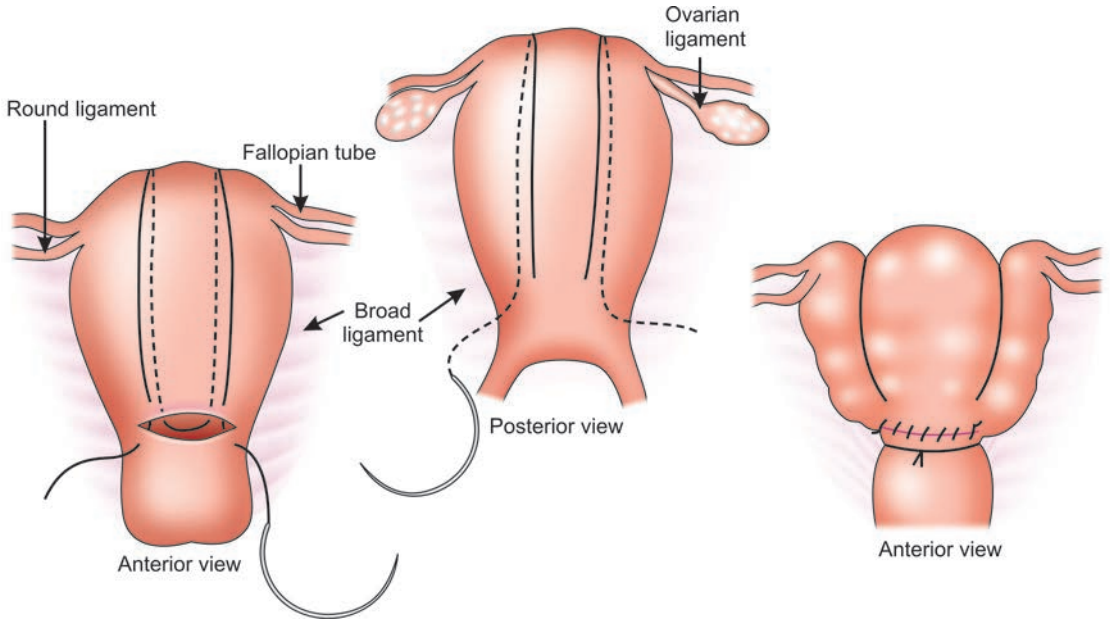


Fig. 10.7: B-Lynch suture

Source: B-Lynch C, Coker A, Lawal AH, Abu J, Cowen MJ. The B-Lynch surgical technique for the control of massive postpartum hemorrhage: An alternative to hysterectomy? Five cases reported. Br J Obstet Gynaecol 1997; 104: 3: 372-5.

anastomosing with the ovarian artery which is a direct branch from the abdominal aorta. The uterine artery also gives off a small descending branch that supplies the cervix and the vagina. The uterine vein follows the uterine artery all along its course and ultimately drains into the internal iliac vein.

Blood supply to anterior and posterior walls is provided by the arcuate arteries, which run circumferentially around the uterus. The arcuate arteries give rise to the radial arteries which enter the endometrium. The ultimate branches of uterine artery which connect maternal circulation to the endometrium are the spiral and the basal arteries.

TYPES OF SURGICAL OPTIONS

B-Lynch Compression Sutures

Compression sutures can be considered as the best form of surgical approach for controlling PPH as it helps in preserving the anatomical integrity of the uterus. Uterine bracing suture, (the B-Lynch suture) has now become the preferred surgical technique to control PPH. This technique is safe, effective and helps in retaining future fertility. These brace like sutures control bleeding by causing hemostatic compression of the uterine fundus and lower uterine segment. In this method, anterior and posterior uterine walls are compressed with help of absorbable sutures, number 2 chromic or number 0 plain or chromic catgut. These sutures are secured vertically around the anterior and posterior uterine walls giving appearance of suspenders. The sutures are first anchored in the anterior aspect of lower uterine segment, passed over the uterine fundus, anchored in the posterior aspect of the lower uterine segment , then again brought back anteriorly passing over the fundus of the uterus. These sutures are finally anchored near the entrance point on the anterior aspect of the lower uterine segment (figure 10.7). Simultaneously, the uterus is also massaged and manually compressed in order to reduce its size. This method has been found to be safe and effective and there have been reports of successful pregnancy following its use. Before using the B-Lynch suture, the following test must be performed to assess the effectiveness of these sutures:

The uterus must be bimanually compressed followed by swabbing the vagina. If the bleeding is controlled temporarily in this fashion, the B-Lynch sutures are likely to be effective. Uterine compression sutures have almost completely replaced uterine artery ligation, hypogastric artery ligation and postpartum hysterectomy for surgical treatment of atonic uterus.

Hypogastric Artery Ligation

The hypogastric artery (Internal iliac artery) is exposed by ligating and cutting the round ligament. The peritoneum over the pelvic sidewall, cephalad and parallel to the infundibulopelvic ligament is incised. The common, internal, and external iliac arteries must then be identified clearly. The common

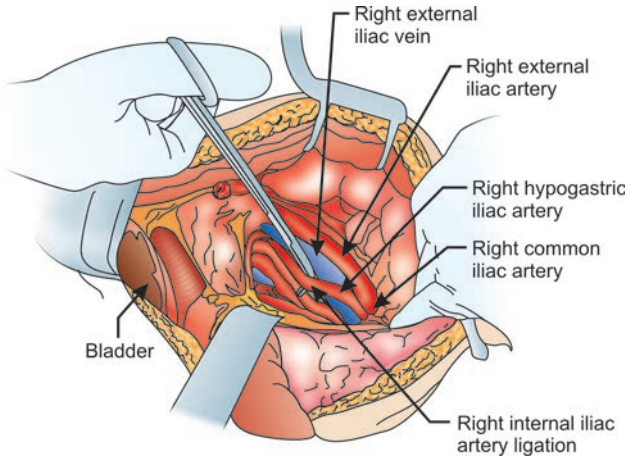
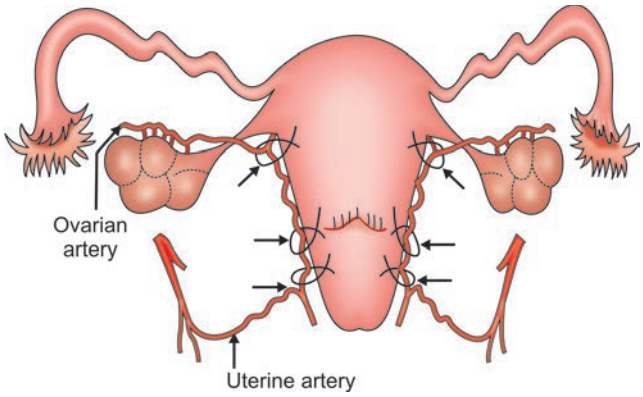


Fig. 10.8: Detailed view of pelvic blood vessels at the time of internal artery ligation



The arrows point towards the likely areas of ligation

Fig. 10.9: Uterine artery ligation

iliac artery is dissected until the bifurcation of external and internal iliac arteries. The areolar sheath over the internal iliac artery is incised longitudinally and a blunt-tipped, right-angled clamp is gently placed around the hypogastric artery, 2.5 to 3.0 cm distal to the bifurcation of the common iliac artery (figure 10.8). The surgeon must pass the tip of the clamp from lateral to medial side under the artery in order to prevent injuries to the underlying hypogastric vein. The Hypogastric artery is double-ligated with a nonabsorbable suture, with 1-0 silk, but not divided. The ligation is then performed on the contralateral side in the same manner. Internal iliac artery ligation is able to bring about 85% reduction in pulse pressure in the arteries distal to the area of ligation. This helps in accomplishing hemostasis via simple clot formation.

Uterine Artery Ligation

Since approximately 90% of the blood supply to the uterus is via the uterine artery, ligation of this vessel through the uterine wall at the level of cervical isthmus above the bladder flap is likely to control the amount of bleeding. If despite of bilateral ligation of uterine vessels, bleeding remains uncontrollable, ligation of utero-ovarian anastamosis is done just below the ovarian ligament (figure 10.9). However, this method may not prove useful to control bleeding in case of placenta previa or rupture uterus. Bilateral ligation of the uterine vessels has not been observed to interfere with future reproduction.

Uterine Artery Embolization

Nowadays a commonly used alternative to uterine artery or internal iliac artery ligation is angiographic arterial embolization of the bleeding vessel with gelatine sponge. In this method gelatine foam or polyvinyl alcohol can be injected through the internal iliac vessels. This method has been found to be particularly useful in cases of retroperitoneal hematomas where surgery may be difficult. Success rate of up to 95% has been reported with this method. Though this method has been found to be generally safe, secondary amenorrhea has been reporded following this method due to necrosis of the uterline wall and obliteration of the cavity.

UTERINE INVERSION

Uterine inversion is rare but may be sometimes present in the third stage of labor, occurring in 0.05% of deliveries. In this condition, the uterus is turned inside out, either partially or completely. The inverted uterus usually appears as a bluish-gray mass protruding from the vagina. The practices of applying undue fundal pressure, undue cord traction and Crede's expression of placenta have been thought to be the causative factors. Active management of the third stage of labor may reduce the incidence of uterine inversion.

Diagnosis

Abdominal examination may show dimpling of the uterine fundus. Bimanual examination helps in confirming the diagnosis. Often, the degree of shock is disproportionate to the amount of bleeding.

Treatment

The mainstay of treatment is urgent manual replacement of the uterus, preferably under general anesthesia. The placenta often is still attached to the uterus and it should be left in place until after reduction. Every attempt should be made to replace the uterus quickly. Acute inversion can be managed with manual reposition (Johnson's method) or hydrostatic replacement (O'Sullivan's method). Tocolysis or general anesthesia is usually required to facilitate uterine reposition.

The Johnson method of manual reposition involves the following steps:

- The protruding fundus is grasped by the obstetrician with the help of palms of the hand in such a way that the fingers are directed toward the posterior fornix (figure 10.10A).
- The uterus is returned to its original position by lifting it up through the pelvis and into the abdomen (figure 10.10B). The part of the uterus that has inverted last must be replaced first. While the uterus is returned back, counter support must be applied with the hand placed over the abdomen.
- Once the uterus is reverted, uterotonic agents should be given to promote uterine tone and to prevent recurrence. Additionally after the replacement, the hand should remain inside the uterine cavity until the uterotonic agents have taken their effect (figure 10.10C)

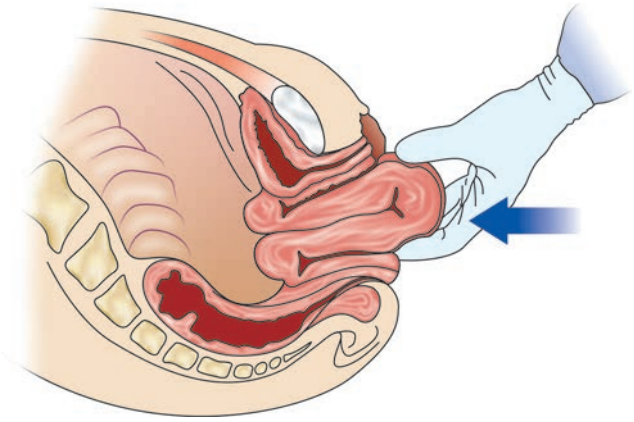


Fig. 10.10A: Grasping the protruding fundus

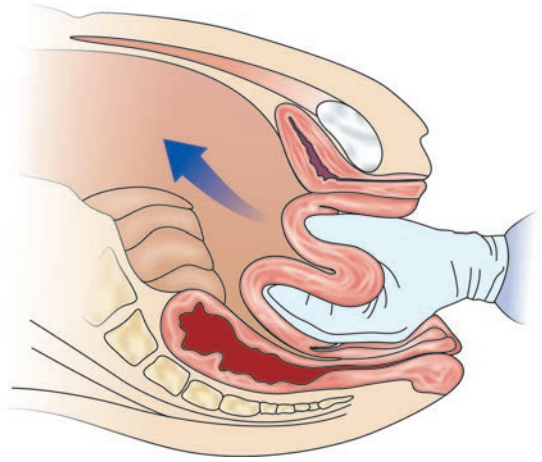


Fig. 10.10B: Gentle repositioning of the uterus

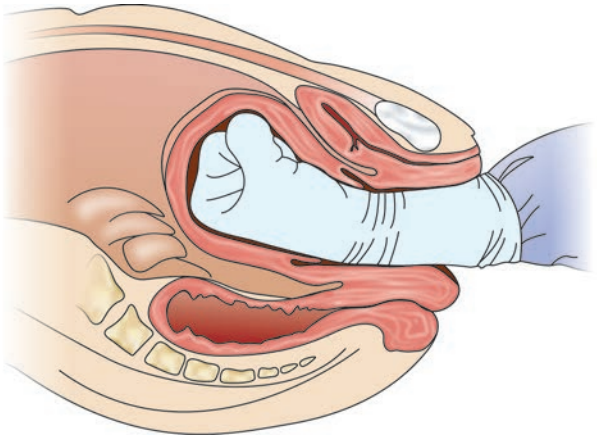


Fig. 10.10C: The clinician's hand must remain inside the uterine cavity, until the uterus has contracted

THE PLACENTA HAS YET NOT DELIVERED

Nonadherent Placenta

The mean time from delivery until placental expulsion is eight to nine minutes. Longer intervals are associated with an increased risk of postpartum hemorrhage, with rates doubling after 10 minutes. The following steps can be taken to facilitate the placental delivery:

- A maternal uterine massage must be performed to expel any clots.
- The dose of oxytocics can be repeated, for e.g. Syntocinon 10 IU intravenous or 10 IU intramuscular. Ergometrine/syntometrine must be avoided for retained placenta because they may cause tonic uterine contraction, which may delay expulsion.
- The urinary bladder must be emptied by catheterizing if, if it has previously not been done.
- Controlled cord traction must be repeated to deliver the placenta.
- If possible a portable ultrasound scan must be done to see if the placenta is still in the upper segment or whether it has separated and is in the lower segment of the uterus.
- If the placenta appears to be in trapped in the lower uterine segment, a vaginal examination must be performed to remove the placenta and other clots.
- Injection of the umbilical vein with 20 mL solution of 0.9% saline and 20 units of oxytocin significantly helps in reducing the need for manual removal of the placenta in comparison with injection of saline alone.
- If the placenta does not deliver even within thirty minutes of the delivery of the baby, the patient must be taken to the OT for manual exploration of placenta under general anesthesia. Further clinical management depends on whether or not a distinct cleavage plane between the placenta and the uterine wall can be located or not. If a distinct

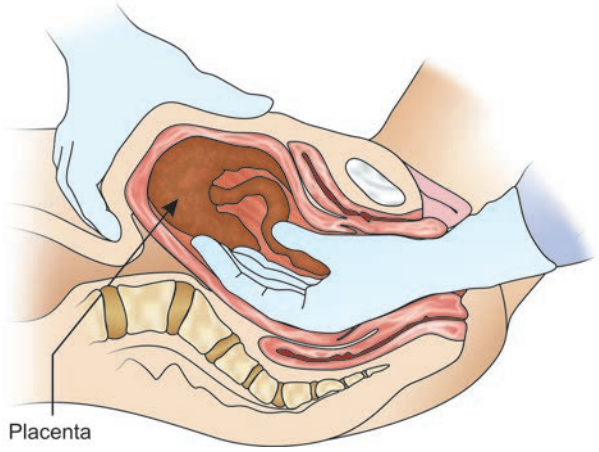


Fig. 10.11: Manual removal of the placenta

cleavage plane between the placenta and the uterine wall can be located, management options include manual removal of the placenta, using appropriate analgesia.

Manual removal of placenta (figure 10.11)

The procedure must be performed under adequate anesthesia after taking adequate aseptic precautions. The patient must be placed in lithotomy position and bladder must be catherized.

Abdomen should be stabilized with one hand placed over the abdomen, while the other hand, smeared with antibiotics is introduced inside the vagina in a cone-shaped manner. It is then passed into the uterine cavity along the umbilical cord. As the placental margin is reached, the ulnar border of the hand is used to gradually separate the placenta from the uterine wall. The placental tissue is gradually separated by using the sideways slicing movements of the fingers. Once the placenta has separated, it can be grasped with the entire hand and gradually taken out. The abdominal hand helps in stabilizing the fundus and helps in guiding the movements of the fingers inside the uterine cavity until the placenta has completely separated.

Adherent Placenta

If a distinct cleavage plane between the placenta and the uterine wall cannot be located and if the tissue plane between the uterine wall and placenta cannot be developed through blunt dissection with the edge of the gloved hand, diagnosis of invasive placenta should be considered.

Invasive placenta can be a life threatening condition. The incidence has increased from 0.003% to 0.04% of deliveries since 1950s; this increase is likely as a result of the increase in cesarean section rates. Adherent placenta can be classified into three: Placenta accreta, Placenta increta and Placenta percreta. Table 10.7 describes these different types of placentas based on their depth of myometrial invasion.

Table 10.7: Types of adherent placentas

Classification	*Description*
Placenta accreta	Placenta adheres to the myometrium
Placenta increta	Placenta invades the myometrium
Placenta percreta	Placenta penetrates the myometrium to or beyond the serosa

In placenta accreta, the abnormally firm attachment of the placenta to the uterine wall prevents the placenta from separating normally after delivery. The retained placenta interferes with uterine contraction that is necessary to control bleeding after delivery, thereby resulting in PPH. Several risk factors for placenta accreta have been identified. Among these, the most important one appears to be placenta previa (chapter 4). In patients with placenta previa the incidence of placenta accreta appears to correlate with the number of previous cesarean sections. Maternal age greater than 35 and placental location overlying the previous uterine scar also increases the risk of accreta. Other reported risk factors include multiple previous pregnancies, previous uterine surgery and previous D&C. In a patient with a previous cesarean section and a placenta previa, the risk of placenta accreta is dependent upon the number of previous cesarean sections as follows:

- Woman with previous one cesarean section has 14% risk of placenta accreta.
- Woman with previous two cesarean sections has a 24% risk of placenta accreta.
- Woman with previous three cesarean sections has 44% risk of placenta accreta.

Management of an Adherent Placenta

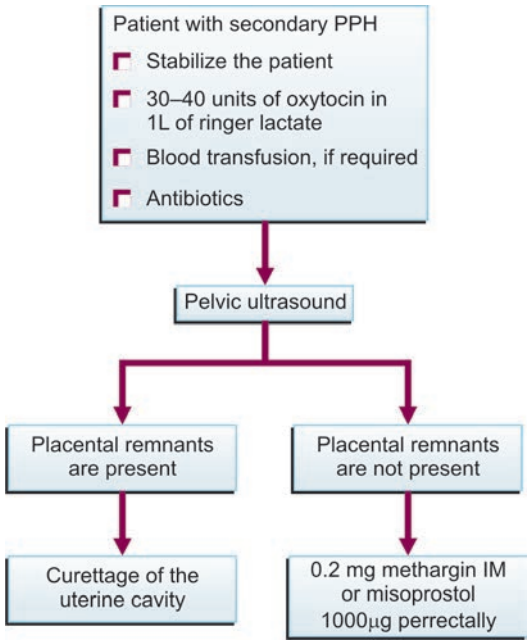
Conservative management

- In case of densely adherent placenta, the clinician must not try to remove any nonadherent portions of the placenta
- The cord can be trimmed
- The patient's vital signs and amount of bleeding should be closely observed.
- Antibiotics should be administered.
- In the woman who is stable, hysterectomy may be avoided by the use of methotrexate

Surgical management

If the bleeding remains uncontrolled despite of using conservative management, the following surgical options can be used:

Flow chart 10.2: Treatment of secondary PPH



- Uterine artery embolization,
- Low and high bilateral uterine vessel ligation.
- Ligation of internal iliac arteries
- If the above mentioned surgical options are unable to control the hemorrhage, hysterectomy is the only choice left to save the woman's life.

SECONDARY POSTPARTUM HEMORRHAGE

The most common cause for secondary postpartum hemorrhage is retained tissue fragments inside the uterine cavity. Treatment of secondary postpartum hemorrhage is shown in flow chart 10.2 and involves the following:

- Stabilization of the patient, blood may be transfused if required.
- Administration of antibiotics.
- Ultrasound examination for detection of remnant bits of placenta inside the uterine cavity.
- Removal of placental remnants.
- Curettage of the uterus, preferably under general anesthesia.

Complications

PPH is one of the important causes of maternal morbidity and mortality. Some of the complications related to PPH include the following:

- Blood loss resulting in Shock, DIC, septicemia and death
- Renal Failure
- Puerperal sepsis
- Lactation failure
- Blood transfusion reaction
- Thromboembolism
- Sheehan's syndrome
- Hypovolemic shock
- Puerperal shock
- Multiple organ failure associated with circulatory collapse and decreased organ perfusion
- Need for emergency surgical intervention including hysterectomy and loss of childbearing potential.

Important Questions and Answers

Q.1. What could have been the likely cause of shock in the above mentioned case study?

Ans. The above case scenario is suggestive of postpartum hemorrhage. Since uterus was well contracted at the time of shifting the patient to the postpartum ward, atonic uterus as a cause of PPH can be ruled out. The history of delivery a large sized baby (weight ≥ 4 kg) points towards an increased likelihood of trauma to the vagina and cervix. Small cervical or vaginal lacerations can also be associated with slight vaginal bleeding. Such traumatic injuries, if left unattended can result in significant amount of blood loss over a period of time.

Q.2. What should be the further line of management in this case?

Ans. The first priority should be towards the maternal resuscitation. While resuscitating the patients (steps have already been described in the text), a per abdominal examination should be simultaneously performed to check the uterine tonicity. If the uterus is found to be well contracted, arrangements for a proper vaginal inspection and examination should be made as soon as possible. The vagina and cervix, both should be thoroughly inspected. Any tear, injury or laceration in the genital tract should be appropriately handled and repaired.

Q.3. What are contraindications for the use of methargin?

Ans. Contraindications for the use of methargin include the following:

- Patients with preeclampsia/eclampsia: In these patients use of methargin can result in an excessive increase in blood pressure.
- Rh-negative mother: In these patients, use of methargin can be associated with a feto-maternal microtransfusions resulting in increased chances of Rh negative isoimmunmization.
- Maternal organic heart disease: Sudden squeezing of blood from the uterine circulation due to the use of methargin

can cause overloading of the heart thereby precipitating heart failure.

- Suspected or confirmed multifetal geatation: Routine use of methargin at the delivery of the anterior shoulder of the first twin must be withheld as this can lead to inadvertent trapping of the second twin inside the uterine cavity.

Q.4. What steps should be taken to prevent the occurrence of atonic PPH in cases of preeclampsia?

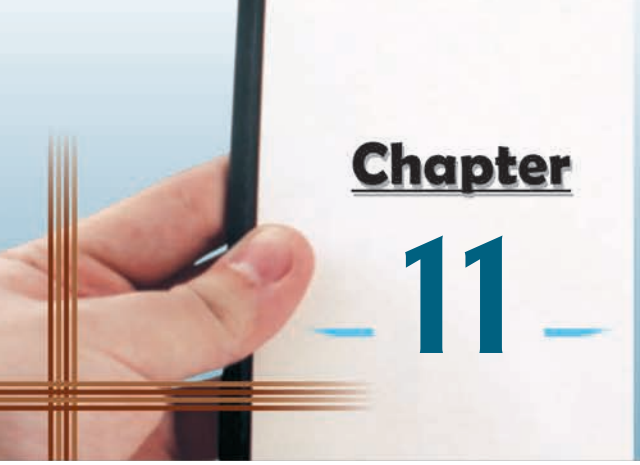
Ans. In cases of preeclampsia, routine use of methargin (0.2 mg) at the time of delivery of the anterior shoulder of the baby must be withheld due to the danger of sudden rise in blood pressure. However in these cases other oxytocic drugs including oxytocin, misoprostol and carboprost can be administered in doses described previously in the chapter. Also, bimanual uterine massage is useful in maintaining uterine tonicity in these patients.

Q.5. What are the advantages and disadvantages of the use of active management of labor as a routine?

Ans. Active management of third stage of labor is associated with clinically significant reduction in amount of estimated postpartum blood loss, improvement in postpartum hemoglobin levels and reduction in requirement for blood transfusion. However, active management of labor is also associated with some disadvantages including an increased incidence of nausea, vomiting, headache, postpartum hypertension, retained placenta and secondary PPH.

Bibliography

1. Allahbadia G. Hypogastric artery ligation: A new perspective. Obstet Gynecol Surv. 1993;48:613-15.
2. American College of Obstetricians and Gynecologists. Postpartum hemorrhage. ACOG educational bulletin 1998; Number 243. In 2001 Compendium of selected publications, Washington DC: ACOG.
3. Api M, Api O, Yayla M. Fertility after B-Lynch suture and hypogastric artery ligation. Fertil Steril. 2005;84(2):509.
4. B-Lynch C, Coker A, Lawal AH, Abu J, Cowen MJ. The B-Lynch surgical technique for the control of massive postpartum hemorrhage: An alternative to hysterectomy? Five cases reported. Br J Obstet Gynaecol. 1997;104(3):372-5.
5. Chitrit Y, Zafy S, Pelage JP, et al. Amenorrhea due to partial uterine necrosis after uterine artery embolization for control of refractory postpartum hemorrhage. Eur J Obstet Gynecol Reprod Biol. 2006;127(1):140-2.
6. Chou MM, Ho ESC, Lee YH. Prenatal diagnosis of placenta previa accreta by transabdominal color Doppler ultrasound. Ultrasound Obstet Gynecol. 2000;15:28-35.
7. Combs CA. Murphy EL, Laros RK. Factors associated with postpartum hemorrhage in cesarean birth. Obstet Gynecol. 1991;77:77-82.
8. Combs CA. Murphy EL. Factors associated with postpartum hemorrhage with vaginal birth. Obstet Gynecol. 1991;77:69-76.
9. Dehbashi S, Honarvar M, Fardi. Manual removal or spontaneous placental delivery and postcesarean endometritis and bleeding. Int J Gynaecol Obstet. 2004;86(1):12-5.
10. Derman RJ et al. Oral misoprostol in preventing postpartum hemorrhage in resource-poor communities: A randomised controlled trial. Lancet. 2006;368:1248-53.
11. Druzin ML. Packing of lower uterine segment for control of post cesarean bleeding in instances of placenta previa. Surg Gynecol Obstet. 1989;169:543-45.
12. French LM, Smaill FM. Antibiotic regimens for endometritis after delivery. Cochrane Database Syst Rev 2004;(4):CD001067.
13. Habek D, Vranjes M, Bobic Vukovic M, et al. Successful term pregnancy after B-Lynch compression suture in a previous pregnancy on account of massive primary postpartum hemorrhage. Fetal Diagn Ther. 2006;21(5):475-6.
14. Hofmeyr GJ, Walraven G, Gulmesoglu AM, et al. Misoprostol to treat postpartum hemorrhage: A systemic review. Br J Obstet Gynecol. 2005;112:547-53.
15. International Confederation of Midwives (ICM) and theInternational Federation of Gynecology and Obstetrics (FIGO). Management of the third stage of labour to prevent postpartum hemorrhage. J Obstet Gynaecol Can. 2003;25(11):952-3.
16. Magann EF, Evans S, Hutchinson et al. Postpartum hemorrhage after vaginal birth: An analysis of risk factors. South Med J. 2005;98(4):419-22.
17. O'Leary JA, SO. Hemorrhage with uterine artery ligation. Contemp Ob/Gyn Update Surg. 1986;27:13-16.
18. Pelage JP, Le Dref O, Mateo J, et al. Life-threatening primary postpartum hemorrhage: Treatment with emergency selective arterial embolization. Radiology. 1998;208(2):359-62.
19. Roberts WE. Emergent obstetric management of postpartum hemorrhage. Obstet Gynecol Clin North Am. 1995;22(2): 283-302.
20. Scottish Executive Committee of the RCOG (2000). Scottish Obstetric Guidelines and Audit Project. The Management of Postpartum Hemorrhage [online] Available from http://www.nhshealthquality.org/nhsqis/files/MATERNITYSERVICES_PostpartumHaemorrage_SPCERH6_JUN98.pdf. [Accessed March 2009]
21. Seror J, Allouche C, Elhaik S. Use of Sengstaken-Blakemore tube in massive postpartum hemorrhage: A series of 17 cases. Acta Obstet Gynecol Scand. 2005;84(7):660-4.
22. Silver RM, Landon MB, Rouse DJ, et al. Maternal morbidity associated with multiple repeat cesarean deliveries. Obstet Gynecol. 2006;107(6):1226-32.
23. Soriano D, Dulitzki M, Schiff E, et al. A prospective cohort study of oxytocin plus ergometrine compared with oxytocin alone for prevention of postpartum hemorrhage. Br J Obstet Gynaecol. 1996;103(11):1068-73.
24. Stanco LM. Schrimmer DB. Paul RH. Mishell DR Jr. Emergency peripartum hysterectomy and associated risk factors. Am J Obstet Gynecol. 1993;168:879-83.



Chapter 11

Intrauterine Growth Restriction

Case Study

28-year-old G4P3L3 patient with three live babies, who is 34 weeks pregnant, presented for a regular antenatal check-up. She has no particular problems and has been experiencing normal fetal movements. The symphysis-fundal (S-F) height had not shown any increase over the past three antenatal visits. The estimated fetal weight taken at the time of last antenatal visit had fallen below the 10th centile of the average for that particular gestational age. The patient is a farm laborer and she smokes.

Introduction

A diagnosis of FGR (fetal growth restriction) was established in this case as the fetal weight (estimated on ultrasound examination) was found to be below the 10th percentile of the average for that particular gestational age.

Definition

FGR or fetal growth restriction refers to low birth-weight infants whose birth weight is below the 10th percentile of the average for the particular gestational age. Previously the term fetal growth retardation was used. However this term has now been discarded because it implies abnormal mental functioning. The fetal weight is estimated using ultrasound parameters like biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur length (FL) etc. These parameters would be described in details later in this chapter. Some clinicians consider growth restriction when the fetal abdominal circumference or the ratio of HC/AC or Fl/AC is below the 10th percentile (or 2.5 standard deviation below the mean) of the average for that particular gestational age.

Even if the infant's birth weight is less than 10th percentile, he/she may not be pathologically growth restricted. The small size of the infant could be related to normal biological factors. These infants are simply termed as small for gestational age. However, if the growth restriction is due to some pathological process (either intrinsic or extrinsic), it can be associated with significant neonatal mortality and morbidity. Intrinsic FGR usually occurs due to some fetal problem like fetal infections or chromosomal abnormalities. On the other hand, extrinsic FGR is due to placental conditions or maternal disease. The pathologically growth restricted fetus (PFGR) is unable to reach its genetically determined potential size, which is detrimental to its health. On the other hand, small for gestational age (SGA) fetus is defined as one which has failed to achieve a specific weight or biometric size in accordance with the gestational age. Not all fetuses which are SGA have PFGR and not all fetuses which have PFGR are SGA. The difference between the small for gestational age infants and infants with pathological growth restriction (PFGR) is described in table 11.1. Pathologically growth restricted infants can be of two types i.e., symmetric intrauterine growth retarded and asymmetric intrauterine growth retarded, depending on the stage of fetal growth (table 11.2) at which the pathological insult occurred. If the pathological insult occurs at stage 1 of fetal growth, the process of cellular hyperplasia is mainly affected. This results in symmetrically growth restricted infants. If the pathological insult occurs at stage 3 of fetal growth, cellular hypertrophy is mainly affected. This results in asymmetrically affected growth restricted infants. The other differences between symmetric IUGR and asymmetric IUGR infants are enumerated in table 11.3.

History

History taking is of prime importance in cases of IUGR in order to elicit the exact cause of IUGR. Maternal and fetal risk factors (table 11.4) are associated with intrauterine growth restriction. It is important to elicit each of these factors while taking history. Proper history taking in cases of IUGR is of extreme importance as usually a cause for IUGR can be found.

The following points need to be asked in the history:

- History of maternal malnutrition, chronic illness, drug abuse, bleeding, etc.

Table 11.1: Difference between the small for gestational age infants and infants with pathological growth restriction (PFGR)

Characteristics	*Small for gestational age infants (normal)*	*Infants with pathological growth restriction (PFGR)*
Birth weight	Less than 10% of the average weight. Birth weight is usually less than 2.5 Kg.	Less than 10% of the average weight, but may also be less than 25%. Birth weight is usually less than 2.5 Kg, but may be larger.
Ponderal index	Normal	Low
Amount of subcutaneous fat	Normal	Reduced
Neonatal course	Usually uneventful	May develop complications like hypoglycemia, hypocalcemia, hyperviscosity, hyperbilirubinemia, necrotizing enterocolitis etc.
RBC count	Normal RBC count	Elevated number of nucleated RBC's.
Platelet count	Normal	Thrombocytopenia is usually present.
Investigations	Fetal biometric tests which help in measuring fetal size and gestational age are usually abnormal. Results of Doppler waveform analysis are within normal limits	Fetal biophysical tests, which help in assessing fetal wellbeing are usually abnormal. Doppler waveform analysis of umbilical and uterine arteries may be associated with reduced diastolic flow; absent or sometimes even reversed flow.

Table 11.2: Stages of fetal growth

Stage of fetal growth	*Growth characteristics*	*Weeks of gestation*
Stage 1	Cell hyperplasia	4–20 weeks of gestation
Stage 2	Cellular hyperplasia	20–28 weeks of gestation
Stage 3	Cellular hypertrophy	28–40 weeks of gestation

- Past history of giving birth to IUGR fetuses.
- Low maternal weight gain during the antenatal visits.

Accurate estimation of the gestational age is the first prerequisite before making a diagnosis of IUGR. Therefore accurate estimation of last menstrual periods need to be done at the time of taking history.

RISK FACTORS

Maternal factors

- Constitutionally small mothers: Constitutionally small sized mothers may give birth to small sized babies.
- Low maternal weight, especially a low body mass index resulting from undernutrition: A detailed nutritonal history history must be elicited.
- Tobacco smoking: Poor placental function is uncommon in a healthy woman who does not smoke.
- Excessive alcohol intake.
- Strenuous physical work.
- Poor socioeconomic conditions.
- Preeclampsia and chronic hypertension.
- Poor maternal weight gain is of very little value in diagnosing intrauterine growth restriction.
- Maternal anemia, especially sickle cell anemia.

Fetal factors

- Multiple pregnancy.
- Chromosomal abnormalities, e.g. trisomy 21.
- Severe congenital malformations.
- Chronic intrauterine infection, e.g. congenital syphilis, TORCH infections (especially rubella and CMV), viral, bacterial, protozoal and spirochetal infection. CMV infection causes cytolysis thereby resulting in loss of cells, where as rubella results in vascular insufficiency by causing endothelial damage. Hepatitis A and B are associated with preterm delivery, whereas listeriosis, tuberculosis and syphilis can cause fetal growth restriction.

Placental factors

Poor placental function (placental insufficiency or inadequacy) is usually due to a maternal problem such as preeclampsia. In preeclampsia reduced blood flow is caused by insufficient trophoblastic invasion of the spiral arteries in the placental bed. In case of normal pregnancy, the trophoblastic invasion of the spiral arteries extends beyond the decidual layer into the myometrium. However, in case of preeclampsia the trophoblastic invasion is limited to the decidual layer. These changes result in increased vascular resistance and reduced placental blood flow. Placental abnormalities including chorioangioma, circumvallate placenta, marginal or velamentous cord insertion, placenta previa, placenta abruption etc may also be sometimes responsible.

General Physical Examination

There may be no specific findings on general physical examination. The women may be constitutionally small and may have a low body mass index. She may be showing signs of

Table 11.3: Difference between symmetric IUGR and asymmetric IUGR

Symmetric IUGR	*Asymmetric IUGR*
Growth is affected before 16 weeks of gestation	Fetal growth is affected later in gestation
Fetus is proportionately small	Fetus is disproportionately small
Cell hyperplasia is affected	Cellular hypertrophy is mainly affected
Causes of symmetric IUGR mainly include congenital abnormalities, chromosomal aberrations, intrauterine infections etc.	Causes of asymmetric IUGR include hypertension, anemia, heart disease, accidental hemorrhage, etc.
Pathological process is intrinsic to the fetus	Pathological process is extrinsic to the fetus
Such neonates are small in all parameters	Head circumference is not as much affected as is abdominal circumference
Catchup growth occurs poorly after birth	Catchup growth occurs reasonably well after birth
Neonatal prognosis is usually poor	Neonatal prognosis is usually good
Ponderal index is normal	Ponderal index is low
HC/AC and FL/AC ratios are normal. In normal pregnancies FL/AC is 22 for all gestational ages from 21 weeks onwards. Also HC/AC at less than 32 weeks of normal gestation is more than one; between 32–34 weeks of gestation is 1; at more than 34 weeks of gestation is less than one	These ratios are elevated. Head circumference and femur length remains unaffected, whereas abdominal circuference is reduced. As a result HC/AC and FL/AC are elevated.
Also termed as type II (low profile IUGR)	Also termed as type I (late flattening IUGR)
Less common: Usually responsible for 20% cases of IUGR	More common: Usually responsible for 80% cases of IUGR.

Table 11.4: Risk factors for the development of IUGR

Maternal factors	*Fetal factors*
Constitutionally small mothers Maternal undernutrition	Multiple pregnancy
Tobacco smoking, excessive alcohol intake, drug abuse during pregnancy, etc.	Congenital malformations (congenital heart disease, renal agenesis, etc).
Chronic placental insufficiency due to preeclampsia, chronic hypertension, renal disease, connective tissue disorders, gestational diabetes, etc.	Chromosomal abnormalities (trisomy 21, 13, 18, 16, etc).
Maternal consumption of drugs including hydantoin, coumarin, etc.	
Maternal hypoxia (pulmonary diseases, cyanotic congenital heart disease, etc).	Intrauterine fetal infections (rubella, CMV, herpes, toxoplasmosis, tuberculosis, syphilis, etc).
Endocrine disorders (e.g. diabetic nephropathy, hyperthyroidism, addison's disease).	

poor nutritional status such as anemia, chronic malnutrition etc.

Specific Systemic Examination

ABDOMINAL EXAMINATION

The approximate size of the fetus can be estimated on abdominal examination. Palpation of fetal head gives an estimation of fetal size and maturity. The diagnostic accuracy of abdominal palpation in predicting IUGR is limited. Thus abdominal palpation itself should not be used for diagnosing IUGR. Instead, it should be used in combination with ultrasound parameters for diagnosing IUGR.

Estimation of symphysis-fundal height

Symphysis-fundal height (SFH) is measured in centimeters from the upper edge of the symphysis pubis to the top of the fundus of the uterus. If the uterus is deviated towards one side, it should be stabilized in the middle using one hand, before taking measurement. While taking the measurement, the readings of the measurement tape should be facing the patient's abdomen and not the examiner in order to prevent the measurement bias. After 24 weeks of gestation, symphysis-fundal height corresponds to the period of gestation. A lag of four cm or more is suggestive of fetal growth restriction. Ideally the S-F height in centimeters should be plotted against the gestational age on the S-F growth curve (figure 11.1). A customized fundal height chart which is adjusted for various

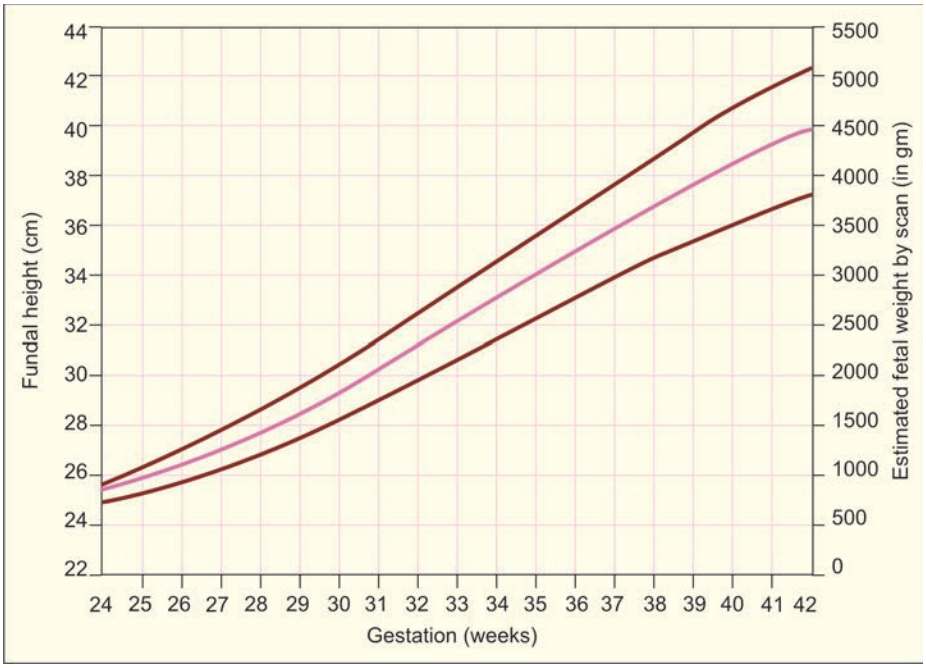


Fig. 11.1: The symphysis-fundus growth curves

maternal variables including, height, weight, parity, ethnicity etc, helps in improving the accuracy of SFH in predicting a SGA fetus. These charts may not be useful after 36 weeks of gestation. Due to the descent of the presenting part into the pelvis from 36 weeks of gestation onwards, measurement of the S-F height would no longer be accurate. At this time, even a reduction in the S-F height may be observed.

The symphysis-fundus growth curve compares the S-F height with the period of gestation. The growth curve should preferably form part of the antenatal card. The middle line of the growth curve represents the 50th centile, whereas the upper and lower lines represent the 90th and 10th centiles, respectively. If intrauterine growth is normal, the S-F height will fall between the 10th and 90th centiles. If intrauterine growth restriction is present, the S-F height and the expected baby's weight would fall below the 10th centile. Growth restriction is also suggested when three successive measurements of fetal weight "plateau" at approximately the same level, without necessarily crossing below the 10th centile. Growth restriction is considered as severe when the discrepancy between the actual duration of pregnancy and that suggested by plotting S-F height is four weeks or more.

If the baby's weight falls above the 90th centile, it points towards a macroscomic baby (see chapter 14).

Like abdominal palpation, measurement of symphysis fundal height is also associated with limited diagnostic accuracy in predicting a baby which would be affected by IUGR. Measurement of SFH is associated with low rates of sensitivity, high false positive rates and significant intra- and inter-observer variation.

Management

Management comprising of investigations and definitive obstetric management is discussed below.

Investigations

A distinction needs to be made between the biometric tests (which help in measuring fetal size and gestational age) and biophysical tests (which help in assessing fetal wellbeing). Biophysical tests are not important in measuring fetal growth but provide an important measure of fetal wellbeing. According to the RCOG (2002), the fetal abdominal circumference (AC) and expected fetal weight are most accurate parameters for predicting IUGR. Measurement of growth velocity using various ultrasound parameters is also useful in predicting FGR. For measurement of growth velocity, the interval between two individual scans must be about 3 to 4 weeks. Ratio measurements (HC/AC or FL/AC) are poorer than both AC and EBW in predicting FGR. Various biometric and biophysical investigations for diagnosing IUGR are listed in table 11.5. Each of these investigations would be described below in details.

Table 11.5: Investigations for diagnosing IUGR

Biometric tests	*Biophysical tests*
Ultrasound biometry	Non-stress test
Ultrasound estimated fetal weight	Biophysical profile, amniotic fluid volume
–	Ultrasound Doppler flow velocimetry
–	Fetal cardiotocography

Ultrasound Biometry

Estimation of gestational age can be accurately done using ultrasound biometry. Besides the accurate dating of fetal gestation, ultrasound examination is also important for excluding serious congenital abnormalities in the fetus, estimating the amount of liquor and for ruling out multifetal gestation. The various ultrasound measurements and parameters which help in accurately predicting the gestational age are described below. Out of all these parameters, AC is considered to be the most accurate in predicting fetal growth restriction.

Crown rump length

CRL is an ultrasonic measurement which is made earliest in pregnancy, when the gestational age is between 7 and 13 weeks (figures 11.2A and B). The measurement of the crown-rump length of the fetus gives most accurate measurement of the gestational age. Early in pregnancy, the accuracy of determining gestational age though CRL measurement is within ± 4 days, but later in pregnancy due to different growth rates of the fetus, the accuracy of determining gestational age with help of ultrasound is less. In that situation, other parameters can be used in addition to CRL. The graphical measurement of CRL according to the gestational age is shown in figure 11.2C. The upper and lower curves respectively represent the 95th and 5th percentiles for the CRL measurement according to the gestational age.

Biparietal diameter

Biparietal diameter is the distance between the two sides of the head. Biparietal diameter can be measured at the level of the plane defined by the frontal horns of the lateral ventricles and the cavum septum pellucidium anteriorly, flax cerebri in the midline, the thalami symmetrically positioned on either side of the falx in the center and occipital horns of the lateral ventricles, sylvian fissure, cisterna magna and the insula posteriorly (figures 11.3A and B). Septum pellucidum can be visualized at one third the frontooccipital distance. The measurement of biparietal diameter is taken from outer table of the proximal skull to the inner table of the distal skull with the septum cavum perpendicular to the ultrasound beam.

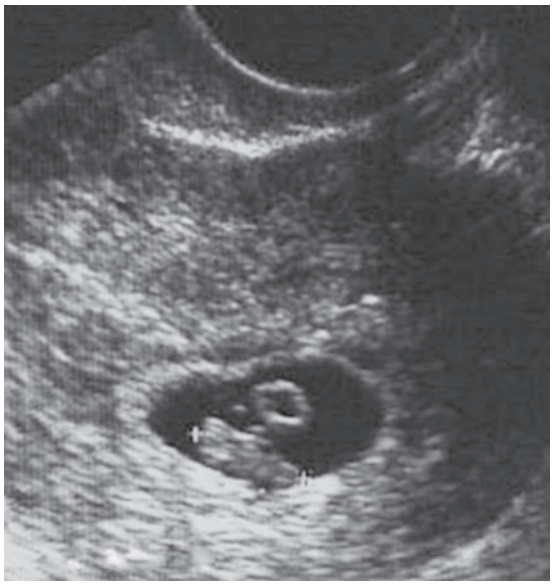


Fig. 11.2A: Ultrasound measurement of CRL

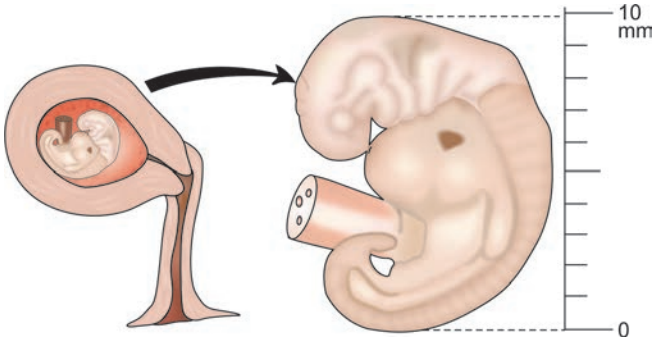


Fig. 11.2B: Method of measuring CRL

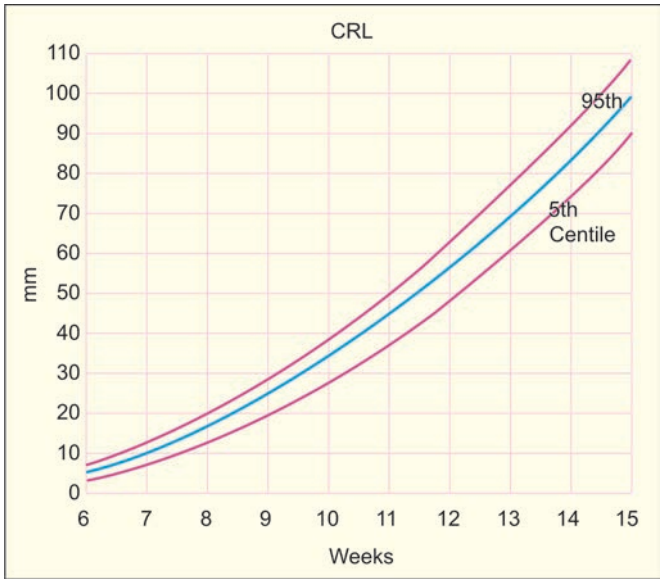


Fig. 11.2C: Graphical representation of CRL measurement

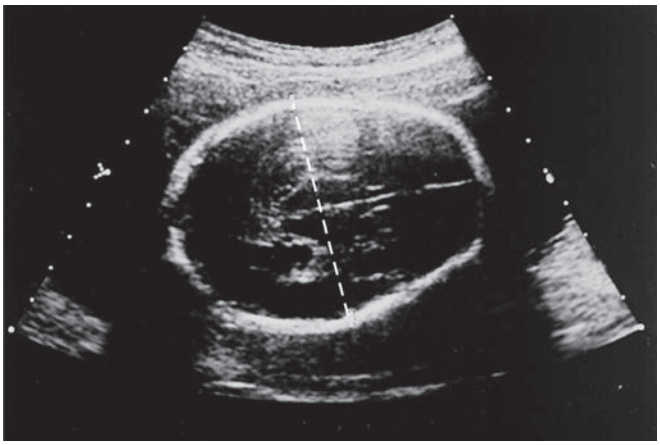
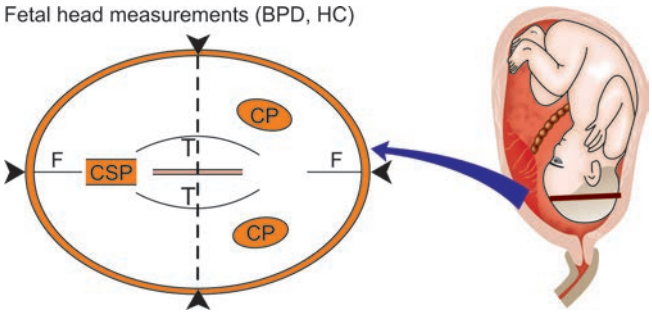


Fig. 11.3A: Ultrasound measurement of BPD



T: Thalamus; F: Falx; CSP: Cavum septum pellucidum; CP: Choroid plexus

Fig. 11.3B: Method of measuring BPD

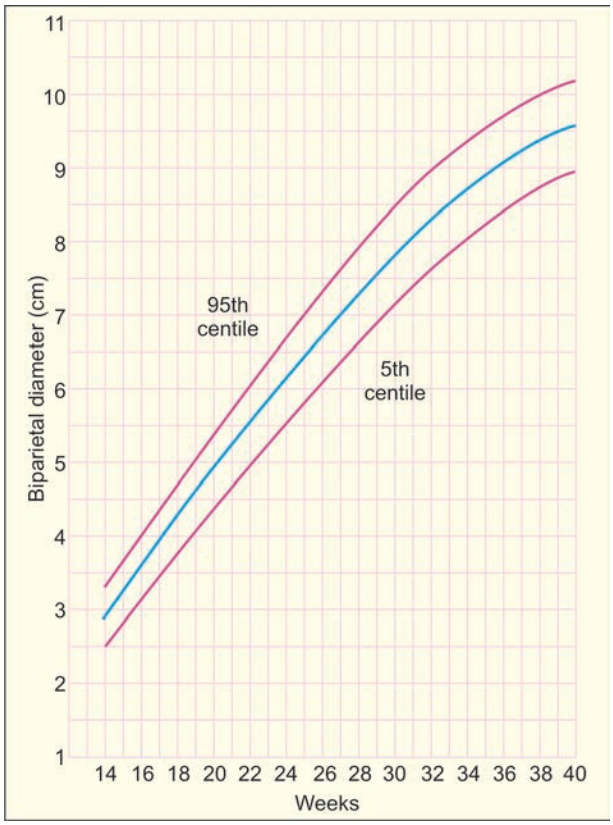


Fig. 11.3C: Graphical representation of BPD measurement

BPD is usually measured after 13 weeks of pregnancy for dating of pregnancy. It increases from about 2.4 cm at 13 weeks to about 9.5 cm at term. Different babies of the same weight can have different head size, therefore dating in the later part of pregnancy is generally considered unreliable. The graphical measurement of BPD according to the gestational age is shown in figure 11.3C. The upper and lower curves represent the 95th and 5th percentiles for the BPD measurement according to the gestational age. An obstetrician maintaining such a chart is able to efficiently monitor the fetal growth. The BPD remains the standard against which other parameters of gestational age assessment are compared. At 20 weeks of gestation, accuracy of BPD is within 1 week.

The BPD can be smaller (and sometimes much smaller than is expected) in fetuses with flatter heads. If the head really looks flat on the scan, the corrected BPD (in which the head area or circumference has been taken into consideration) is used. If the value of corrected BPD is within the normal range, then most likely the discrepancy is due to a flat head. The obstetrician must monitor the growth of the fetal head with the head circumference from then onwards. The cephalic index will also be useful.

Corrected BPD

Corrected BPD can be calculated using the following formula:

$$\text{Corrected BPD} = (\text{BPD} \times \text{OFD}/1.265)^{1/2}$$

where OFD = Occipitofrontal diameter.

The shape of fetal head can also be obtained by calculating the CI (cephalic index)

$$\text{Corrected BPD} = (\text{BPD} \times \text{OFD}/1.265)^{1/2}$$

$$\text{CI (\%)} = \frac{\text{BPD (outer to inner)}}{\text{OFD (outer to outer)}} \times 100$$

Cephalic index of less than 74% represents dolichocephaly (longheaded, whereas that greater than 83% represents brachycephaly (shortheaded).

Occipitofrontal diameter is measured in the same plane as the BPD. However instead of taking measurement from outer table to inner table, the measurement is taken from outer table of proximal skull to outer table of the distal skull.

Abdominal circumference

Abdominal circumference is a measure of fetal abdominal girth. The abdominal circumference is measured in an axial plane at the level of the stomach and the bifurcation of the main portal vein into the right and left branches

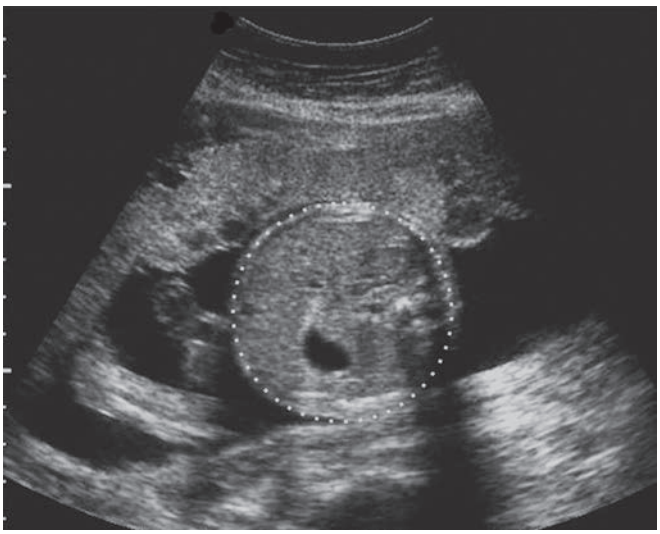


Fig. 11.4A: Ultrasound measurement of abdominal circumference

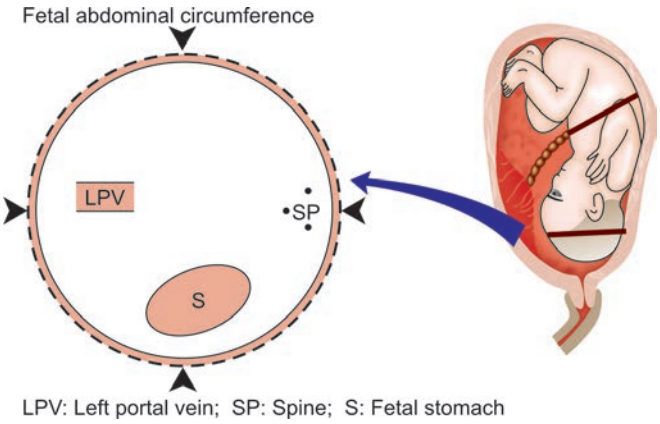


Fig. 11.4B: Method of measuring abdominal circumference

(figures 11.4A and B). While measuring the abdominal circumference, the radiologist must be careful about keeping the section as round as possible and not letting it get deformed by the pressure from the probe. Figure 11.4C shows the graphical representation of abdominal circumference measurement in relation to the gestational age. If the AC measurement falls below the 5th percentile on the graph, a diagnosis of fetal growth restriction is made.

Transverse cerebellar diameter

Another parameter which is gaining increasing importance in measurement of gestational age is the transverse cerebellar diameter (TCD). This diameter refers to the widest diameter of the cerebellum and is the distance between the outer borders of the two cerebellar hemispheres (figures 11.5A to C). The major advantage of measuring cerebellar diameter is that this parameter allows for the estimation of gestational age that

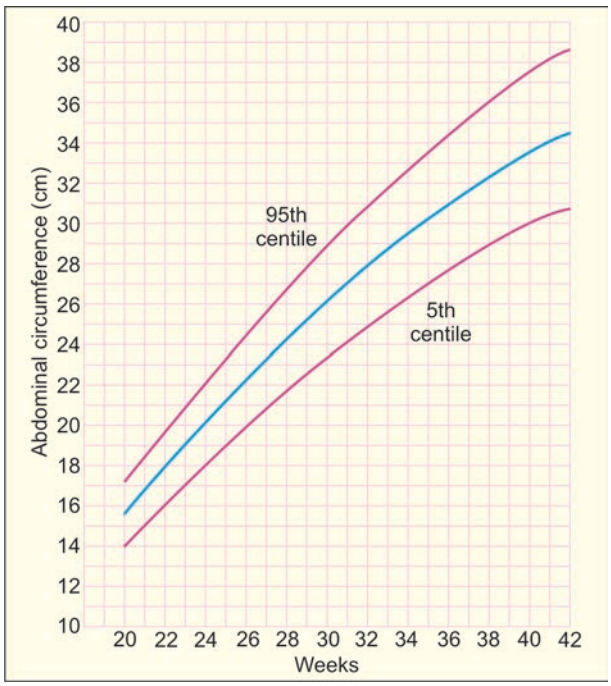


Fig. 11.4C: Graphical representation of abdominal circumference measurement

is independent of the shape of the fetal head, through out the pregnancy. Conditions which may alter the shape of the fetal skull and affect the biparietal diameter include conditions like breech presentation, oligohydramnios, multiple gestation and uterine anomalies. Since the posterior fossa is not affected by these pressure effects, cerebellar diameter can be considered as a more accurate reflection of gestational age than biparietal diameter in such cases. Determination of TCD also helps in the evaluation of anomalous development of the central nervous system. It has been shown to be an accurate predictor of gestational age, even in the third trimester of pregnancy.

Grading of cerebellar appearance on ultrasound

The ultrasound appearance of the cerebellum seems to change progressively from an "eyeglass" (grade I), to a "dumbbell" (grade II) and finally to a "fan" shape (grade III) with advancing gestation. Figure 11.5A shows grade I cerebellar appearance whereas figure 11.5B shows grade III cerebellar appearance. A gradual change in ultrasound appearance of the fetal cerebellum is seen with advancing gestation (figure 11.5C).

Femur length

Femur length is the length of femoral diaphysis, the longest bone in the body and represents the longitudinal growth of the fetus. It is measured from the origin of the shaft to the distal end of the shaft, i.e. from greater trochanter to the lateral femoral condyle (figures 11.6A and B). The femoral diaphysis

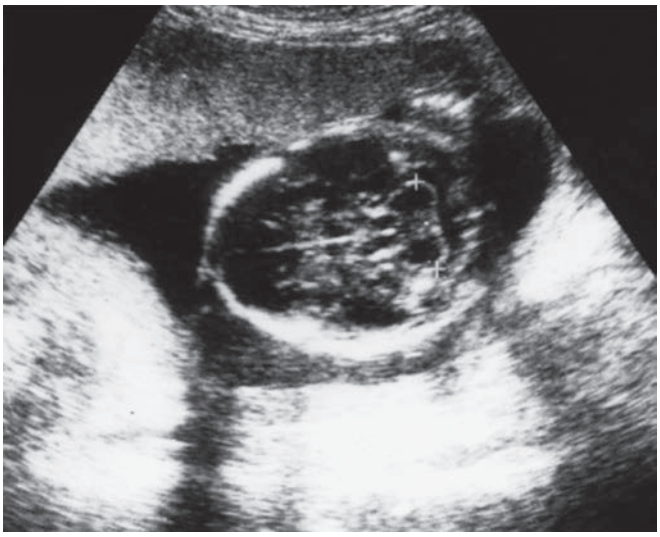


Fig. 11.5A: Grade I appearance of cerebellum

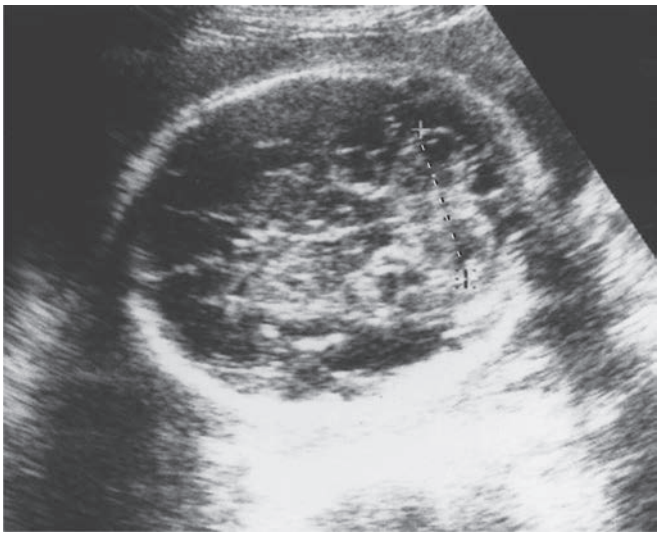


Fig. 11.5B: Grade III appearance of the cerebellum

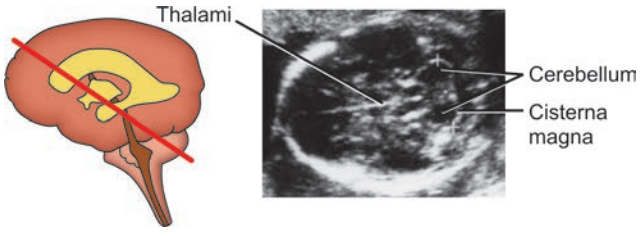


Fig. 11.5C: Measurement of transverse cerebellar diameter

should be horizontal showing a homogeneous echogenicity. The femoral head and distal femoral epiphysis present after 32 weeks are not included in the measurements. Its usefulness is similar to the BPD. It increases from about 1.5 cm at 14 weeks to about 7.8 cm at term (figure 11.6C). Besides telling

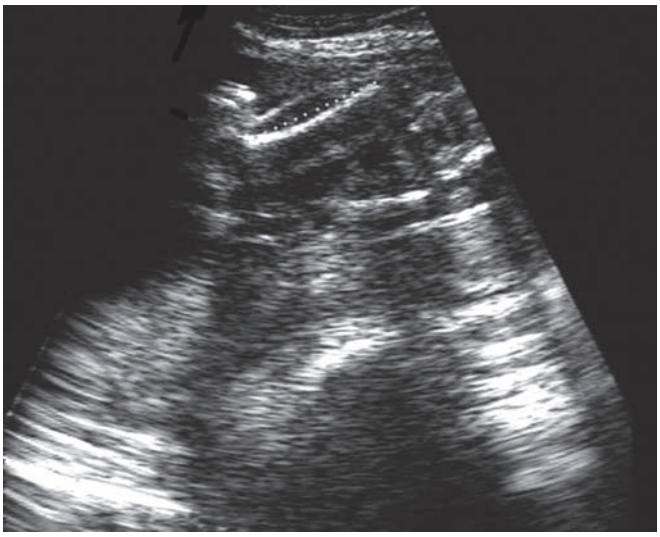


Fig. 11.6A: Ultrasound measurement of femur length

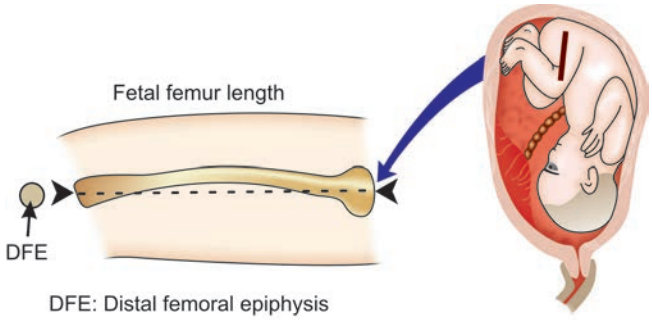


Fig. 11.6B: Method of measuring femur length

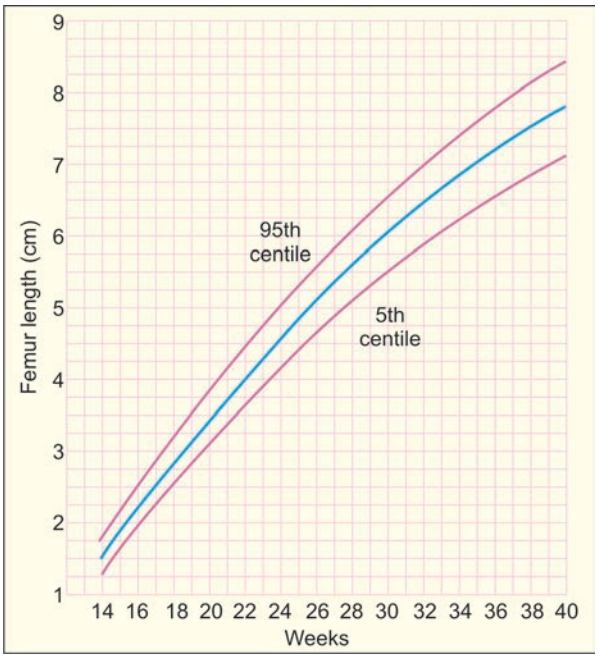


Fig. 11.6C: Graphical measurement of femur length

Table 11.6: Prediction of fetal gestational age using ultrasound biometric parameters

Period of gestation	*Ultrasound parameter to be used*
8 weeks to 12 weeks	Crown-rump length measurement
Second trimester	Corrected BPD
Third trimester	corrected BPD, HC, FL or TCD

about the longitudinal growth of the fetus, measuring the FL also helps in excluding dwarfism in the fetus. The ultrasound ratio of AC/FL is an important measure of IUGR. The use of FL in dating is similar to the BPD and is not superior unless a good plane for the BPD cannot be obtained or that the head has an abnormal shape.

Prediction of Gestational Age (Table 11.6)

Measurement of single ultrasound parameter for determination of gestational age is unreliable after 30 weeks of gestation. The best time to determine gestational period based on a single ultrasound parameter is between 18–24 weeks of gestation. If both BPD and LMP are available, BPD should be used to predict term. Crown-rump length of 15–60 mm (corresponding to gestational period varying from 8–12.5 weeks) is found to have the greatest accuracy in determining the period of gestation in the first trimester, but then BPD (at least 21 mm) is found to be more precise after this period of gestation, i.e. in the second trimester. The corrected BPD (either area corrected or circumference corrected) and the HC are equally accurate and both are more accurate than is the BPD. This could be due to the fact that the first two predictors (corrected BPD and the HC) take head shape into account, whereas BPD does not.

ln the early third trimester, no significant difference in accuracy is seen among corrected BPD, HC and FL. All predictors have been found to be imprecise late in the third trimester, so gestational age assigned on the basis of a sonographic measurement made during this stage of pregnancy is not reliable. Femoral length is to be measured routinely in an obstetric ultrasound after 14 weeks. If a skeletal deformity is suspected, the tibial or fibular length can also be taken. Combining more than one ultrasonic measurement is not seen to improve dating accuracy. Recently numerous new parameters like kidney length, scapula length, cerebellar diameter, etc are being researched in order to accurately determine the period of gestation.

The accuracy of each predictor of gestational age has been found to worsen progressively as the pregnancy proceeds. If the previous sonogram is available, the age must be calculated from the earliest sonogram available.

Head circumference/abdominal circumference ratio (HC/AC ratio)

The use of this ratio in diagnosis of IUGR in based on the idea that the head circumference is usually preserved in asymmetric PFGR babies, whereas the abdominal circumference is reduced. Normally HC/AC is usually more than one till 32 weeks; one between 32–36 weeks gestation and less than one after 36 weeks. Pathological growth restriction is diagnosed when HC/AC ratio is above the 95th percentile for the gestational age.

Femoral length/abdominal circumference (FL/AC ratio)

The normal value of this ratio remains 22 ± 2, irrespective of the period of gestation. IUGR can be suspected if the ratio is more than 24.

Transverse cerebellar diameter/abdominal circumference (TCD/AC ratio)

Similar to head circumference and femur length, the transverse cerebellar diameter is supposed to remain unaffected in the IUGR fetuses. If this happens, the TCD/AC ratio would be expected to increase in cases with asymmetric IUGR. The normal TCD/AC ratio is 0.137 ± 0.012. However the present evidence regarding the effect of fetal growth restriction on the TCD has presented with conflicting results. While some investigators have shown that TCD remains unaffected in IUGR fetuses, other studies have indicated that in case of intrauterine growth retardation, cerebellar size is reduced in proportion to the severity of the disease. Therefore, presently the measurement of TCD and/or the TCD/AC ratio (transverse cerebellar diameter by abdominal circumference) does not provide reliable information as to whether or not fetuses are growth-restricted.

Fetal ponderal index

Fetal ponderal index is another ultrasound measured fetal index which is used for diagnosing IUGR. Fetal ponderal index (FPI) is calculated with help of the formula as described below:

$$\text{FPI} = \frac{\text{Estimated fetal weight}}{\text{Femur length}^3}$$

Ultrasound Estimated Fetal Weight

Some of the commonly used formulas for estimating fetal weight using various ultrasound parameters are described in table 11.7. In clinical practice, estimation of fetal weight is usually based on Hadlock's formula.

Table 11.7: Ultrasound based estimation of fetal weight

Shepard's formula	Log10EFW = 1.2508 + (0.166 x BPD) + (0.046 x AC) – (0.002646 x AC x BPD)
Aoki's formula	EFW = (1.25647 x BPD3) + (3.50665 x FAA x FL) + 6.3
Hadlock's formula	Log10EFW = 1.3596 – 0.00386(AC x FL) + 0.0064(HC) + 0.00061(BPD x AC) + 0.0425 (AC) + 0.174 (FL)

EFW = estimated fetal weight (g); BPD = biparietal diameter (cm); FAA = fetal abdominal area (cm^2);

FL = femur length (cm); AC = abdominal circumference (cm); FAA = fetal abdominal area; HC = head circumference

Table 11.8: Schedule for conducting various antepartum surveillance tests in patients with IUGR

Test	*Timing*
Fetal movement count	Daily
Amniotic fluid volume	Weekly
Non-stress test	Twice weekly
Biophysical profile	Weekly if NST is abnormal
Oxytocin challenge test	Every fortnightly, if biophysical profile is less than 8
Umbilical artery Doppler	Every 2–3 weeks

Measures of Fetal Surveillance/Biophysical Tests

Fetal surveillance measures include the biophysical tests which aim at identifying the fetus with IUGR before it becomes acidotic. Some of these measures have been enumerated in flow chart 11.1 and would be described below in details. The schedule for conducting various antepartum surveillance tests in patients with IUGR is shown in table 11.8. Fetal surveillance is of utmost importance in cases of IUGR. The patient must be instructed to maintain a daily count of number of fetal movements she experiences daily. NST should be done biweekly. If NST is abnormal, BPP must be performed on weekly basis. Ultrasound for measuring fetal growth velocity must be carried out on bimonthly basis. Frequency of Doppler monitoring in IUGR fetuses need not be more than once every fortnightly.

Ultrasound Doppler Flow Velocimetry

The evaluation of fetal wellbeing by Doppler velocimetry in cases of intrauterine growth restriction (IUGR) is of great importance as it is very useful in detecting those IUGR fetuses that are at high risk because of hypoxemia. Several Doppler studies which were initially performed on fetal arteries (umbilical arteries, uterine arteries, middle cerebral arteries, etc) and recently on the fetal venous system (ductus venosus) provide valuable information for the clinicians concerning the optimal time of delivery. The various types of indices which provide information regarding the amount of blood flow in various vessels are described in table 11.9 and figure 11.7.

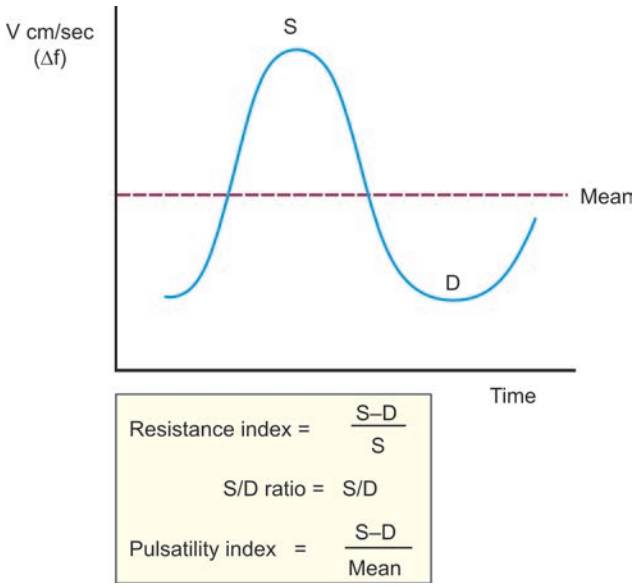


Fig. 11.7: Description of various Doppler indices

Changes occurring in various Doppler velocity waveforms in IUGR fetuses (flow chart 11.2)

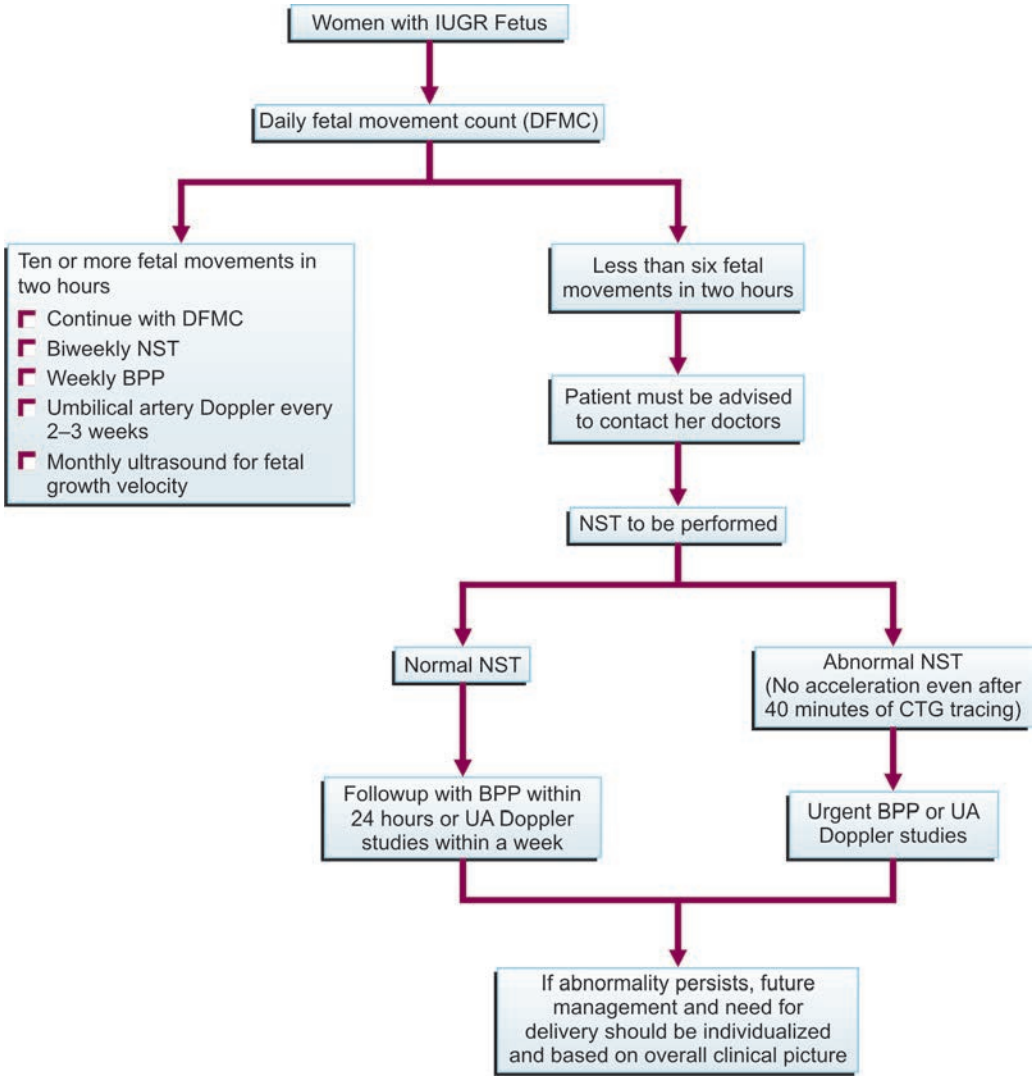
Umbilical artery Doppler serves as the primary surveillance tool for management of IUGR fetuses. The Doppler measurements from umbilical artery, uterine artery, middle cerebral artery and ductus venosus are important for diagnosing placental insufficiency. The major Doppler detectable modifications in the fetal circulation associated with IUGR and fetal hypoxemia include increased resistance in the umbilical artery, fetal peripheral vessels and maternal uterine vessels, in association with decreased resistance in the fetal cerebral vessels.

Uterine artery Doppler: The uterine artery Doppler is indicative of uteroplacental circulation by showing presence or absence of resistance to the blood flow. In normal

Table 11.9: Types of Doppler indices

Doppler index	*Calculation of Doppler index*
S/D ratio (Stuart, 1980)	Peak systolic blood flow/end diastolic velocity
Pulsality Index (PI) [Pourcelot, 1974]	(Peak systolic velocity – end diastolic velocity)/mean systolic velocity
Resistance index (RI) [Gosling and King, 1977]	(Peak systolic velocity – end diastolic velocity)/peak systolic velocity

Flow chart 11.1: Fetal surveillance in women with IUGR

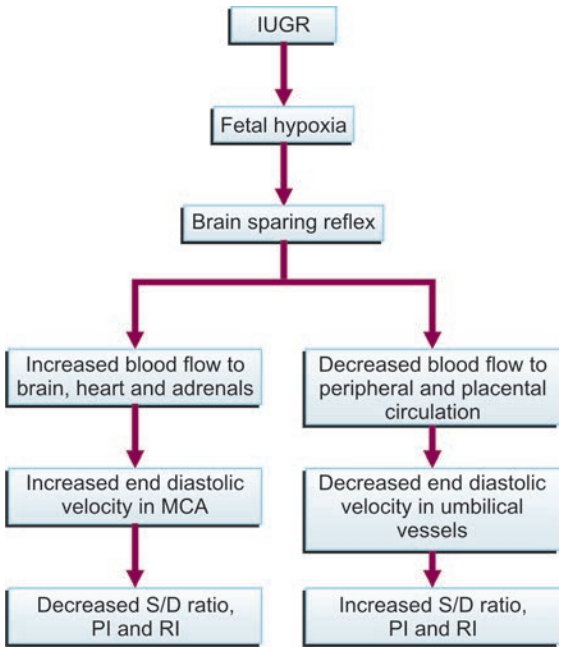


pregnancy, both uterine artery in the placental bed and the fetal umbilical arteries circulations, exhibit high diastolic flow velocities caused by low resistance. Abnormal uterine artery Doppler studies characterized by reduced diastolic flow suggest a maternal cause for IUGR. Increased resistance to the blood flow in uterine vessels, resulting in reduced diastolic flow causes increased systolic-diastolic ratio of flow velocities in uterine vessels.

Middle cerebral artery (MCA) Doppler studies: In IUGR, deficiency of oxygen causes the redistribution of the blood flow resulting in increased blood flow to the brain causing a drop in the cerebral resistance. These changes can be attributed to the "brain sparing effect", in which there is preferential perfusion of the brain, heart and adrenals at the expense of the integument and viscera, gut and kidneys in the hypoxic fetuses. This leads to a decrease in the S/D ratio as well as the pulsatility and resistance index in the MCA. At the same time, there is reduced flow to the peripheral and placental circulations resulting in decreased end diastolic velocity in umbilical vessels and thereby increase in the S/D ratio, PI and RI. With the worsening of the fetal condition, as the blood flow to the brain also reduces, MCA blood flow velocity may return to normal. Changes in the cerebral flow parameters, however, have not been observed to correlate with the degree of asphyxic compromise. Therefore, these parameters are not helpful in choosing timing for delivery.

Umbilical artery Doppler: In normal pregnancy, the placental vascular bed is a low resistance bed, where impedance decreases with the advancing gestational age. The assessment of umbilical blood flow provides information regarding blood perfusion of the fetoplacental unit. In normal pregnancy, the fetal umbilical circulation is characterized by continuous

Flow chart 11.2: Changes occurring in various Doppler velocity waveforms in IUGR fetuses



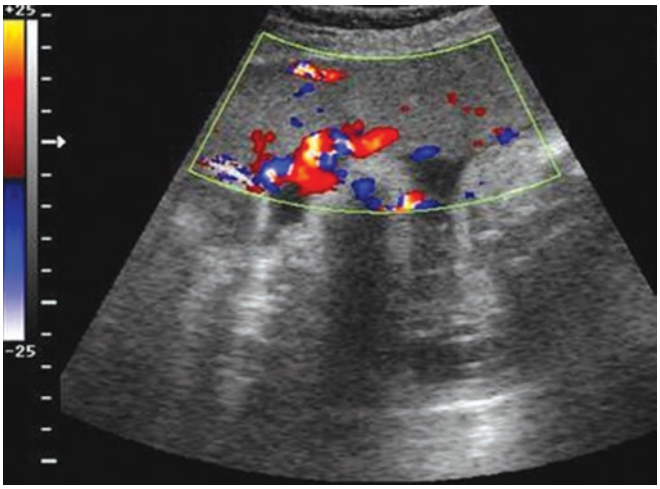


Fig. 11.8A: Umbilical artery circulation on color Doppler ultrasonography

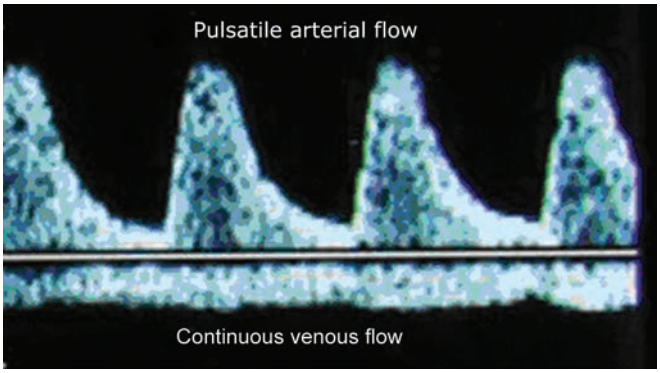


Fig. 11.8B: Umbilical artery Doppler ultrasound waveforms

Table 11.10: Changes in umbilical blood flow with increasing vascular resistance

Elevated PI and RI
Early diastolic notch (figure 11.9A)
Absent end diastolic blood flow
Reversed end diastolic blood flow (figure 11.9B)

forward flow. Characteristic umbilical blood flow has saw tooth appearance of arterial flow in one direction and continuous umbilical venous blood flow in the other (figures 11.8A and B). The systolic/diastolic (S/D) ratio serves as an index of measurement which compares the systolic with the diastolic flow in the umbilical arteries and identifies the amount of resistance in the placental vasculature. The end diastolic blood flow in umbilical artery increases with advancing gestation in normal pregnancies. As a result there is a decline in both PI and S:D ratio with increasing gestation. As resistance decreases, RI values approach zero. On the other hand, when the resistance increases, end diastolic flow approaches zero, therefore RI approaches one. If the end diastolic flow is absent, according to the equations mentioned in table 11.9, S/D ratio would be equal to infinity and RI would be equal to one. Therefore in these cases, the blood flow is assessed with the help of PI.

In cases of IUGR (especially due to placental insufficiency) if the resistance to blood flow does not decrease sufficiently, the umbilical circulation is characterized by presence of abnormal systolic to diastolic ratio, pulsatility index (PI) or resistance index (RI). The umbilical artery indices are considered as abnormal if they become greater than 95th percentile for the gestational age or if the diastolic flow is either absent or reversed. Generally an S/D ratio of equal to or less than 3.0 is considered as normal. A rising S/D ratio indicates a worsening fetal prognosis and warrants closer more frequent monitoring. Various changes in Doppler waveform analysis with increased resistance in umbilical vessels are summarized in table 11.10.

Ductus venosus Doppler: The ductus venosus (figure 11.10) is a very important part of fetal venous circulation. This vessel acts as a shunt and helps in directly connecting the umbilical vein to the inferior vena cava. The fetus receives oxygenated blood from the mother through placenta in form of umbilical veins. As this oxygenated blood bypasses ductus venosus, some of the oxygenated blood goes to the liver, but most of it bypasses the liver and empties directly into the inferior vena cava, which enters the right atrium. This

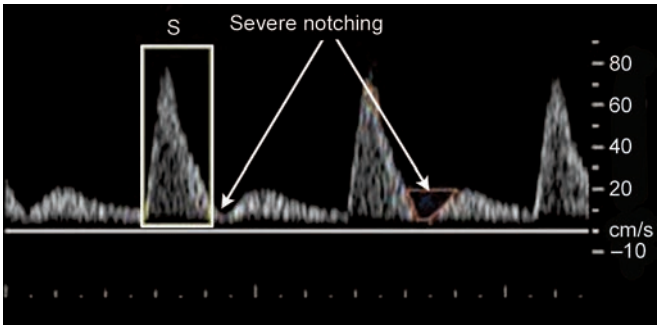


Fig. 11.9A: Diastolic notching on Doppler analysis

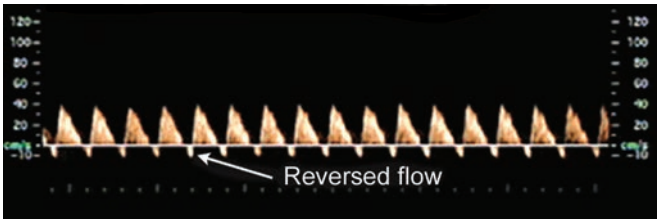


Fig. 11.9B: Reversed flow on Doppler analysis

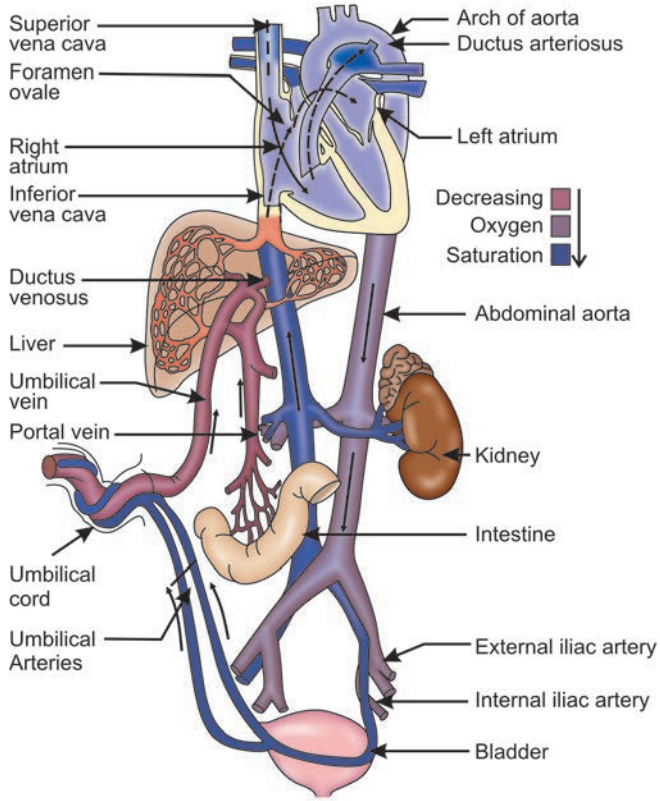


Fig. 11.10: Fetal circulation just before birth showing ductus venosus

highly oxygenated and nutrient-rich umbilical venous blood is eventually supplied to the fetal brain and myocardium instead of the fetal liver. It has been estimated that, during the

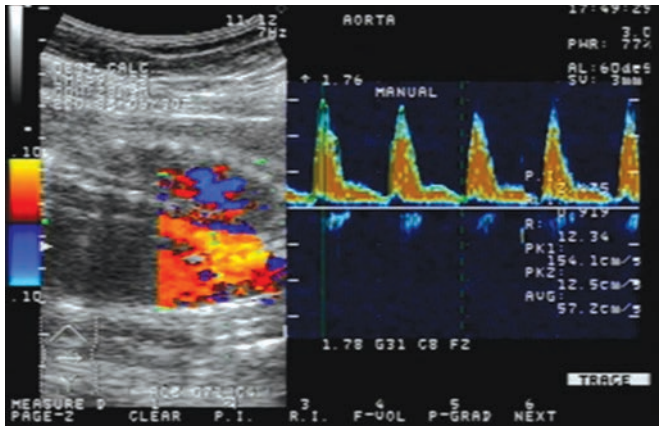


Fig. 11.11: Doppler analysis of venous blood flow

periods of fetal hypoxia, a compensatory mechanism occurs. This results in transient dilatation of the ductus, which is supposed to increase oxygenated blood flowing through it during these periods of hypoxia or reduced umbilical flow. In order to increase the cerebral blood flow at the time of hypoxia, the blood flow shunted through the DV increases and could amount to as much as 70% of the umbilical blood flow.

However in normal pregnancies with increasing gestation there is significant reduction in the umbilical blood flow shunted through the DV from 40% at 20 week of gestation to 15% at 38 week of gestation. This is so, as late in normal pregnancy DV plays a less important role in shunting well-oxygenated blood to the brain and myocardium in comparison to that in the early gestation.

The typical waveform for the blood flow in the venous vessels consists of three phases related to cardiac cycle (figure 11.11). Peak S wave corresponds to ventricular systole, peak D wave to early diastole and peak A wave to atrial contraction. In normal fetuses, the blood flow in the ductus venosus is always in the forward direction throughout the cardiac cycle (figure 11.12). Forward blood flow in the venous system is a function of cardiac compliance, contractibility and after load. A decline in forward velocities in venous system results in increased Doppler indices and suggests impaired circulation. Absence or even reversal of the A wave is the hallmark of the advancing circulatory deterioration since this documents the inability of the heart to accommodate venous return (figure 11.13).

Since the DV shunt would increase during fetal hypoxia, examination of dilated DV would help in the identification of patients with IUGR, preeclampsia, etc, who are at a high risk for fetal distress. The presence or absence of fetal cardiac failure secondary to hypoxia and acidosis is indicated by Doppler studies of ductus venosus.

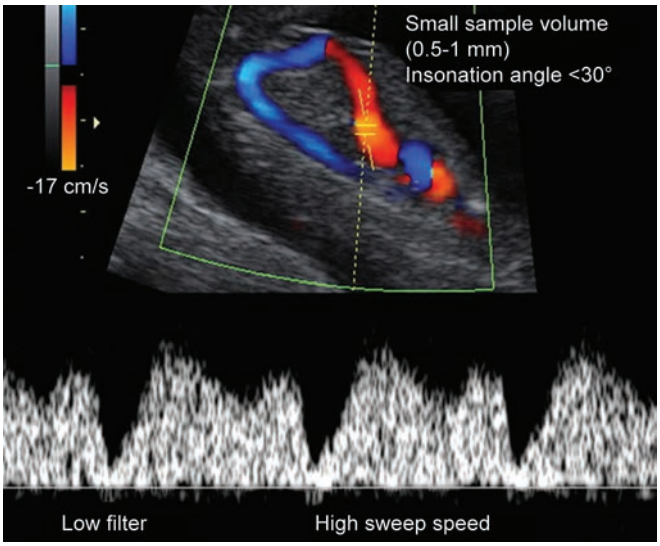


Fig. 11.12: Normal blood flow through ductus venosus on Doppler waveform analysis

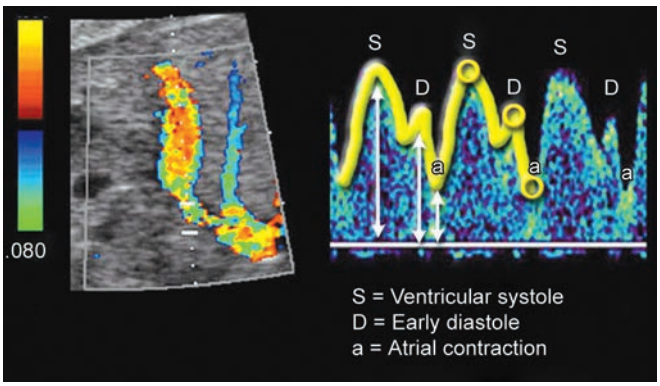


Fig. 11.13: Blood flow through the ductus venosus showing reversal of the A wave

Sequence of changes occurring in various Doppler velocity waveforms in IUGR fetuses

Doppler velocimetry is one of the best methods of fetal surveillance during IUGR and helps in diagnosing the associated fetal acidosis and hypoxia. The sequences of changes occurring in fetal vessels occur in parallel to the extent of the fetal compromise. Initially there is appearance of changes on fetal artery Doppler analysis, followed by changes on fetal venous Doppler analysis. This is followed by changes on BPP and CTG. The usual order of the findings on CTG trace indicating fetal hypoxia include the initial loss of accelerations, followed by decreasing variability and presence of late decelerations. The arterial changes on Doppler analysis are indicative of brain damage, whereas venous changes point towards fetal heart failure.

The normal placental sufficiency is indicated by normal Doppler waveforms in the uterine, umbilical and fetal middle cerebral arteries. Increased S/D ratio in the uterine artery suggests increased resistance at the maternal end, whereas increased S/D ratio in the umbilical artery suggests increased resistance at the fetal end.

Amniotic Fluid Volume

Measurement of amniotic fluid volume is an important method of fetal surveillance. Estimation of amniotic fluid can be done in two ways: Maximal vertical pocket depth of amniotic fluid and amniotic fluid index. The classification of amniotic fluid volume based on these two parameters is shown in table 11.11. Determination of maximal vertical pool of liquor involves in the measurement of maximum vertical diameter of the deepest pocket of amniotic fluid identified upon ultrasound examination. Amniotic fluid index (AFI) is obtained by measuring the vertical depth of the largest fluid pockets in each of the four uterine quadrants. These four measurements are added in order to obtain a total amniotic fluid index. The AFI uses the 5th and 95th percentiles for gestational age to signify oligohydramnios and polyhydramnios respectively. If the AFI measures less than 5 centimeters (5th centile), the pregnant woman is supposed to have oligohydramnios. If amniotic fluid levels add up to more than 25 centimeters (95th centile), she is supposed to have polyhydramnios. Use of amniotic fluid volume evaluation has become important in

Table 11.11: Volume of amniotic fluid inside the amniotic cavity (based on ultrasound findings)

Amount of amniotic fluid	*Total amount of amniotic fluid*	*Maximum vertical pool of liquor*	*Amniotic fluid index (AFI)*
• Normal	700 ml to one liter at full term	Adequate fluid, seen everywhere between the fetus and uterine wall	AFI of 5 to 25 cm
• Oligohydramnios	Less than 200 ml of amniotic fluid	Maximum vertical pool of liquor less than 2 cm	AFI of < 5 cm
• Polyhydramnios	Amniotic fluid volume of 2000 ml or greater at term	Presence of maximum vertical fluid pocket seen greater than 8 cm in diameter	AFI > 25 cm

the assessment of pregnancy at risk for an adverse pregnancy outcome as it forms basis of two important tests of fetal well-being used commonly, namely the biophysical profile and the modified biophysical profile both of which include ultrasound estimation of amniotic fluid volume. If the amount of amniotic fluid is reduced, the frequency of NST must be increased.

Non-stress test

The fetal non-stress test is a simple, noninvasive test performed in pregnancies over 28 weeks of gestation. The test is named "non-stress" because no stress is placed on the fetus during the test. Antepartum non-stress testing performed on weekly basis may be considered as a method of fetal surveillance in IUGR fetuses.

Procedure

- The test involves attaching one belt to the mother's abdomen to measure fetal heart rate and another belt to measure uterine contractions (figure 11.14A). Fetal movement, heartrate and "reactivity" of fetal heart (acceleration of fetal heart rate) are measured for 20–30 minutes. If the baby does not move, it does not necessarily indicate that there is a problem; the baby could just be asleep.
- The mother is handed a probe which she is asked to press whenever she feels a fetal movement. The fetal heart tracing is observed for fetal heartrate accelerations that peak (but do not necessarily remain) at least 15 beats per minute above the baseline and last for 15 seconds between baseline to baseline. NST is defined as reactive if there is a presence of two or more accelerations that peak 15 beats per minute above the baseline, each lasting for 15 seconds or more and all occurring within a 20 minutes period from beginning the test (figure 11.4 B). Fetal movement may or may not be recognised by the patient. The test is defined as non-reactive if there are no fetal heart rate accelerations over a 40-minute period (table 11.12).
- It may be necessary to continue the tracing for 40 minutes or longer to take into account the average period of nonrapid eye movement (NREM) sleep when fetal movement and subsequently heart rate variability are reduced. When the fetal heart tracing is continued for 40 minutes, it is termed as an "extended NST".

Table 11.12: Classification of NST as either reactive or non-reactive

Test result	*Interpretation*
A reactive non-stress result	If there are accelerations of the fetal heartrate of at least 15 beats per minute over the base line, lasting for at least 15 seconds, occurring within a 20 minute time block.
Non-reactive non-stress	If these accelerations don't occur, the test is said to be non-reactive. Additional testing may be required to determine whether the result is truly due to poor oxygenation

Fig. 11.14A: Procedure of performing a non-stress test

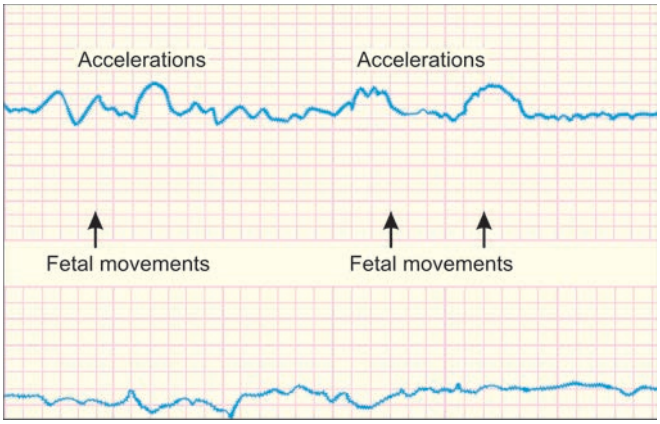


Fig. 11.14B: Reactive NST

Implications of a reactive (normal) non-stress test

A reactive non-stress result indicates fetal wellbeing, i.e. the fetus is receiving an adequate supply of blood and oxygen. In most cases, a normal NST is predictive of good perinatal outcome for one week (provided that the feto-maternal condition remains stable), except in women with IUGR, in which case, NSTs are recommended at least twice weekly.

Implications of a non-reactive (abnormal) non-stress test

A non-reactive test could be due to fetal hypoxia or fetal inactivity (i.e. fetal sleep patterns, certain maternal drugs). A non-reactive non-stress test does not indicate definite fetal compromise. It just requires additional testing to determine

Table 11.13: Biophysical profile criteria

Component	*Score of 2*	*Score of 0*
Amniotic fluid volume	Single vertical pocket of amniotic fluid greater than 2 cm in two perpendicular planes.	Largest vertical pocket of amniotic fluid is 2 cm or less
Fetal breathing movements	One or more episodes of rhythmic fetal breathing movements of 30 seconds or more within 30 minutes	Abnormal, absent or insufficient breathing movements
Fetal movement	Three or more discrete body or limb movements within 30 minutes	Abnormal, absent or insufficient movements
Fetal tone	At least one episode of flexion-extension of fetal extremity with return to flexion, or opening or closing of hand within 30 minutes	Abnormal, absent or insufficient fetal tone
Non-stress test	Reactive (normal)	Non-reactive (abnormal)

whether the result is truly due to poor oxygenation, or whether there are other reasons for fetal non-reactivity. The additional testing can be in the form of prolonged NST, a contraction stress test, or a biophysical profile.

Biophysical Profile

When the primary surveillance with umbilical artery Doppler is abnormal, BPP is likely to be a useful surveillance tool as it has good negative predictive value in high risk populations. The biophysical profile (BPP) was first described by Manning in 1980. It utilizes multiple ultrasound parameters of fetal wellbeing and the NST. It is more accurate than a single test as it correlates five measurements to give a score. As a result, it is associated with much lower rates of false positives and false negatives. The ultrasound parameters of the test are fetal tone, fetal movement, fetal breathing and amniotic fluid volume. Table 11.13 shows the parameters of each observation. An NST, which is not an ultrasonic measurement, is also performed. Two points are given if the observation is present and zero points are given if it is absent. A BPP test score of at least 8 out of 10 is considered as reassuring. A score of 6 or 7 out of 10 is equivocal and must be repeated within 24 hours. A score of 4 or less out of 10 is a positive test and strongly indicates fetal compromise. If the BPP falls below 4, the patient should be urgently prepared for delivery.

Initially, the performance of a BPP score included analysis of all five components in every pregnancy. Of the various parameters recorded by biophysical profile, the first one to get affected is NST, followed by fetal breathing, fetal movements and lastly the fetal tone. First sign of acidosis (cord arterial pH < 7.2) was thought to result in an abnormal NST and absent fetal breathing. Advanced or chronic acidosis was thought to compromise fetal tone and movement. Assessment of amniotic fluid volume helps in quick evaluation of long-term uteroplacental function as in the late second and all through the third trimester, amniotic fluid is essentially fetal urine. With uteroplacental dysfunction, redistribution of blood flow takes place. This leads to decreased renal perfusion and thus to oligohydramnios. Manning described the modified BPP in 1990, combining an NST, amniotic fluid volume and fetal breathing. It was less cumbersome than the original BPP and its results were just as predictive.

However the recent approach is to carry out only the ultrasound components of the test in the beginning. If there appears to be an abnormality in either of the ultrasound component, the NST is performed. If all the ultrasound components are within normal limits, there is no need to perform a NST. This approach is based on the fact that the ultrasound fluid index is the indicator of longterm uteroplacental function, while the NST is the shortterm indicator of fetal acid-base status. Weekly biophysical profile is recommended for evaluation of fetal wellbeing in the pregnancies complicated with IUGR.

Components of BPP (table 11.13 and figure 11.15)

The various components of BPP are as follows:

Non-stress test: See table 11.12.

Fetal breathing movements: Normal fetal breathing movements are defined as presence of one or more episodes of rhythmic fetal breathing movements of 30 seconds or more within a period of 30 minutes.

Fetal movement: Normal fetal movement is defined as three or more discrete body or limb movements within a period of 30 minutes.

Fetal tone: Normal fetal tone is defined as one or more episodes of extension of a fetal extremity with return to flexion, or opening or closing of a hand.

Determination of the amniotic fluid volume: A single vertical pocket of amniotic fluid exceeding 2 cm is considered as an indicator of adequate amniotic fluid volume.

A total score of 8 or 10 is considered as normal, a score of 6 is considered equivocal and a score of 4 or less is abnormal. Regardless of the composite score, in the presence of oligohydramnios (largest vertical pocket of amniotic fluid volume

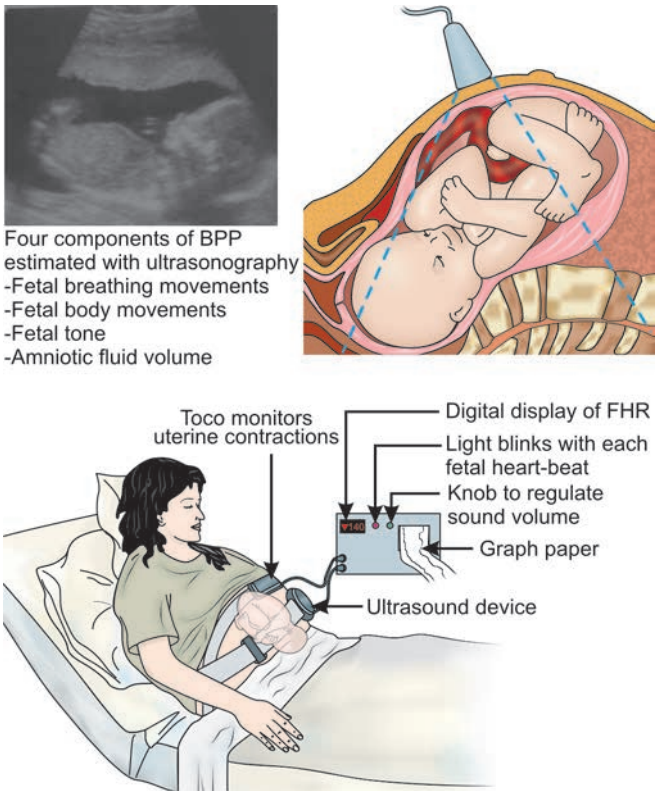


Fig. 11.15: Components of biophysical profile

< 2 cm), further evaluation (Doppler ultrasound examination) is warranted in cases of IUGR.

Modified Biophysical Profile

In the late second or third trimester fetus, amniotic fluid volume reflects fetal urine production. Placental dysfunction may result in diminished fetal renal perfusion, leading to oligohydramnios. Amniotic fluid volume assessment can therefore be used to evaluate longterm uteroplacental function. This observation encouraged the development of "modified BPP" as a primary method for antepartum fetal surveillance. The modified BPP combines NST (with the option of acoustic stimulation in case of non-reactive NST after 20 minutes) with the amniotic fluid index (AFI). While NST is a short-term indicator of fetal acid base status, the amniotic fluid index (AFI) serves as an indicator of long-term placental function. An AFI greater than 5 cm generally is considered to represent an adequate volume of amniotic fluid. Thus, the modified BPP is considered normal if the NST is reactive and the AFI is more than 5 and abnormal if either the NST is non-reactive or the AFI is 5 or less. If the results of a modified BPP indicate a possible abnormality, then the full BPP is performed.

Rx Treatment/Obstetric Management

Antenatal Period

Identifying the underlying cause for IUGR

If FGR is diagnosed, one of the most important tasks of the clinician is to identify and treat the underlying cause and observation of adequate fetal surveillance. Various techniques for fetal surveillance have already been discussed before. Some of the steps which can be taken to identify the underlying cause for IUGR are described below:

- Screening for congenital infections may be important in cases of symmetrical IUGR.
- Preeclampsia needs to be excluded as the cause for IUGR. This requires regular maternal blood pressure monitoring and urine analysis (for ruling out proteinuria).
- Fetal karyotyping for chromosomal defects.
- Maternal assessment for the presence of nutritional deficiency.
- Since smoking and abuse of alcohol or other substances of abuse is commonly associated with IUGR, it is important to rule out these causes of IUGR. Many women may not be open about their smoking or drinking habits. The clinician may need to maintain a lot of tact to elicit this history.

Precautions to be taken in the antenatal period

The women must be advised to take the following precautions in the antenatal period:

- The women must be advised to take rest in the left lateral position for a period of at least 10 hours every day (8 hours in the night and two hours in the afternoon). Presently there is no evidence regarding the effect of bed rest in improving perinatal outcome in cases with IUGR.
- If the gestational age is 28 weeks or more, the patient must be instructed to count her fetal movements daily and maintain it in form of a chart (figure 11.16). If she is able to perceive at least ten or more movements with in two hours, the test can be considered as normal. She should continue with DFMC. Other tests for ensuring fetal wellbeing can be conducted at regular intervals (flow chart 11.1). In case she perceives less than six fetal movements within two hours, she should be advised to immediately consult her doctor.
- The patient should be advised to quit smoking, drinking alcohol or taking drugs of abuse.
- Smoking cessation programmes, particularly those using behavioral strategies can be effective for preventing IUGR in women who smoke.

1	start time:						16	start time:					
	stop time:							stop time:					
2	start time:						17	start time:					
	stop time:							stop time:					
3	start time:						18	start time:					
	stop time:							stop time:					
4	start time:						19	start time:					
	stop time:							stop time:					
5	start time:						20	start time:					
	stop time:							stop time:					
6	start time:						21	start time:					
	stop time:							stop time:					
7	start time:						22	start time:					
	stop time:							stop time:					
8	start time:						23	start time:					
	stop time:							stop time:					
9	start time:						24	start time:					
	stop time:							stop time:					
10	start time:						25	start time:					
	stop time:							stop time:					
11	start time:						26	start time:					
	stop time:							stop time:					
12	start time:						27	start time:					
	stop time:							stop time:					
13	start time:						28	start time:					
	stop time:							stop time:					
14	start time:						29	start time:					
	stop time:							stop time:					
15	start time:						30	start time:					
	stop time:							stop time:					

Fig. 11.16: Daily fetal movements count chart

- Women must be counseled to abstain from alcohol and other drugs of abuse. The women may be enrolled in deaddiction programmes if they are unable to quit their habit of drug addiction.
- If under-nutrition is suspected as a cause of IUGR, the patient should be given nutritional supplements.
- Therapies under research (prescription of intermittent oxygen therapy, low dose aspirin, dipyridamole, glutamine, amino acid infusion, infusion of atrial natriuretic peptide, betamimetics, calcium channel blockers, etc) have not shown any significant effects on perinatal outcome. Despite the lack of good quality evidence, low dose aspirin therapy (colsprin) in the dose of 1–2 mg/kg body weight is commonly prescribed to the women in whom IUGR is suspected.

Intrapartum Period

Since the growth restricted fetus is especially prone to develop asphyxia, continuous fetal monitoring using external or internal cardiotocographic examination needs to be done in the intrapartum period. If at any time, the fetal heart rate appears to be non-reassuring (table 11.14), emergency cesarean may be required. However elective cesarean section is not justified for delivery of all IUGR fetuses. Other indications

Table 11.14: Interpretation of fetal heart rate features

	Baseline heart rate	*Variability*	*Deceleration*	*Acceleration*
Reassuring	100–160	≥ 5	None	Present
Non-reassuring	100–109 161–180	< 5 or ≥40 for < 90 minutes	Early deceleration, variable decelerations, single prolonged decelerations upto 3 minutes	The absence of accelerations with an otherwise normal CTG is of uncertain significance
Abnormal	<100, >180 Sinusoidal pattern for ≥ 10 minutes	< 5 for ≥ 90 minutes	Atypical variable decelerations, late decelerations, single prolonged decelerations greater than 3 minutes	

Table 11.15: Indications for emergency cesarean section in growth retarded babies

Intrauterine growth restriction along with reduced fetal movements
Presence of an obstetric complication (placenta previa, abruption placenta, etc)
Non-reassuring fetal heart sounds
Meconium stained liquor
IUGR fetus with breech presentation
Absent or reversed umbilical artery blood flow on Doppler examination
Biophysical profile becomes less than four

for emergency cesarean section in growth retarded babies are enumerated in table 11.15. Precautions which need to be taken at the time of labor during the intrapartum period include the following:

- Delivery must be carried out in the unit with optimal neonatal expertise and facilities.
- The patient should be lying on bed as far as possible in order to prevent premature rupture of membranes.
- Continuous electronic fetal monitoring either external (if membranes are intact) or internal (if membranes have ruptured) needs to be done.
- Administration of strong analgesic or sedatives to the mother must be avoided due to the risk of transmission of the drugs to the fetus.
- Amnioinfusion may be required in cases with low amniotic fluid index and meconium stained liquor.
- A skilled pediatrician, who is trained in neonatal resuscitation techniques must be present at the time of delivery.
- Administration of intramuscular corticosteroids is required in case the delivery takes place between 24–36 weeks of gestation. The dosage regimen of corticosteroids is as follows:
  - 2 doses of 12 mg each of betamethasone IM at intervals of 24 hours.
  - 4 doses of 6 mg each of dexamethasone IM at the intervals of 12 hours.

Timing of Delivery

There is wide variation in practice in the timing of delivery of growth restricted fetuses. The most important goal of management is to deliver the most mature fetus in the least compromised position and at the same time causing minimum harm to the mother (figure 11.17). A randomized controlled trial was conducted by the GRIT group (Growth Restriction Investigation Trial) in order to evaluate whether it was safe to deliver compromized fetuses between 24–36 weeks of gestation or to delay delivery until there was no clinical doubt left that the delivery was necessary or until fetal maturity was reached. In this trial, 548 pregnant women between 24 and 36 weeks of gestation, having fetal compromise, from 69 hospitals across 13 European countries were involved. In all cases considered in the study, it was uncertain whether immediate delivery was indicated. Though a small increase in the rates of fetal death was observed with delayed delivery of the fetus and a small increase in the rate of neonatal deaths if early delivery was chosen, the trial was unable to inform the obstetrician regarding the optimal time of delivery. This study failed to definitively identify the optimal intervention required in high-risk pregnancies remote from term.

Presently the RCOG (2002) recommends that the clinician needs to individualize each patient and decide the time for delivery by weighing the risk of fetal demise due to delayed intervention against the risk of longterm disabilities resulting from preterm delivery due to early intervention. The two main parameters for deciding the optimal time of delivery include results on various fetal surveillance techniques and gestational age. Also, the patient needs to be counseled regarding the potential risks associated with the two strategies. Preterm delivery could be associated with future disabilities, intraventricular hemorrhage, sepsis and retinopathy of prematurity, etc (The EPICURE study Group, 2000). Delayed delivery on the other hand may be associated with ischemic brain injury, periventricular leukomalacia, intraventricular hemorrhage and intrauterine death.

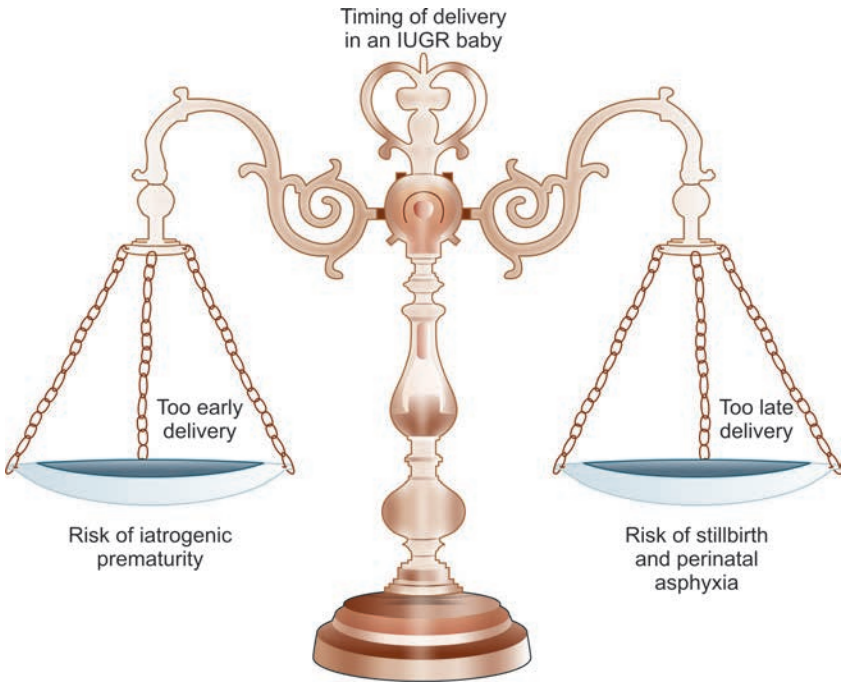


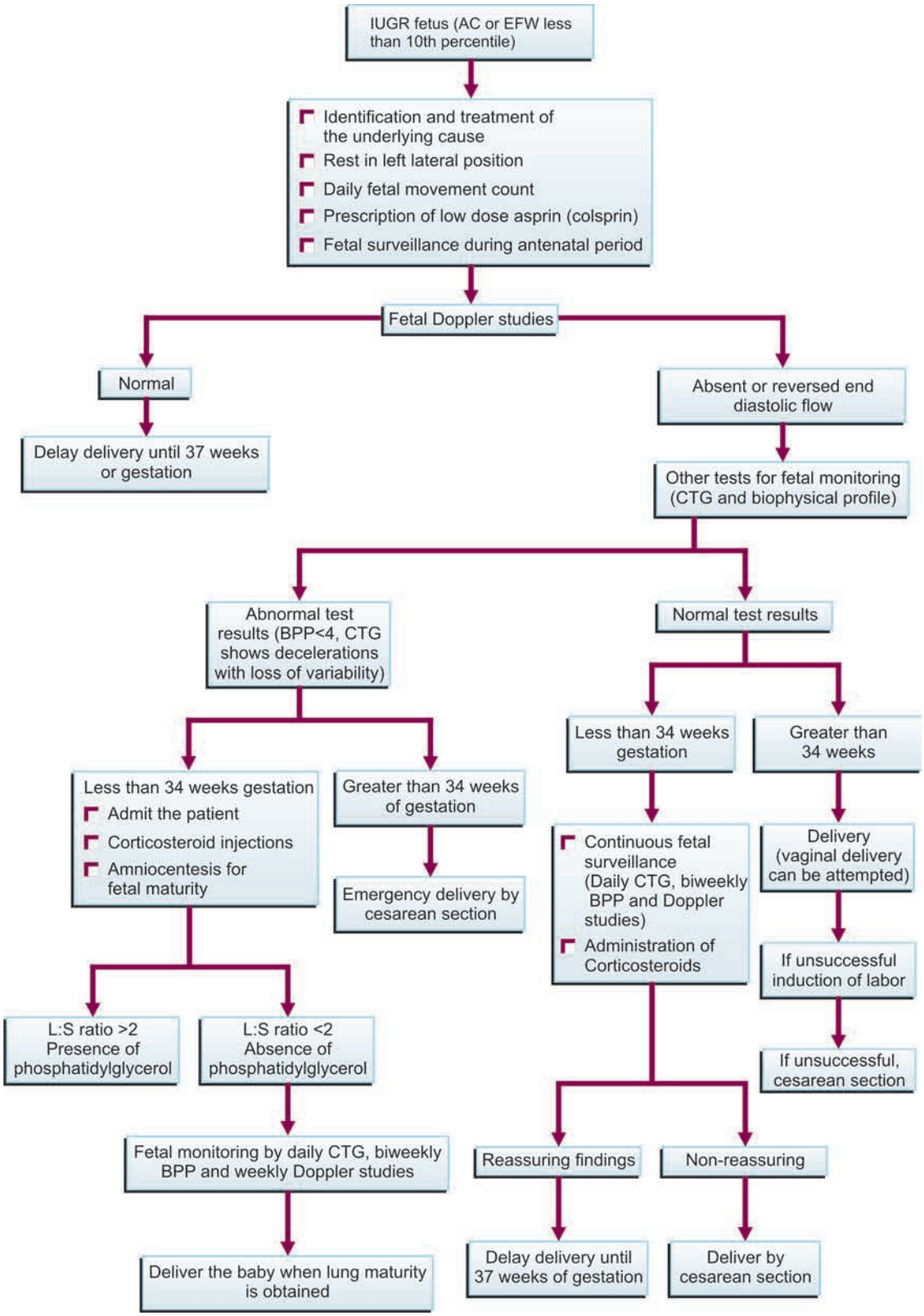
Fig. 11.17: Deciding the time of delivery in IUGR babies

The management plan for patients with IUGR is presented in flow chart 11.3. The various tests used for fetal surveillance vary from one center to the other. However, the main method of fetal surveillance which helps in determining the decision for delivery is Doppler analysis of umbilical blood vessels at most tertiary centers. The other methods used for fetal surveillance include NST and CTG. Doppler sonography in combination with the other methods of antepartum surveillance such as antepartum cardiotocogram and biophysical profile score should be used in everyday practice for fetal monitoring, especially in cases of high-risk pregnancy (IUGR, preeclampsia, etc). Umbilical artery Doppler velocimetry is a highly sensitive and specific, noninvasive, simple, outpatient procedure for detection of chronic fetal hypoxia and acidosis in cases of IUGR. This technique allows fetal umbilical bloodflow patterns to be observed from as early as twelve weeks of gestation.

When end diastolic flow is present on Doppler analysis of umbilical vessels, delivery must be delayed until at least 37 weeks, provided other surveillance findings are normal. Absent end diastolic blood flow in the umbilical artery is associated with increasing hindrance of flow towards the placenta along with decrease in the number of functioning tertiary villi. This finding has been found to be associated with significant increase in the rate of fetal acidosis, fetal compromise and an increased rate of perinatal mortality and morbidity.

If the umbilical artery end diastolic flow is reduced, absent, or reversed, this is taken as an indication for enhanced fetal surveillance or delivery. If preterm delivery is required, improved lung maturity should be achieved through maternal administration of glucocorticoids. Fetuses with reversed end diastolic umbilical flow should be provided intensive fetal surveillance until the time of delivery. In case, abnormal findings on Doppler ultrasound are recognized along with abnormalities in other antenatal measures of fetal surveillance (CTG, BPP, CST, etc), urgent delivery may be required. If gestation is over 34 weeks, even if other results are normal delivery may be considered. The major dilemma for the clinician occurs when the fetal gestation is less than 34 weeks and the results of various antepartum surveillance tests are abnormal. In these cases the tests of fetal lung maturity (L:S ratio; presence of phosphatidylglycerol, etc) must be done. If these tests indicate pulmonary maturity, the fetus can be delivered. Until the fetal lung maturity is achieved, intramuscular corticosteroids must be administered to the mother. Also while awaiting fetal lung maturity; fetal surveillance must be done using daily CTG, biweekly BPP and weekly Doppler studies. The frequency of fetal testing can be changed depending on the severity of fetal compromise.

Flow chart 11.3: Management plan for IUGR fetuses



Complications

FETAL COMPLICATIONS

Antepartum Complications

These may include the following:
- Fetal hypoxia and acidosis
- Stillbirth
- Oligohydramnios

Intrapartum Complications

Neontal asphyxia and acidosis is especially common in these fetuses. Some of the neonatal complications associated with this include the following:
- *Respiratory distress syndrome:* The pulmonary system of the growth restricted babies is often immature at birth resulting in the development of respiratory distress syndrome.
- *Meconium aspiration syndrome:* Aspiration of meconium is a significant cause of mortality and morbidity in a FGR baby.
- *Persistent fetal circulation:* This condition is characterized by severe pulmonary vasoconstriction and persistent blood flow through the ductus venosus even after birth. This is responsible for producing hypoxia, hypercarbia and signs of right-to-left shunting.
- *Intraventricular bleeding:* This condition is produced as a result of bleeding inside or around the cerebral ventricles in a growth restricted baby.
- *Neonatal encephalopathy:* This condition can occur as a consequence of severe birth asphyxia and can produce a constellation of neurological signs and symptoms (seizures, twitching, irritability, apnea etc).

NEONATAL COMPLICATIONS

The newborn child typically shows an old man like appearance. There are signs of soft tissue wasting including reduced amount of subcutaneous fat and lossened, thin skin. The muscle mass of arms, buttocks and thighs is greatly reduced. The abdomen is scaphoid and the ribs are protrubent. The head circumference may appear to be obviously larger than the abdominal circumference. Some of the metabolic complications which can be frequently encountered in these babies include the following:
- *Hypoglycemia*: Neonatal hypoglycemia can be defined as blood glucose levels of less than 30 mg/dl. It can be associated with symptoms like jitteriness, twitching, apnea, etc. Early feeding of the newborn baby can help prevent hypoglycemia.
- *Hypoinsulinemia*
- *Hypertriglyceridemia*
- *Hypocalcemia:* Hypocalcemia may be common in the first few days of life due to relative hypoparathyroidism
- *Polycythemia*
- *Meconium aspiration*
- *Hyperphosphatemia*
- *Birth asphyxia*
- *Hypothermia*: The growth restricted fetus has a poor temperature control due to which there is an increased tendency to develop hypothermia.
- *Hyperbilirubinemia*
- *Sepsis*
- *Necrotizing enterocolitis*
- *Hyperviscosity syndrome*: It is mainly associated with polycythemia and increased hematocrit levels above 65%.

Long Term Sequel of IUGR

Postnatal growth: In some cases catchup growth may occur in first six months of life.
Cerebral palsy
Adult disease: These children are supposed to be at an increased risk of developing disorders such as obesity, diabetes mellitus, hypertension, cardiovascular disease, etc later in life.

Important Questions and Answers

Q.1. What do the S-F height measurements in the above case study indicate?

Ans. The measurement of symphysis fundal height (SFH) is associated with limited diagnostic accuracy in predicting a baby which would be affected by IUGR. Since in the above mentioned case study, the fetal growth was found to be plateauing on the S-F growth curves, IUGR was suspected. An ultrasound examination was done in order to rule out IUGR.

Q.2. What can you say about fetal condition at the time of presentation?

Ans. At the time of presentation the fetus appeared to be healthy as the mother perceived normal fetal movements. Doppler analysis of fetal umbilical vessels was performed at 34 weeks gestation (the present visit). The end diastolic blood flow in umbilical arteries was normal and S/D ratio was less than 3. Thus the fetus does not appear to be in a compromised state. The possibility of fetal distress or fetal death over the next few days (at least a week) appears to be unlikely.

Q.3. What are the probable causes of the poor fetal growth in the above mentioned case?

Ans. In this case, the most likely cause for poor fetal growth appear to be hard physical labor and smoking. Given the patient's poor socio-economic history, it was important to rule out undernutrition as the cause of IUGR in this case. Therefore, a detailed nutritional history was taken and she was seen to be taking an adequate diet. Also preeclampsia and anemia were excluded out as the likely causes for IUGR. Her hemoglobin levels, blood pressure readings and urine analysis (for proteinuria) was found to be within normal limits during all the previous antenatal visits.

Q.4. What would be your management in this case? What can be done to improve fetal growth?

Ans. The patient was counseled to quit smoking, to avoid physical exertion and to take atleast 10 hours of rest every day (8 hours in the night and two hours in the afternoon). Arrangements should be made, if possible, for the patient to stop working. She should continue taking a good diet containing adequate amounts of calories and proteins. She was advised to continue taking iron and folic acid supplements as she had been previously taking during her pregnancy.

Q.5. How should this patient be managed?

Ans. She was advised to come for regular antenatal visits at weekly intervals. She was given a DFMC chart and instructed to record her fetal movements everyday on that chart. She was supposed to bring the chart with her at time of each antenatal visit. She was advised to report immediately for check-up, if at any time she perceived reduced fetal movements. Other tests for fetal surveillance in this case include biweekly NST, weekly BPP, monthly fetal ultrasound biometry and Doppler analysis at every 2–3 weeks. Even if no abnormality is detected, there is little point in continuing pregnancy beyond 37 completed weeks of gestation. Labor must be induced at 37 completed weeks of gestation.

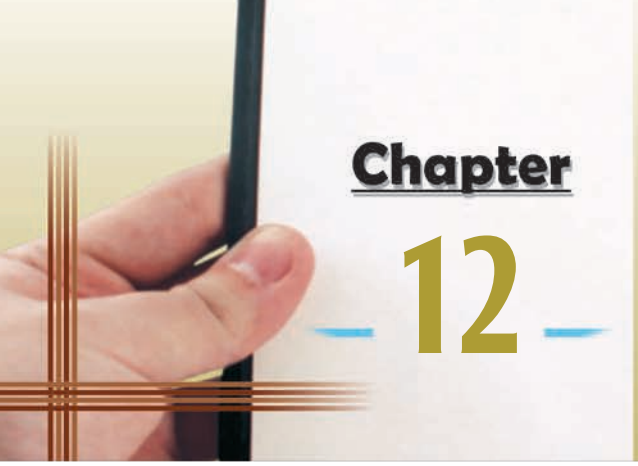
Bibliography

1. GRIT Study Group. A randomised trial of timed delivery for the compromised preterm fetus: Short term outcomes and Bayesian interpretation. BJOG. 2003;110(1):27-32.
2. Hadlock FP, Harris RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body and femur measurements - a prospective study. Am J Obstet Gynecol. 1985;151:333-37.
3. Royal College of Obstericians and Gynecologists. (2002). The investigation and management of the small-for-gestational-age fetus. Guideline No. 31
4. The EPICURE study Group. Neurologic and developmental disability after extremely preterm birth. NJEM. 2000;343(6): 378-384.

Section 3

Medical Disorders Related to Pregnancy

- Preeclampsia
- Gestational Diabetes
- Anemia in Pregnancy
- Heart Disease during Pregnancy



Chapter

12

Preeclampsia

Case Study

A 34-year-old primi gravida patient with 39 completed weeks of gestation presented with the complaints of headache since last 10 days. Her blood pressure was 144/95 mm of Hg and dipstick examination revealed a 1+ proteinuria. She had never been diagnosed to be suffering from hypertension previous to the present pregnancy.

Introduction

Increased blood pressure is a problem commonly encountered among pregnant women. Management of high blood pressure is of utmost importance during pregnancy because high blood pressure if remaining uncontrolled can result in the development of significant maternal and fetal morbidity and mortality. High blood pressure could occur as a syndrome specific to pregnancy (preeclampsia/gestational hypertension) or as a manifestation of chronic hypertension present before pregnancy. Blood pressure normally falls in the first and second trimesters of pregnancy; therefore women with high blood pressure before the 20th week of gestation are assumed to have pre-existing hypertension. According to the Working group report on high blood pressure in pregnancy (2000), the presence of high blood pressure in pregnancy can be classified into three types: Preeclampsia, gestational hypertension and chronic hypertension.

Preeclampsia

Preeclampsia can be considered as a potentially serious disorder, which is characterized by high blood pressure and proteinuria. It usually develops after the 20th week of pregnancy and goes away after the delivery (table 12.1 and figure 12.1).

Gestational Hypertension

This form of high blood pressure develops after the 20th week of pregnancy and goes away after the delivery. Affected women do not have proteinuria (table 12.2). However, some women with gestational hypertension may develop preeclampsia later during pregnancy. Gestational hypertension is often also known as transient hypertension. Sometimes, women with gestational hypertension, besides showing absence of the proteinuria may develop other signs of preeclampsia including symptoms like headache, epigastric pain, etc. Worsening hypertension even in absence of proteinuria may present significant risk to both the mother and the fetus, especially in the second half of the pregnancy.

Chronic Hypertension

This can be defined as high blood pressure that is diagnosed before pregnancy or before the 20th week of pregnancy in absence of gestational trophoblastic disease (table 12.3). The condition does not return to normal following delivery.

However, in clinical practice considerable overlap is observed to occur between these three entities. Sometimes, preeclampsia may be superimposed on chronic hypertension.

Table 12.1: Characteristics of preeclampsia

Appearance of high BP (>140/90 mm Hg) for the first time during pregnancy after 20 weeks of gestation.
Presence of Proteinuria (> 300 mg/L or >1 + on the dipstick).
BP returns to normal within 12 weeks of postpartum period.

Table 12.2: Characteristics of gestational hypertension

Appearance of high BP (>140/90 mm Hg) for the first time during pregnancy after 20 weeks of gestation.
No proteinuria.
BP returns to normal within 12 weeks of postpartum period.

Table 12.3: Characteristics of chronic hypertension

Appearance of high BP (>140/90 mm Hg) before 20 weeks of gestation or even before pregnancy
No proteinuria
BP does not return to normal within 12 weeks of postpartum period.

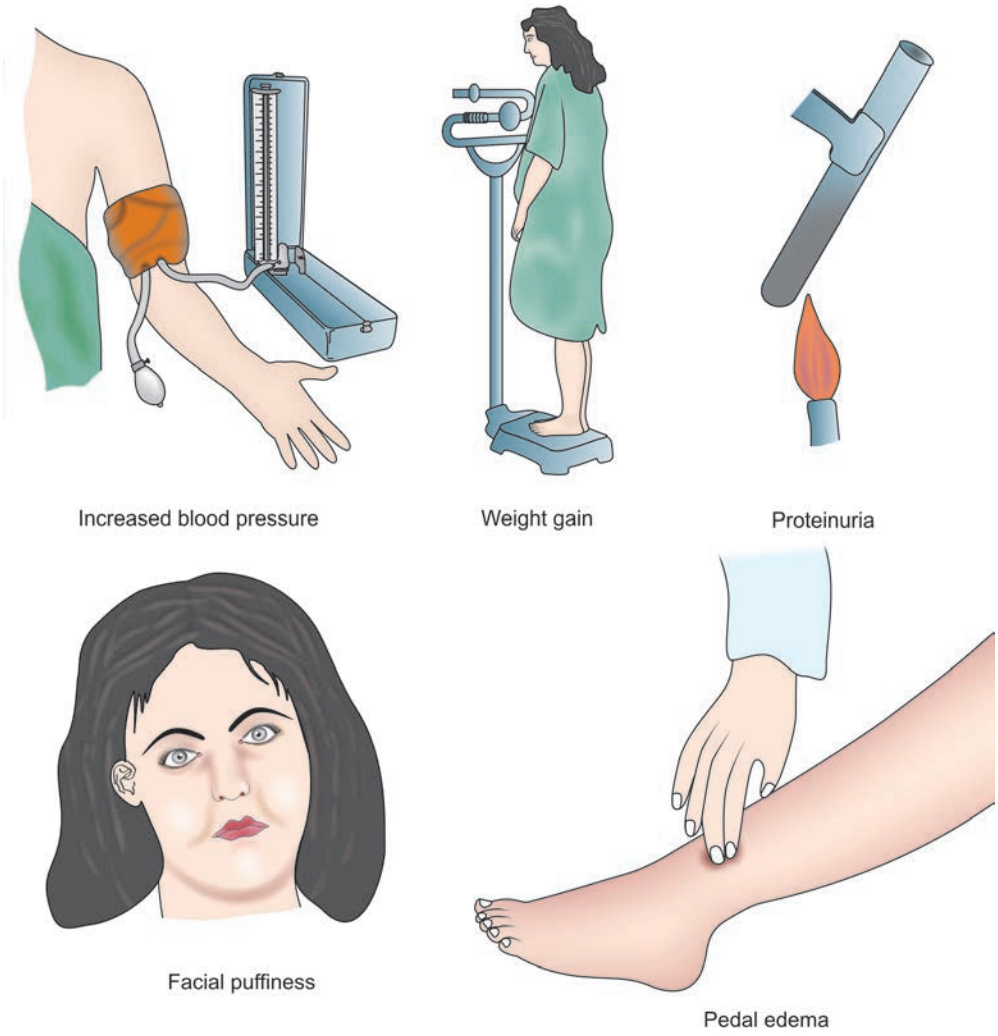


Fig. 12.1: Characteristic features of preeclampsia

Table 12.4: Indicators of preeclampsia superimposed upon chronic hypertension

New-onset proteinuria in women with presence of hypertension and no proteinuria early in pregnancy (<20 weeks).
A sudden increase in blood pressure in a woman whose hypertension has previously been well controlled.
Thrombocytopenia (platelet count <100,000 cells/mm^3).
An increase in ALT or AST to abnormal levels.

Preeclampsia Superimposed Upon Chronic Hypertension

There is ample evidence that preeclampsia may occur in women already suffering from chronic hypertension prior to pregnancy. This condition holds importance because the prognosis for mother and fetus is much worse than with either condition alone. The obstetrician's task is to distinguish superimposed preeclampsia from worsening chronic hypertension. The presence of following findings (table 12.4) is likely to indicate the diagnosis of superimposed preeclampsia.

Clinical course of preeclampsia can vary from one patient to the other. Preeclampsia always presents potential danger to mother and baby. Sometimes, mild preeclampsia (especially if remains untreated) can progress into severe preeclampsia. Some of the indicators of severe hypertensive disorders during pregnancy are listed in table 12.5. Severe preeclampsia may ultimately result in development of eclampsia, which can be defined as the occurrence of seizures, which cannot be attributed to other causes, in a woman with preeclampsia. Preeclampsia-eclampsia can be considered as a spectrum of abnormality associated with preeclampsia at one end and the most severe manifestation of preeclampsia, i.e. eclampsia at the other.

Table 12.5: Indicators of severe preeclampsia during pregnancy

Diastolic BP ≥ 110 mm Hg and/or systolic BP ≥ 160 mm Hg
Proteinuria 2 + or more on the dipstick
Presence of symptoms like headache, visual disturbances, oliguria (urine volume ≤ 500ml/ 24 hours), convulsions, etc.
Investigations show presence of thrombocytopenia (platelet count <1,00,000 cells/mm^3); elevated serum creatinine levels (>1.2 mg/dL, unless known to be previously elevated); serum uric acid of more than 4.5 mg %; elevated liver enzymes [alanine aminotransferase (ALT) or aspartate aminotransferase (AST)]; evidence of microangiopathic hemolytic anemia; fetal IUGR, etc.

History

RISK FACTORS

The various factors which are associated with increased risk of preeclampsia and need to be elicited on history include the following:

- Obesity: A prepregnancy BMI of ≥35 almost quadruples the risk of developing preeclampsia
- Diabetes
- Renal disease
- Extremes of age (under 18 or over 40 years)
- History of having preeclampsia in a previous pregnancy, particularly if its onset was before the third trimester. Women with severe preeclampsia in their previous pregnancies are at an increased risk of recurrence during their next pregnancies. However, the disorder is generally less severe and manifests 2 to 3 weeks later than in the first pregnancy.
- Certain autoimmune conditions, including antiphospholipid antibody syndrome are associated with an increased risk for preeclampsia (see chapter 9 for details).
- Previous history of chronic hypertension
- African-American or Hispanic ethnicity
- Family history of preeclampsia: Having a sister, mother or daughter who has had preeclampsia or high blood pressure in pregnancy increases the chances of the woman to develop preeclampsia during her present pregnancy.
- A change of male partner: Having a male partner whose previous partner had preeclampsia may increase the woman's risk of developing preeclampsia during her future pregnancies. This suggests that the father's genetic material, passed onto the fetus and its placenta, may play a role, thereby suggesting the role of genetic factors in the etiopathogenesis of preeclampsia.
- Nulliparity.
- Multifetal gestation.
- Although smoking is associated with an increased risk of various adverse pregnancy related outcomes, ironically it is associated with a reduced risk of hypertension during pregnancy.

SYMPTOMS

Presenting symptoms of preeclampsia which need to be elicited while taking the history include the following:

Edema of the hands and face: Since edema is a universal finding in pregnancy, it is not considered as a criterion for diagnosing preeclampsia. The best way to ask the patient about development of edema is to enquire if she has been experiencing tightening of rings on the fingers of her hands or facial puffiness and swelling of feet on getting up from the bed. Some swelling of the feet and ankles is considered normal with pregnancy. Nondependent edema such as facial or hand swelling (the patient's ring may no longer fit her finger) is more specific than dependent edema. Vulvar edema or the presence of edema over ankles in the morning on getting up from the bed is also pathological.

Virtually, any organ system in the body may be affected due to severe preeclampsia. Some of the symptoms which may be sometimes observed, especially in association with severe disease may include the following:

Headache: Dull, throbbing headaches, often described as migraine-like, which would just not go away.

Visual problems: Vision changes include temporary loss of vision, sensations of flashing lights, sensitivity to light auras and blurry vision or spots. The problems related to vision are usually related to the spasm of retinal vessels.

Epigastric or right upper quadrant abdominal pain: Epigastric or the right upper quadrant pain is usually indicative of hepatocellular necrosis, ischemia, edema, etc, all of which are responsible for stretching the Glisson's capsule of the liver. This pain is usually associated with elevation in liver enzymes like AST and ALT (reflecting hepatic ischemia or derangement). There may be associated nausea and vomiting as well. The liver may swell as a result of local edema secondary to the presence of inflammatory infiltrates and obstruction to the blood flow in the sinusoids. Hemorrhage can occur beneath the liver capsule and may be so extensive as to cause rupture of the capsule into the peritoneal cavity. If a hematoma or hemorrhage is suspected, the liver should be examined by ultrasonography. Liver involvement could be a part of HELLP syndrome, which would be discussed later. Substantial hepatic dysfunction can also result in development of coagulation abnormalities.

Shortness of breath or dyspnea: This could be reflective of pulmonary edema or acute respiratory distress syndrome.

Oliguria: Reduced urinary output of less than 300–400 ml in 24 hours could be indicative of reduced plasma volume or ischemic acute tubular necrosis.

Reduced fetal movements: The patient may give a history of experiencing reduced fetal movements especially in association with IUGR and oligohydramnios.

General Physical Examination

Since the diagnostic features of preeclampsia include high blood pressure and proteinuria, both of these would be described first.

Increased Blood Pressure

Presence of increased BP (>140/90 mm Hg) for the first time during pregnancy, after 20 weeks of gestation, is one of the diagnostic features of preeclampsia.

Method of taking blood pressure

When taking blood pressure, the woman should lie on her right side with a 30° lateral tilt or she can be made to sit on a chair. The blood pressure can also be taken while the woman is lying on the bed. The patient should be advised not to lie on her back while taking her blood pressure as this can give a false low reading due to development of supine hypotension syndrome. The right upper arm must be used and the arm must be taken out of the sleeve. The blood pressure should be taken after 5 minutes of rest. The blood pressure cuff should be of the appropriate size (12 cm wide and 35 cm in length) and should be placed at the level of the heart. If the arm is very fat, a wider cuff must be used to obtain a correct reading (figure 12.2). A BP cuff that encompasses about 80% of arm length and 40% of the width of arm circumference must be used. The cuff must be applied firmly around the arm, not allowing more than one finger between the cuff and the patient's arm. The woman should not use tobacco or caffeine within 30 minutes of the measurement.

RCOG recommends that mercury sphygmomanometers should be used at least to establish baseline blood pressure as a reference, since this reading is supposed to be most accurate.

Measurement of blood pressure reading

Korotkoff phase 5 (disappearance of heart sounds and not simply muffling of sounds) is considered as the appropriate measurement of diastolic blood pressure. On the other hand, the systolic blood pressure is taken at Korotkoff phase 1 (the first sound heard after the cuff pressure is released).

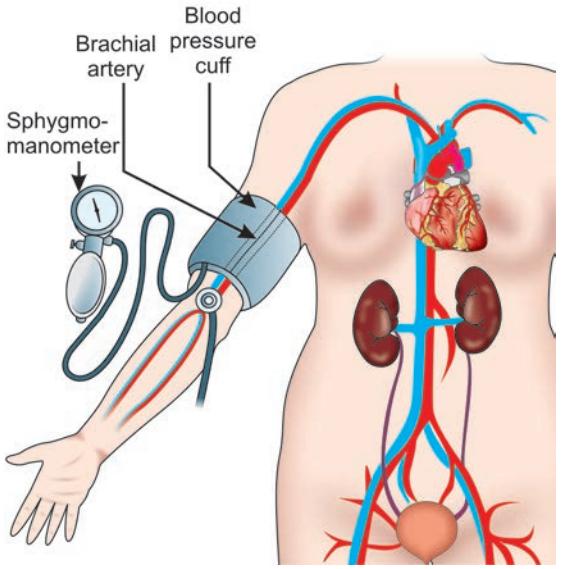


Fig. 12.2: Method of accurately recording the blood pressure

It is also recommended that elevation of gestational blood pressure must be defined on the basis of at least two readings of high blood pressure obtained at least 6 hours apart within a span of 1 week.

Measurement of Proteinuria

The usual screening test for proteinuria is visual assessment of dipstick or a regent strip (figures 12.3A and B). Dipstick is a device in which a strip of paper impregnated with a reagent (used for testing proteins) is dipped into urine in order to measure the quantity of proteins present in the urine. The reagent strips for measuring proteins in the urine have the markings for "trace", 1+, 2+, etc. A reading of trace protein is relatively common and is usually not a cause for concern. A two plus dipstick measurement can be taken as evidence of proteinuria. However, this must be confirmed by a 24-hour urine collection for protein estimation.

Though visual dipstick assessment is associated with both false positive and false negative test results, this test is most commonly used for estimation of proteinuria. The approximate equivalence of the dipstick result and amount of proteins in the urine is shown in table 12.6, with the results

Table 12.6: Grading of proteinuria in the urine

Dipstick result	*Amount of proteins in the urine*
Trace	10 mg daily
1+	0.3 g/L
2+	1 g/L
3+	3 g/L
4+	10g/L

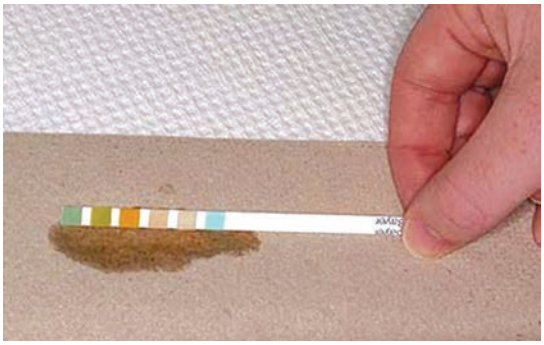


Fig. 12.3A: Method of measuring proteinuria using dipstick

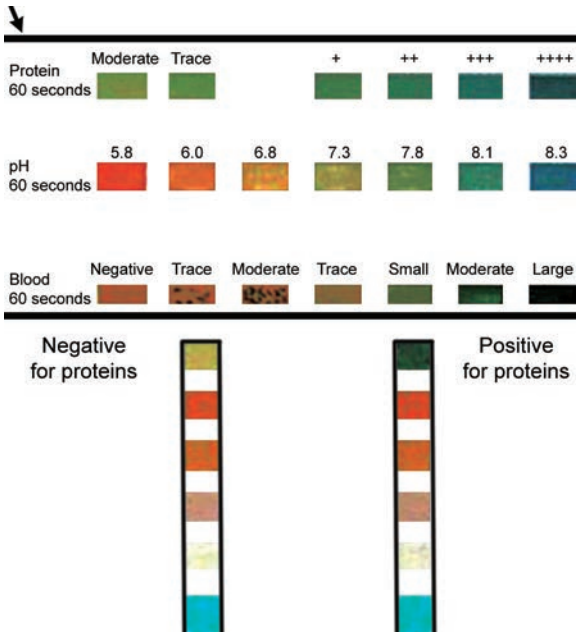


Fig. 12.3B: Measurement of proteinuria through visual assessment of dipstick

of 1+ = 0.3 g/L; 2+ = 1 g/L; 3+ = 3 g/L; and 4+ = 10g/L. Proteinurea is defined as significant if the excretion of proteins exceeds 300 mg/ 24 hours or there is persistent presence of the protein (30 mg/dL or 1 + distick) in random urine sample in absence of any evidence of urinary tract infection. In view of the high false positive rates with visual dipsticks assessment, a 24-hour urine collection for protein estimation or a timed collection corrected for creatinine excretion is sometimes recommended by the obstetrician to confirm significant proteinuria.

Proteinuria is generally associated with the classic pathological finding of glomeruloendotheliosis, which is not permanent but recovers after delivery. Increased urinary excretion of proteins and an increase in capillary endothelial permeability leads to an increase in extracellular volume and a reduction in intravascular volume. These changes may be responsible for the development of tissue edema in cases of preeclampsia.

Procedure for determining proteinuria

- A fresh specimen of urine must be collected. Reagent strips may give false positive result if a very concentrated or very dilute specimen of urine is used. The first urine specimen passed in the morning may be concentrated and, may give a falsely high reading. Therefore, first morning specimen must preferably not be used.
- Following the removal of reagent strip from the bottle, the cap must be replaced.
- The reagent strip must be dipped into the urine in such a way that the entire test area is completely covered, following which the strip should be immediately removed from the urine sample.
- For the accurate color changes to take place, the clinician must wait for at least 60 seconds and let the tested area get air-dried.
- The reagent strip must be held horizontally and the color must be compared with that of the color blocks on the side of the bottle. The darker the color of the reagent strip, the greater is the amount of proteinuria.

Other Features on GPE Suggestive of Preeclampsia

The other features on general physical examinations which are suggestive of severe preeclampsia are described below:

Edema of the hands and face: As previously mentioned, pedal edema is no longer considered as the diagnostic criteria of preeclampsia as it can be present in the normal pregnancy as well. Nondependent edema such as facial edema or hand swelling (edema in the fingers) is more specific than dependent edema. The obstetrician must specifically look for vulvar edema, facial edema and edema over the fingers.

Weight gain: The weight of a patient with suspected or diagnosed preeclampsia must be taken at each antenatal visit because preeclampsia is associated with a significant weight gain. Weight gain of more than 2 pounds per week or 6 pounds in a month or a sudden weight gain over 1 – 2 days can be considered as significant.

Petechiae: Presence of petechiae may reflect a bleeding tendency which may serve as an indicator of HELLP syndrome. Platelet count may fall below 100×10^6/L.

Ankle clonus: Presence of ankle clonus is indicative of excessive neuromuscular irritability, which can progress to seizures (eclampsia).

Knee jerks: Evaluation of knee jerks is especially important in patients receiving magnesium sulfate as reduced or

absent knee jerks in a patient on magnesium sulfate therapy is usually indicative of magnesium toxicity.

Papilledema: This can be described as the swelling of optic disc diagnosed on ophthalmoscopy or slit lamp examination in very severe cases of hypertension. Papilledema occurs due to increased intracranial pressure, usually in association with malignant hypertension.

Specific Systemic Examination

ABDOMINAL EXAMINATION

On abdominal examination, there may be evidence of placental insufficiency in form of oligohydramnios or/and IUGR. Oligohydramnios can be defined as presence of less than 200 ml of amniotic fluid at term or an AFI of less than 5 cm or presence of the largest pocket of fluid, which does not measure more than 2 cm at its largest diameter. For specific abdominal findings in relation to IUGR, refer to chapter 11. Findings on abdominal examination suggestive of oligohydramnios are as follows:

- The fundal height is less than that estimated on the basis of LMP.
- Uterus may appear full of fetus and/or evidence of IUGR may be present.

Differential Diagnosis

It is important for the obstetrician to differentiate between preeclampsia, gestational hypertension and chronic hypertension. The differentiating features of all these have been described in the introduction above.

Management

Management comprising of investigations and definitive obstetric management is discussed below:

Investigations

Laboratory tests which must be performed in these patients include the following:

- CBC, platelet count
- Liver function tests
- Measurement of serum electrolytes, BUN
- Kidney function tests (creatinine, creatine clearance, and 24-h urine protein)
- Urinalysis
- Ophthalmoscopic examination

Hematocrit

The decrease in blood volume in preeclampsia can lead to an increase in maternal hemoglobin concentration resulting in increased hematocrit.

Platelet count

In normal pregnancy, the platelet count can fall below 200×10^9/L due to the normal maternal blood volume expansion. In preeclampsia, the platelet count falls further and is associated with progressive disease. This fall is probably a result of both increased platelet consumption and intravascular destruction related to preeclampsia. Coagulation abnormalities are unlikely to occur if the platelet count remains above 100×10^9/L. Normal platelet count varies between 150–400 $\times$ 10^9/liter. A low platelet count could also be indicative of the HELLP syndrome which would be discussed later in the chapter.

Kidney function tests

Renal function is generally maintained in preeclampsia until the late stage, unless the HELLP syndrome develops.

Serum creatinine levels

In normal pregnancy, there is an increase in creatinine clearance with a concomitant decrease in serum creatinine and urea concentrations. If creatinine is found to be elevated early in pregnancy, underlying renal disease should be suspected. In severe preeclampsia, serum creatinine can be seen to rise and is associated with a worsening outcome. However, with the increase in use of antihypertensive drugs and magnesium sulfate in patients with preeclampsia, the incidence of renal failure is progressively decreasing. When renal failure does occur, it is usually associated with hemorrhage, HELLP syndrome or sepsis.

Serum uric acid levels

Serum concentrations of uric acid fall in normal pregnancy because renal excretion increases. In preeclampsia, there can be a rise in uric acid concentrations mostly due to decrease in renal excretion, but could also be related to increased production secondary to tissue ischemia and oxidative stress. Increased serum uric acid levels are usually related to poorer outcomes both for the mother and baby.

Liver function test

- Liver function tests including the measurement of alanine and aspartate aminotransferase and lactate dehydrogenase activities must be performed.

- An AST level of above 75 IU/L is seen as significant and a level above 150 IU/L is associated with increased morbidity to the mother.

Ophthalmoscopic examination

The following findings may be observed on the ophthalmoscopic examination:

- Presence of retinal edema
- Constrictions of the retinal arterioles: Narrowing of the retinal arterioles is related to the severity of hypertension.
- Alteration of normal ratio of Vein: Arteriolar diameter: Due to the arteriolar narrowing, the vein: Arteriolar diameter is altered from 3:2 to 3:1.
- There is nicking of the veins where they are crossed by the arterioles.

Treatment/Obstetric Management

PREVENTION

Although there is no known way to prevent preeclampsia, it is important for all pregnant women to start prenatal care early and continue it throughout the pregnancy. This allows the healthcare provider to find and treat conditions such as preeclampsia early. Use of aspirin, calcium, vitamin C (1,000 mg per day); vitamin E (400 mg per day) has shown potential promise towards prevention of preeclampsia. However large, randomized trials in future are required to show definite benefits with the use of these supplements.

Presently, most evidence suggests little or no benefit of low-dose aspirin in prevention of PIH in the women belonging to the low risk category. Evidence regarding the use of calcium supplements for prevention of preeclampsia has also presented with conflicting results. Levine et al have shown that calcium supplementation with 2 grams of calcium daily during pregnancy did not reduce the incidence or severity of preeclampsia or delay its onset, nor did it reduce the incidence of pregnancy-associated hypertension without preeclampsia. The results of this study contraindicated the study of other trials which have shown that daily supplementation with calcium helps in preventing preeclampsia. When the analyses were stratified according to compliance, calcium supplementation was observed to produce no effect on preeclampsia or on pregnancy-associated hypertension without preeclampsia, even among the women who were most compliant with treatment. World Health Organization's randomized controlled trial of calcium supplementation among pregnant women with low calcium intake showed that prescription of 1.5 grams calcium supplements to nulliparous and normotensive pregnant women from populations with dietary calcium intake of less than 600 mg/d, before 20 weeks of gestation, given throughout their pregnancy did not prevent preeclampsia. However, it did reduce the severity of preeclampsia. Maternal and neonatal mortality was also significantly reduced. Calcium intake by the woman during second trimester of pregnancy is inversely associated with high blood pressure in the offspring. This issue is an important one because, if confirmed, ensuring adequate calcium intake among pregnant women could be a way to prevent hypertension and its sequel in the next generation.

Other Nutritional Advice Commonly Prescribed for Preeclampsia

A variety of nutritional interventions have been evaluated for their potential role in prevention of preeclampsia. It is commonly believed that salt restriction during pregnancy helps in providing relief from increased blood pressure in preeclampsia. Dietary salt restriction and inappropriate diuretic therapy had been used since long for treatment of eclampsia. Presently, there is absence of any evidence which shows beneficial action of salt restriction in preeclampsia. In the absence of evidence that advice to alter salt intake during pregnancy has any beneficial effect for prevention of preeclampsia or any other outcome, salt consumption during pregnancy should remain a matter of personal preference. Supplementation with fish oil has also been tried as a therapeutic option for preeclampsia. In a study by Oslen et al, fish oil supplementation was observed to have no effect on intrauterine growth retardation or pregnancy induced hypertension. Use of antiplatelet drugs, particularly aspirin have also been tried for prevention of preeclampsia. However, various studies have presented with conflicting results. In the CLASP (Collaborative low dose aspirin study in pregnancy) trial, use of aspirin (60 mg daily) was associated with a nonsignificant reduction in the incidence of proteinuric preeclampsia. Also, no significant effect was observed on the incidence of IUGR or of stillbirth and neonatal death. Aspirin did, however, significantly reduce the incidence of preterm delivery among preeclamptic women. Use of low-dose aspirin was observed to be safe for the fetus and newborn infants, with no evidence of an increased likelihood of bleeding. Use of aspirin did not cause a significant increase in incidence of placental hemorrhages or in bleeding during preparation for epidural anesthesia. However, it did result in a slight increase in the need of blood transfusion after delivery. Thus the use of low dose aspirin in the early second trimester may be justified in women suffering from severe, early-onset preeclampsia who may require a very preterm delivery. The results of the BLASP trial (Barbados Low Dose Aspirin Study in Pregnancy) and ECPPA (Estudo Colaborativo Para Prevenção

da Préeclampsia com Aspirina) trial do not support the routine use of low-dose aspirin for prevention of preeclampsia or its complications.

Oxidative stress, a condition characterized by peroxidants predominated over by antioxidants has been recently suggested to play an important role in the pathogenesis of preeclampsia.

The use of α-tocopherol and vitamin C, either alone or in combination, has been reported in several clinical studies evaluating potential benefit of anti-oxidants in preeclampsia.

However the results, so far have largely been disappointingly negative. Supplementation with antioxidants like vitamins C and E during pregnancy does not reduce the risk of preeclampsia, the risk of intrauterine growth restriction, or death or other serious outcomes in the infants of nulliparous women.

Management of cases with preeclampsia is described in flow chart 12.1. Management of preeclampsia would be discussed under two headings: Management in cases of mild preeclampsia and management in cases of severe preeclampsia.

MANAGEMENT OF MILD PREECLAMPSIA

Maternal Management

When the mother is diagnosed with mild type of preeclampsia in the antenatal period, she should be admitted in the hospital in order to assess the severity of condition and decide further management. Domiciliary treatment has no role in an established case of preeclampsia and the patient must be hospitalized. In an under-resourced setting where it might not be possible to admit every patient with mild preeclampsia, the patient must be at least referred to an antenatal day unit for further investigations. The following assessments need to be carried out:

- Daily detailed examination for the symptoms indicative of severe preeclampsia, including history of headache, visual disturbances, epigastric pain, edema, etc.
- Regular weight measurement at weekly intervals to assess if the woman is gaining weight at a rapid rate.
- Daily examination of urine for the presence of the protein by dipstick. If proteinuria of 2+ or more on dipstick is present, 24-hour protein estimation may be required.
- Blood pressure measurement to be done every 4 hourly (at least four times a day).
- The following investigation to be done on weekly basis: Hematocrit with platelet count, KFT (blood urea; serum uric acid; and serum creatinine); LFT (AST, ALT and LDH) and ophthalmoscopic examination. The frequency of the investigation can be changed depending upon the severity of symptoms and the results of the investigations.
- Absolute bed rest, as recommended in the past is not required.
- Prescription of the sedatives or tranquilizers is not required.
- Well balanced diet, rich in protein and calories is prescribed.
- Low dose aspirin in the dose of 60 mg daily can be prescribed: This is thought to reduce the production of vasoconstrictors like thromboxane A_2 without having any affect on the production of vasodilators like prostacyclin.
- Calcium supplementation: Though no definite role of calcium supplementation in prevention of preeclampsia has been shown during pregnancy, nevertheless supplementation with 300–600 mg of exogenous calcium preparations from 20th week of gestation has been significantly shown to increase the density of fetal bones.

Most cases of the gestational hypertension and mild preeclampsia respond to conservative management. However, fetal surveillance is required until the baby has attained maturity because the underlying pathophysiology behind preeclampsia would be corrected only following the delivery of the baby. The pregnancy should not be allowed to continue beyond EDD.

Fetal Evaluation

Until the fetal maturity is attained, fetal surveillance comprises of the following tests:

- Daily fetal movement count
- Weekly measurement of fundal height and abdominal girth in order to detect IUGR
- Non-stress test weekly
- Ultrasound examination for evaluating the period of gestation in early pregnancy and in the third trimester at every two weekly intervals.
- BPP after every two weeks.
- Doppler ultrasound at every three–four weekly intervals.

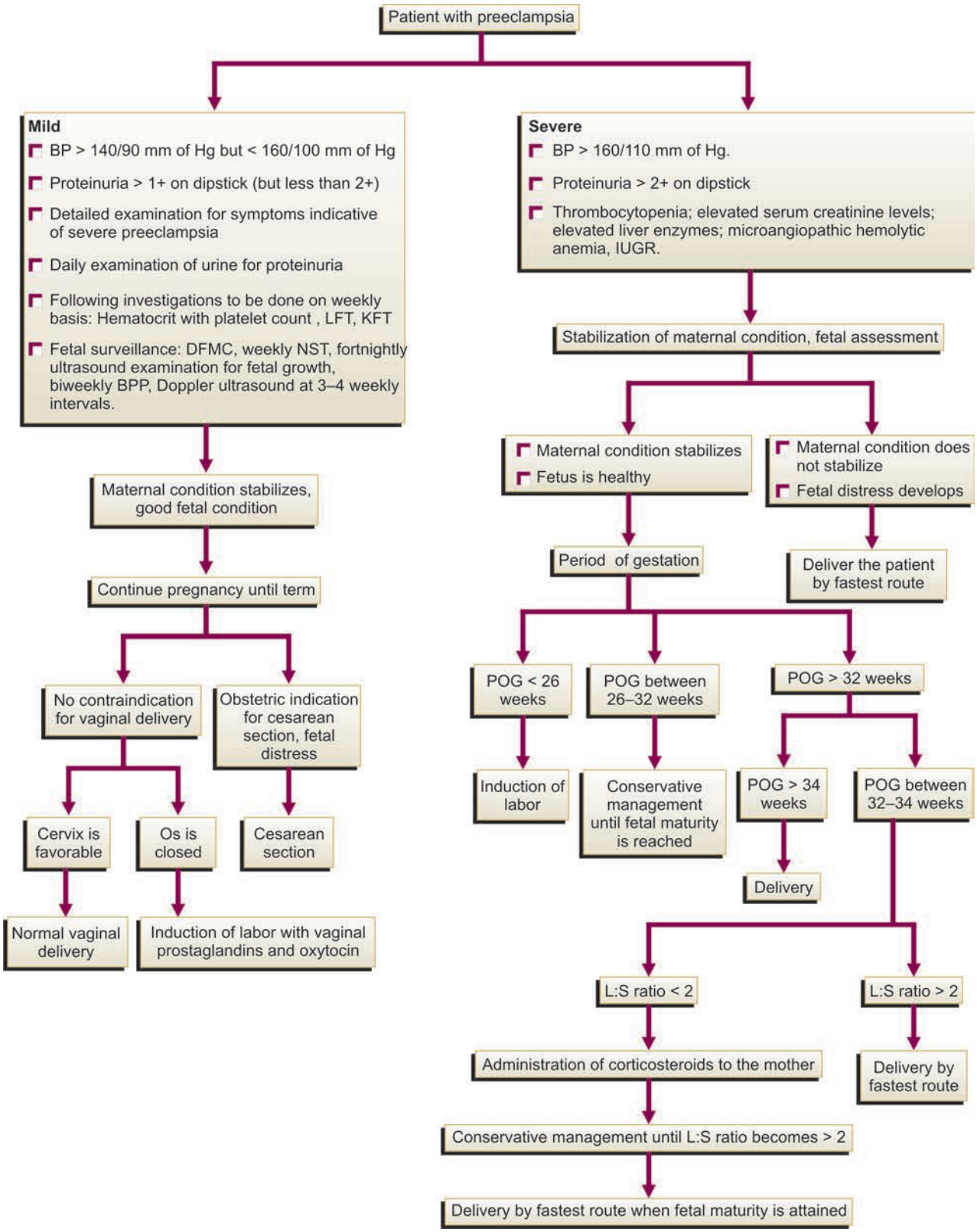
Mode of Delivery

There is no advantage of performing a cesarean over normal delivery. There is no need to hasten the delivery in cases of mild preeclampsia. The obstetrician can continue until term; however the pregnancy must not be allowed to exceed the EDD.

Postpartum Period

The obstetrician must remain vigilant regarding the high chances for the occurrence of PPH. This is all the more

Flow chart 12.1: Management of cases with preeclampsia



important since the routine use of methargin at the time of delivery of the baby's anterior shoulder is contraindicated in hypertensive women.

Following delivery, the ACE inhibitors can be restarted. Use of methyldopa is to be stopped due to risk of development of psychological changes, like depression in the mother.

MANAGEMENT OF SEVERE PREECLAMPSIA

The parameters for describing a patient to be suffering from severe preeclampsia are described in table 12.5. The aim of treatment in cases of severe preeclampsia is to protect both the mother and the fetus from the adverse effects of high BP and to prolong the pregnancy as far as possible in order to prevent the risk of fetal prematurity. Management of severe preeclampsia must be preferably done in tertiary unit, following a multidisciplinary team approach involving the obstetrician, physician, pediatrician and the anesthetist. Management of cases with preeclampsia is all the more important because there is danger of progression to eclampsia (a stage in which the patient experiences fits), if the blood pressure remains uncontrollably high. The management of severe preeclampsia is to be based on careful fetal assessment, maternal stabilization, continued monitoring and delivery at the optimal time for the mother and her baby. The only cure for preeclampsia is the delivery of the baby. Therefore, while deciding the time for delivery, a fine balance between fetal maturity and maternal wellbeing needs to be maintained.

Maternal Stabilization

Since there is a risk for eclampsia, patients with severe preeclampsia or imminent eclampsia must always be stabilized before they are transferred to a tertiary unit, or before delivery is planned. One way of doing this is by prescribing antihypertensive medicines to keep BP under control. Prescriptions of antihypertensive medicines help prevent the development of the complications related to high BP (e.g. intracranial hemorrhage). Another strategy, which is commonly employed, is starting magnesium sulfate (would be described later). These strategies usually help in prevention of eclampsia and help in buying time until the fetus has gained sufficient maturity so that it can be delivered. The following steps also need to be taken:

- Patients with severe preeclampsia must be hospitalized to a tertiary unit.
- Senior obstetric and anesthetic staff and experienced midwives should be involved in the care of such patients.
- Continuous maternal BP monitoring: The blood pressure should be checked at every 15 minutes in the beginning, until the woman has stabilized and then after every 30 minutes in the initial phase of assessment. Once the patient has become stable and asymptomatic, the blood pressure may be checked at 4-hourly intervals, especially if a conservative management plan is in place.
- Urine should be carefully monitored for proteinuria twice daily. In presence of significant proteinuria, a 24-hour estimation of urine proteins may be done.
- Maternal weight must be measured every day.
- Tests like platelet count, kidney function tests (serum uric acid concentration, blood urea and serum creatinine concentration) and tests of liver function must be done at the time of admission and then twice weekly.
- Antihypertensive drugs must be used to keep the diastolic blood pressure under 110 mm of Hg.
- Prophylactic use of magnesium sulfate to prevent eclampsia.

Fetal Management in Case of Severe Preeclampsia

In cases of preeclampsia, the fetuses are at risk due to prematurity as premature delivery may be required to save mother's life. On the other hand, if the pregnancy is allowed to continue, placental insufficiency resulting from preeclampsia may cause intrauterine growth restriction. IUGR occurs in approximately 30% of pregnancies with preeclampsia. Thus, fetal monitoring forms an important aspect of management of patients with preeclampsia.

Conservative management

If conservative management is planned, until fetal maturity is attained, the following investigations need to be done:

- Daily Fetal Movement Count,
- Weekly measurement of fundal height and abdominal girth in order to detect IUGR,
- Ultrasound measurement of fetal growth after every two weeks,
- Serial assessment of umbilical blood flow velocity by Doppler ultrasonographic assessment after every two weeks. Umbilical artery Doppler analysis showing absent or reversed end diastolic flow is associated with poor neonatal outcomes and mandates immediate delivery.
- Regular cardiotocography (non-stress test) at twice weekly intervals.
- BPP at weekly or twice intervals. Reduced liquor volume is also associated with placental insufficiency and fetal growth restriction. Serial estimations of liquor volume can help detect fetal compromise.

The frequency of various tests for fetal and maternal surveillance is not fixed. It can vary from patient to patient based on the clinical situation.

Table 12.7: Parameters for deciding the timing of delivery in cases with severe preeclampsia

Fetal maturity
Fetal condition
Maternal condition
Bishop's score
Period of gestation

Delivery is planned

In case the delivery is planned and a preterm fetus needs to be delivered, the following steps need to be undertaken:

- Administration of corticosteroids.
- Measurement of L: S ratio in the amniotic fluid; L: S ratio > 2 is indicative of fetal maturity.
- Fetus should be closely monitored at the time of labor, preferably with continuous electronic fetal monitoring.

Timing of delivery

The only way to cure preeclampsia is to deliver the baby. Therefore, termination of pregnancy is the treatment of choice in all patients with severe preeclampsia where the fetus has attained maturity. The timing of delivery needs to be decided based on various parameters enumerated in table 12.7. The timing of delivery based on the period of gestation in cases with severe preeclampsia is described below.

- *More than 32 weeks of gestation:* In cases of severe preeclampsia, when the pregnancy is more than 32 weeks of gestation, delivery is the treatment of choice. In case the period of gestation is less than 34 weeks, prophylactic steroids should be given to induce fetal lung maturity. A policy of administering corticosteroids, 12 mg betamethasone IM every 24 hours for two doses or 6 mg dexamethsone IM every 12 hours for four doses to women who are likely to have a preterm delivery can be expected to achieve substantial reduction in neonatal morbidity and mortality.
- *Before 26 weeks of gestation:* In women with severe preeclampsia before 26 weeks of gestation, prolonging the pregnancy at this gestational age may result in grave complications for the mother. Therefore labor must be induced for pregnancies less than 26 weeks, although it is quite unlikely that the fetus would survive at this time.
- *Between 26–32 weeks of gestation:* Pregnancies between 26–32 weeks represent a "gray zone." The obstetrician needs to balance the risk of prolonging the pregnancy, thereby increasing the maternal risk of developing complications related to severe preeclampsia against the risk of delivering a premature fetus which may not even survive.

Table 12.8: Indications for induction of labor in patients with severe preeclampsia

Signs of impending eclampsia including abdominal pain, blurring of vision, severe persistent headache, etc.
Abnormal biophysical profile; non-reassuring results on electronic fetal monitoring.
Diastolic blood pressure over 110 mm of hg
Abnormal liver function tests (lactate dehydrogenase > 1000 IU/L)
Eclampsia
Intrauterine growth retardation
HELLP syndrome
Rising serum creatinine levels
Fetal death
Placental abruption
Urine output < 500 ml/24 hours

If the obstetrician decides to continue pregnancy, close maternal and fetal monitoring requires to be done, because simply lowering the blood pressure under conservative management will not slow down the disease process. The risk for preeclampsia related complications, such as abruption, still remain.

Mode of delivery

Severe preeclampsia per se is not an indication for cesarean section. If the cervix is ripe, labor can be induced by using intravenous oxytocin and ARM. Labor may be induced if any of the conditions mentioned in the table 12.8 occur. In case of presence of unfavorable cervix or other complications (e.g. breech presentation, fetal distress, etc.), a cesarean section needs to be done. If delivery has been decided upon before 32 weeks of gestation, the practice in the UK and US is to deliver by elective cesarean section; after 32 weeks of gestation, a vaginal delivery is more likely. This is so as labor can aggravate fluid overload and blood pressure control and therefore vaginal delivery may not be successful in more than 50% of cases. However, most other health care centers with limited neonatal resuscitation facilities throughout the world, prefer attempting a vaginal delivery with varied results.

Maternal Management During Labor

The parameters which need to be taken care of at the time of labor in a patient with severe preeclampsia are enumerated in table 12.9 and would be described below in details.

Maternal vitals monitoring

This involves monitoring of vitals especially maternal pulse and blood pressure at hourly intervals. Urine protein levels using a dipstick must be monitored at every 6-hourly intervals.

Table 12.9: Parameters which need to be taken care of at the time of labor in a patient with severe preeclampsia

Maternal vitals monitoring
Use of intravenous fluids
Use of antihypertensive medication
Use of magnesium sulfate
Choice of anesthesia in case of cesarean delivery

Choice of anesthesia

The choice of anesthetic in cesarean section is important, because tracheal intubation can cause a rise in both systolic and diastolic blood pressure. With an epidural or spinal block, care should be taken to keep the fluid load to a minimum level. However, these methods can be safely used with appropriate supervision.

Antihypertensive therapy should be continued throughout labor. An epidural, by allowing adequate pain relief, can reduce the rise in blood pressure commonly associated with labor. It also allows a planned delivery and easy transition to cesarean section if necessary.

The antihypertensive agents are used to control persistent increase in BP, especially when diastolic BP>110 mm of Hg.

Use of intravenous fluid in women with severe preeclampsia or eclampsia

While in normal pregnancy, there is an increase in plasma volume, in preeclampsia there is contracted plasma volume and hemoconcentration. Therefore, administration of intravenous fluid in women with severe preeclampsia and eclampsia must be monitored carefully. Infusion of excessive fluid may result in the development of pulmonary edema and adult respiratory distress syndrome.

On the other hand, if CVP is between 4–8 mm Hg, the obstetrician must look for the clinical signs of pulmonary edema, such as crepitations in the base of lungs. If crepitations are present, 20 mg of furosemide must be administered via intravenous route. If no response is seen to furosemide, dopamine infusion (1 μg/kg/min up to 5 μg/kg/min) must be given to enhance renal perfusion. One of the complications of pulmonary edema is poor oxygen saturation, so one of the best methods of monitoring fluid status is continuous measurement of oxygen saturation with a pulse oximeter.

Use of antihypertensive medication

Presently, there is little evidence regarding the antihypertensive drug of choice to be used for lowering blood pressure in case of women with severe preeclampsia or the threshold of blood pressure at which therapy with antihypertensive drugs must be initiated. If blood pressure is above 160/110 mm Hg, the antihypertensive drugs must be definitely used for controlling the raised blood pressure. The aim of treatment must be to maintain diastolic BP between 95–105 mm Hg. In mild to moderate cases of preeclampsia, the role of antihypertensive therapy is less clear. Maternal treatment is associated with a reduction of severe hypertension associated complications. If the blood pressure is below 160/100 mm Hg, there is no immediate requirement for antihypertensive therapy. When the blood pressure remains uncontrollable despite the use of antihypertensive medications, delivery is the only option.

Table 12.10: Indications for the use of diuretics

Severe pulmonary edema.
Massive edema, not relieved by rest
Cardiac failure

The most commonly used drugs include: Hydralazine, alpha-methyldopa, labetolol and nifedipine. While these medications to lower blood pressure are safe during pregnancy, others, including drugs like angiotensin converting enzyme (ACE) inhibitors, beta blockers (atenolol), angiotensin receptor blockers (ARB) and diuretics can harm the fetus. Use of atenolol and diuretics has been found to be associated with fetuses having lower birth weights and/or IUGR by decreasing the uteroplacental blood flow. ACE inhibitors and ARB's, when administered in the second and third trimesters, have been found to be associated with a characteristic fetopathy, oligohydramnios, neonatal renal failure and death. Thus, the use of these drugs should be avoided during pregnancy. The use of diuretics should be limited to the cases described in the table 12.10.

Methyldopa and labetalol are the most commonly used first-line drugs, followed by nifedipine as the second-line agent in developing countries, including India. However all antihypertensive drugs (hydralazine, alpha-methyldopa, labetolol and nifedipine) seem to be effective. No single therapy can be successful in all patients and increasing doses and combinations of drugs are generally required. Intravenous labetalol or oral nifedipine is as effective as intravenous hydralazine, with fewer adverse effects. Other rapidly acting agents, like nitroglycerine, diazoxide and sodium nitroprusside are usually preserved for use in an ICU setting or in the OT. In treating severe hypertension, it is important to avoid hypotension, because aggressive lowering of maternal blood pressure may result in fetal distress. In women with preeclampsia, treatment of acute severe hypertension must be started at lower doses, because these patients may be having depleted intravascular volume and thereby may be at an increased risk for hypotension.

Hydralazine

Hydralazine is a directly acting arterial vasodilator, which is preferred antihypertensive for the treatment of hypertensive crisis during pregnancy.

Dosage: For controlling hypertensive crisis during pregnancy, hydralazine is given in the dose of 5 to 10 mg intravenously, repeated every 20 minutes until the desired response is achieved. It can also be administered in form of continuous infusion, given at the rate of 0.5 – 10 mg /hour. Hydralazine can also be administered orally in the dose of 50 to 300 mg/day in 2 to 4 divided doses for control of gestational hypertension or chronic hypertension during pregnancy. The time for onset of action is 10 minutes via intravenous route and 10–30 minutes via intramuscular route.

Side effects: The use of hydralazine can produce maternal side effects like nausea, vomiting, hypotension, flushing, headache, CNS depression, tachycardia, anxiety, restlessness, hyperreflexia, etc. In the fetus, this drug can also produce abnormalities in heart rate sounds, including reduced variability.

Alpha-methyldopa

Methyldopa is the α methyl analogue of dopa and is one of the most widely used drugs for the treatment of hypertension in pregnancy. It results in the formation of methyl NA (a centrally acting α2-adrenergic agonist), which helps in decreasing the efferent sympathetic activity. Blood pressure control occurs gradually over a period of 6 to 8 hours and lasts for about 12–24 hours. It is not thought to have any teratogenic effect in pregnancy. Treatment with methyldopa has been reported to prevent subsequent progression to severe hypertension in pregnancy. Alpha-methyldopa has been considered as the drug of choice in pregnancy according to National High Blood Pressure Education Program (NHBPEP) Working Group Report on High Blood Pressure in Pregnancy.

Dosage: The dose of alphamethyldopa commonly in use is 0.5 to 3.0 g/d in 2-4 divided doses.

Side effects: Alphamethyldopa can commonly produce side effects like sedation, lethargy, cognitive impairment, dryness of mouth, nasal stuffiness, headache, fluid retention, weight gain, etc.

Labetolol

Labetalol, a nonselective β-blocker which also has vascular α1 receptor blocking capabilities, has gained wide acceptance in pregnancy. It helps in lowering BP smoothly but rapidly, without causing tachycardia.

Dose: Labetalol is given as a 20 mg intravenous bolus, followed by 40 mg after 10 minutes. If the first dose is not effective; then 80 mg is administered every 10 minutes. Maximum total dose of 220 mg can be administered. It can also be administered in form of a continuous infusion – 250 mg of labetalol in 250 ml of normal saline, administered at the rate of 20 mg per hour (20 ml per minute). Orally, labetalol is administered in the dose of 100 mg eight hourly, which may be increased to 800 mg /day. The onset of action of intravenous dosage is within 5 to 10 minutes.

Side effects: This drug can produce side effects like flushing, headache, nausea, vomiting. It is contraindicated in women with asthma and first degree heart block. Therefore, its use must be avoided in women with asthma or congestive heart failure. Due to a lower incidence of side effects like maternal hypotension, the use of labetalol now supplants that of hydralazine. When administered orally to women with chronic hypertension, it seems to be as safe and effective as methyldopa, although neonatal hypoglycemia can occur with higher doses.

Nifedipine

Nifedipine is a calcium channel blocker, which should be given orally and not sublingually for control of high blood pressure.

Dosage: Nifedipine should be given in the dose of 5–10 mg/orally, which can be repeated after 30 minutes if necessary, followed by 10–20 mg every 3–6 hours. The slow release preparation is given in the dosage of 30 to 120 mg/day. Nifedipine can also be administered via intragastric route using a Ryles tube. The dose should not exceed 10 mg at a time and should not be repeated more frequently than every 30 minutes. The oral drug starts producing its effect between 10–15 minutes, whereas the slow released drug starts producing its effect within 60 minutes.

Side effects: It can produce side effects like flushing, headache, tachycardia, nausea, etc. Fetal safety of this drug has yet not been established. It has also been shown to inhibit labor and may have synergistic action with magnesium sulfate in lowering of BP. Therefore, a combination of magnesium sulfate and nifedipine is to be avoided as it can cause sudden hypertension.

Magnesium sulfate

Use of Magnesium sulfate in severe preeclampsia: Magnesium sulfate should be considered for women with preeclampsia, especially those with severe preeclampsia in whom there is concern about the risk of eclampsia. In women with less severe disease, the decision is less clear and usually depends on individual case assessment. Magnesium sulfate is usually used in the patients with severe preeclampsia, once the decision for delivery has been made. The MAGPIE study (2002) has demonstrated that administration of magnesium

sulfate to women with preeclampsia reduces the risk of an eclamptic seizure. Magnesium sulfate must be administered while awaiting delivery and in the immediate postpartum period for up to 24 hours following delivery or 24 hours after the last seizure, whichever is the later, unless there is a clinical reason to continue. Magnesium sulfate is now also considered as an anticonvulsant of choice for treating eclampsia.

This agent had commonly been used in the US, following the results of the Collaborative preeclampsia trial (1995). However, following the demonstration of its efficacy in Magpie trial (2002), it is commonly being used in the UK as well for prevention of eclampsia. In 1995, the Collaborative low dose Aspirin Study in Pregnancy (CLASP) group did an impressive study in developing countries and showed unequivocally that magnesium sulfate given intramuscularly or intravenously was superior to either phenytoin or diazepam in reducing recurrent eclamptic seizures. This study showed that the women on magnesium sulfate had a significantly lower risk of recurrent seizures than those on diazepam or phenytoin. Also, the women who received magnesium sulfate were at a lower risk of maternal death in comparison to those on diazepam or phenytoin. However, these results were not statistically significant. Babies of mothers on magnesium were in better condition after delivery and less likely to require special care. Recent Cochrane reviews, have however, also indicated a significant reduction in maternal mortality with magnesium.

Magpie trial (2002), which had recruited over 10,000 women with preeclampsia, showed that there was more than a halving in the risk of eclampsia associated with the use of magnesium sulfate rather than placebo.

Mode of action of magnesium sulfate: Magnesium sulfate is associated with cerebral vasodilatation and is a blocker of N-methyl-D-aspartate (NMDA) receptors in the brain, the pathway for anoxic cell damage.

Dosage: A total dose of 14 g is administered in form of loading and maintenance dose. The following regimens can be given:

Pritchard's regimen:

A Loading dose: A loading dose of 4 g magnesium sulfate is administered slowly intravenously over 10 minutes. Both 50% and 25% solutions of magnesium sulfate can be used. 4 grams solution of magnesium sulfate can be prepared by adding 8 ml of 50% magnesium sulfate (i.e. 2 ampoules) to 12 ml sterile water to make a total of 20 ml. This solution of magnesium sulfate is then given intravenously, slowly over at least 5 minutes. If magnesium is given too quickly, it can result in the development of cardiac arrhythmia or arrest. The intravenous dose must be immediately followed by 5 g (i.e. 10 ml 50% magnesium sulfate) by deep intramuscular injection into each buttock.

Maintenance dose: The maintenance dose comprises of 5 g intramuscularly in each buttock at every four hourly intervals. Intramuscular injections are painful and are complicated by local abscess formation in 0.5% of cases. Addition of 1 ml of 1% xylocaine to the above solution may help to reduce the pain at the injection site.

Zuspan's Regimen: A loading dose of 4 g should be given by infusion pump over 5–10 minutes, followed by a further infusion of 1 g/hour maintained for 24 hours after the last seizure.

Sibai's regimen: A loading dose of 6 g should be given by infusion pump over 5–10 minutes, followed by a further infusion of 1 g/hour maintained for 24 hours after the last seizure.

Recurrent seizures should be treated with either a further bolus of 2 g magnesium sulfate or an increase in the infusion rate to 1.5 g or 2.0 g/hour.

Monitoring of dosage of magnesium sulfate: Too rapid injection of $MgSO_4$ should not be given. When magnesium sulfate is administered, the following parameters must be regularly assessed:

- Urine output
- Maternal deep-tendon reflexes
- Respiratory rate and oxygen saturation.

After the magnesium sulfate has been administered, a foley's catheter is inserted into the patient's bladder, to monitor the urinary output. If available, serum levels of magnesium should be regularly monitored.

With the dose regimen as described previously (5 g IM every 4hrly), there is no need for magnesium concentrations to be checked regularly. However, in many parts of the world, infusions of 1-3 g/hour (Zuspan's and Sibai's regimen) are used. Although checking of magnesium concentrations may be necessary when a higher infusion rate is used, toxic effects are unlikely when deep tendon reflexes are still present.

The therapeutic levels of magnesium range from 4 to 7 mEq/L. Further dose of magnesium is adjusted based on the patient's reflexes, BP, urinary output and serum Mg levels. The aim should be to maintain magnesium concentration at 4 mEq/L. If the Mg levels reach 10 mEq/L, the patellar reflex is lost and at 15 mEq/L respiratory depression sets in. Thus, if the intramuscular regime is used, it is important to ensure the following parameters before the administration of a repeat dose: Urine output is > 30 ml/hr; patellar reflexes are intact and respiratory rate is above 16/minute. An overdose of magnesium sulfate causes respiratory and cardiac depression. Here, the patellar reflex acts as a convenient warning. If the reflex is present, the drug may safely be given, as there is no danger of magnesium toxicity. If the reflexes are absent or reduced, there is a danger of magnesium toxicity and the next dose must not be given. Toxicity to magnesium sulfate is a

life threatening emergency and the following steps must be taken immediately:

- Intubation and bag and mask ventilation must be done.
- External cardiac massage may also be required.
- 10 ml of 10% calcium gluconate must be slowly administered intravenously. This serves as an antidote for magnesium sulfate poisoning.

The fetus is also not immune to the potential effects of magnesium because it can readily cross the placenta. Hypermagnesemia in the neonate is associated with flaccidity, lethargy, hypotonia, hyporeflexia and respiratory depression.

No response to first dose of magnesium sulfate: After giving the first dose of magnesium sulfate, the blood pressure must be measured again. If the diastolic blood pressure is still 110 mm Hg or higher, dihydralazine or oral nifedipine is given as follows:

6.25 mg dihydralazine by intramuscular injection or 10 mg (one capsule) nifedipine orally.

Patients who have received 10 mg nifedipine can be given a second dose of 10 mg nifedipine orally if the diastolic blood pressure remains 110 mm Hg or more even after 30 minutes. If necessary, it can be repeated half-hourly up to a maximum dose of 50 mg.

In case of nonavailability of $MgSO_4$, drugs like diazepam (valium) or phenytoin (dilantin) must be used. Thiopentone is reserved for status eclampticus. However, only single dose of these drugs must be administered. Prolonged use of diazepam is associated with an increase in maternal death rate. If convulsions persist, intubation may be required to protect the airway and maintain oxygenation. Transfer to intensive care facilities with intermittent positive pressure ventilation may appear to be appropriate in these circumstances.

Phenytoin

The loading dose of phenytoin is 15–25 mg/kg, IV. In general, the loading dose is 1 gm/IV, diluted in 200 ml of normal saline given by slow infusion over 20 minutes. This must be followed by 100 mg 6 hourly. The first 750 mg is given at the rate of 25 mg/min and the remaining at the rate of 12.5 mg/min. Side effects include cardiac toxicity, nystagmus, hypertension, ataxia and lethargy.

Diazepam (Lean regimen)

Loading dose of 10 mg, IV is administered over 2 minutes, followed by IV infusion of 40 mg in 500 ml normal saline for next 24 hours. This drug is not preferred as it causes lethargy and apnea of the newborn.

Lytic cocktail regimen or Krishna Menon regimen comprising of chlorpromazine, phenargan and pethedine is no longer used.

Fluid balance

Since pulmonary edema has been found to be a significant cause of maternal death, fluid restriction is advisable to reduce the risk of fluid overload in the intrapartum and postpartum periods. In usual circumstances, total fluids should be limited to 80 ml/hour or 1 ml/kg/hour.

The regime of fluid restriction should be maintained until there is a postpartum diuresis, as oliguria is common with severe preeclampsia. If there is associated maternal hemorrhage, fluid balance is more difficult and fluid restriction is inappropriate.

Management of Hypertension Postpartum

The following steps need to be taken in the postpartum period:

An initial improvement in blood pressure, followed by a relapse of high blood pressure is commonly observed within 24 hours of delivery. Therefore, continued close monitoring must be done following delivery.

Antihypertensive drugs should be given if the BP exceeds 150 mm Hg systolic or 100 mm Hg diastolic in the first 4 days of the puerperium. The medication may then be discontinued when BP normalizes. This may occur days to several weeks postpartum and home BP monitoring by the patient may be helpful in this regards.

After delivery ACE inhibitors can be started, methyldopa is to be stopped due to risk of development of psychological changes, particularly depression.

Most postnatal convulsions occur within the first 24 h after delivery, so anticonvulsant therapy is generally continued for at least 24 hours after delivery.

In the postpartum period, previously normotensive women have been noted to have a rise in BP, which reaches a maximum on the 5th postpartum day, probably as a consequence of physiological volume expansion and fluid mobilization in the postpartum period.

Clinicians should be aware of the risk of late seizures and ensure that women have a careful review before discharge from hospital.

- Obstetricians must remember that nearly half the cases of eclampsia occur postpartum, especially at term, so women with signs or symptoms compatible with preeclampsia should be carefully observed postnatally.
- The decision about discharge from hospital needs to take account of the risk of late seizures. Most women with severe preeclampsia or eclampsia will need inpatient care for 4 days or more following delivery.
- Antihypertensive medication should be continued after delivery depending on the blood pressure recordings. During this time, blood pressure should not be allowed

to exceed 160/110 mm Hg. In most cases, the antihypertensives are not required 12 weeks following delivery, although most women can have their treatment stopped much earlier than this. Currently, there is insufficient evidence to recommend any particular antihypertensive. In breastfeeding women, labetalol, atenolol, nifedipine and enalapril are currently in use, either singly or in combination.

- A regular assessment of blood pressure and proteinuria by the general practitioner at the 6th and 12th weeks following delivery is recommended. If hypertension or proteinuria persists, then further investigation to rule out chronic hypertension or chronic renal disease is recommended.

Complications

All forms of high blood pressure increase the risk for development of pregnancy related complications. However, the risk of complications is highest in women with chronic high blood pressure accompanied by preeclampsia. Some of the maternal and fetal complications related to preeclampsia are enumerated in table 12.11.

Table 12.11: Complications related to preeclampsia

Maternal	*Fetal*
HELLP syndrome	Oligohydramnios
Abruption placenta	Intrauterine death
Cerebral hemorrhage	Prematurity
Sepsis/shock	Intrauterine growth retardation
Eclampsia	
Risk of recurrence of preeclampsia in subsequent pregnancies	Intrauterine asphyxia and acidosis
Impaired renal function	Infant death
Impaired liver function	
Pulmonary edema	
Maternal death	

FETAL COMPLICATIONS

Prematurity

Premature delivery (before 37 completed weeks of pregnancy) may be required in women with severe preeclampsia in order to prevent severe complications to mother and baby. These babies have been shown to be at an increased risk for health problems during the newborn period, such as learning disabilities and cerebral palsy.

Intrauterine Growth Restriction (IUGR)

Uteroplacental insufficiency in patients with preeclampsia restricts the placental blood flow limiting the supply of essential nutrients and oxygen to the fetus. Blood flow in the baby may get restricted to the limbs, kidney and abdomen in an effort to preserve the blood supply to the vital areas like the brain and heart, resulting in the development of growth restricted fetuses. Details related to the management of a pregnancy complicated by IUGR are described in chapter 11. IUGR in the long run can result in the development of fetal acidosis and hypoxia.

MATERNAL COMPLICATIONS

Abruption Placenta

This refers to the premature separation of normally implanted placenta. Preeclampsia is an important cause for development of abruption placenta. Details regarding abruption placenta are described in chapter 4.

Cerebral Hemorrhage

Untreated high blood pressure serves as an important cause for the development of cerebral hemorrhage and stroke.

ECLAMPSIA

Eclampsia is one of the most serious complications of preeclampsia. This can be defined as onset of tonic and clonic convulsions in a pregnant patient with preeclampsia, usually occurring in the third trimester of pregnancy, intrapartum period or more than 48 hours postpartum.

Eclampsia is thought to be related to cerebral vasospasm, which can cause ischemia, disruption of the blood brain barrier and cerebral edema. Once the seizures and severe hypertension has been controlled, delivery is required for the treatment of eclampsia.

Prevention of Eclampsia

- In order to prevent the occurrence of eclampsia, the obstetrician needs to remain vigilant regarding the appearance of signs of imminent eclampsia in patients with severe preeclampsia (see table 12.5).
- The decision for delivery must be made as soon as possible in patients with severe preeclampsia.
- Women with severe preeclampsia (BP > 160/110 along with proteinuria) should be given magnesium sulfate as a prophylactic measure. Magnesium sulfate should be continued for 24 hours after delivery or 24 hours after the last convulsion, whichever is later.

Management of Eclampsia

Every maternity unit must be equipped to deal with this obstetric emergency and must institute emergency

management effectively. There should preferably be a separate eclampsia room in each obstetric ward. This room should be especially reserved for patients with severe preeclampsia or eclampsia and should be free from noise. It should have a railed bed and equipment like suction machine, equipment for resuscitation, syringes, tongue blade and drug tray with drugs such as magnesium sulfate, nephidipine, diazepam, etc. Early involvement of consultant obstetrician, anesthetic staff and other specialists including a hematologist, ophthalmologist, neonatologist, etc may be required. Care of patients with eclampsia requires the following steps:

- Immediate care involves maintenance of airway, oxygenation and prevention of trauma or injury to the patient. Injury to the patient can be prevented by placing her on a railed bed. A tongue blade can be used to prevent her from biting her tongue.
- The patient should be placed in the left lateral position and the airway must be secured. Oxygen should be administered through a face mask.
- Monitoring of vitals including pulse, blood pressure, respiratory rate and oxygen saturation needs to be done every 15 minutes. Knee jerks and urine output need to be monitored every half hourly.
- An IV line must be secured and the patient must be given IV Ringer's lactate or 0.9% normal saline solution. Fluids should be restricted to 80 ml/hr or 1mg/kg body weight. RCOG recommends fluid restriction so as to avoid fluid overload and pulmonary edema. Close monitoring of fluid intake and urine output at every half hourly interval is mandatory.
- Treatment of choice to treat convulsions is the administration of magnesium sulfate. Magnesium sulfate is supposed to act by relieving cerebral vasospasm.
- Once the patient has stabilized, an obstetric examination must be performed and fetal status must be evaluated. An obstetric evaluation and plan to deliver the patient is required.
- Continued fetal monitoring, preferably through continuous electronic monitoring is required until the baby is delivered.

Though definitive treatment of eclampsia is delivery, the maternal wellbeing gets priority over fetal condition. Once the mother has stabilized, she should be delivered as soon as possible. However, it is inappropriate to deliver an unstable mother even if there is fetal distress. Once seizures and severe hypertension has been treated and hypoxia has been corrected, delivery can be expedited. The mode of delivery, whether by vaginal or abdominal route depends on obstetric evaluation of the individual patient. If the cervix appears unfavorable, vaginal prostaglandins can be used for induction of labor. Strict blood pressure monitoring must be continued throughout labor. If the maternal condition stabilizes, convulsions are absent and the fetus is preterm, the delivery can be delayed. During this time, corticosteroids should be administered to attain fetal maturity and continuous fetal surveillance needs to be done. During this time, patient can be shifted to a tertiary care center having adequate neonatal resuscitation facilities.

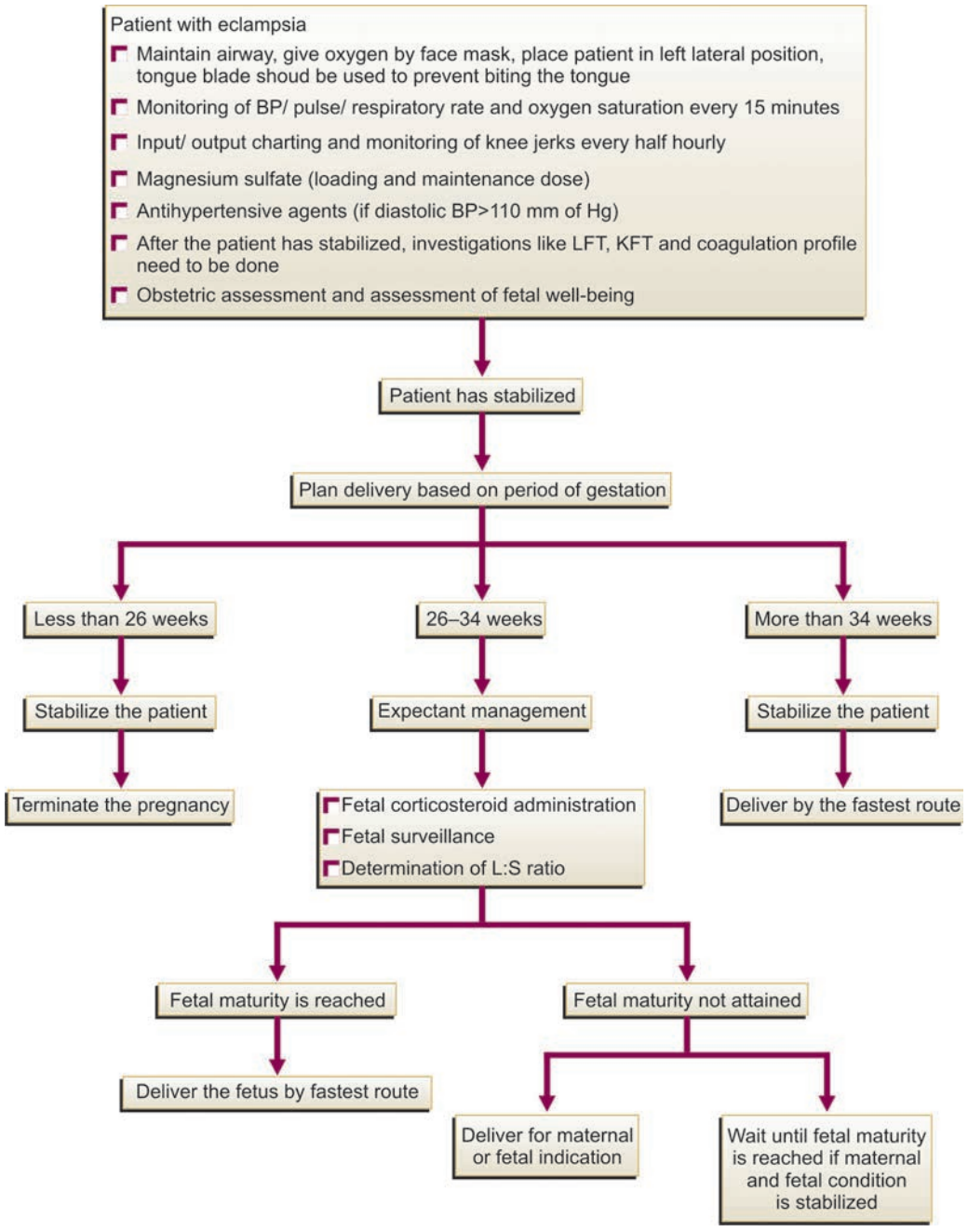
Management in patient with eclampsia is shown in flow chart 12.2. Parameters used for planning the delivery include gestational age; severity of disease; seizures/hypertension and immediate danger to the mother/fetus. If the period of gestation is less than 26 weeks, both the maternal and fetal prognosis would be bad if the pregnancy is allowed to continue in order to attain fetal maturity. In these cases, pregnancy must be terminated following maternal stabilization. In cases the period of gestation is between 26 to 34 weeks, expectant management plan can be followed, provided that the maternal condition remains stabilized. The mother must be administered intramuscular corticosteroids and the fetus must be adequately monitored. The fetus must be delivered when the amniotic fluid L: S ratio becomes more than two, i.e. the fetal lung maturity has been attained. In case the fetal maturity has not been attained, but either the maternal (high blood pressure) or fetal condition (fetal distress) deteriorates, the fetus needs to be delivered by the fastest route. In case the period of gestation is more than 34 weeks, there is no need to continue the pregnancy and the baby may be delivered by the fastest route. The obstetrician may be also required to expedite the delivery in case there is presence of any of the ominous features of eclampsia as described in table 12.12.

If the delivery can be delayed for at least 24 hours and the fetus is premature, steroids for attaining lung maturity can be given (2 doses of 12 mg of betamethasone 24 hours apart). However in patients with eclampsia, due to a requirement for urgent delivery, there may be unavailability of so much time. Therefore, a woman with severe preeclampsia may be administered the dose of corticosteroids in the antenatal

Table 12.12: Ominous features of eclampsia

Long interval between onset of fits and commencement of treatment.
Antepartum eclampsia early in pregnancy.
Number of seizures more than ten.
Systolic BP> 200 mm of Hg.
Temperature > 102°F.
Oliguria.
Non response to treatment.
Jaundice.

Flow chart 12.2: Management of patients with eclampsia



period in anticipation of an emergency preterm delivery. In case an urgent preterm delivery is required, the obstetrician must try to administer at least one dose of corticosteroids, one hour prior to delivery. Patients with severe eclampsia or preeclampsia, who had received even a single dose of IV steroids, one hour prior to delivery, have been observed to be associated with a reduced incidence of intraventricular hemorrhage and necrotizing encephalopathy among the preterm infants.

Intrapartum management

The following steps should be taken during the intrapartum period among the women with severe eclampsia undergoing normal vaginal delivery:

- Second stage of labor should be cut short and assisted operative vaginal delivery (forceps/ vacuum) can be considered.
- Ergometrine at the delivery of anterior shoulder must be withheld as this may result in further increase in the blood

pressure. Due to this, there may be increased chances for development of postpartum hemorrhage. In order to prevent PPH in cases of preeclampsia, the therapeutic modalities listed in table 12.13 can be tried.

Management in the postpartum period

Following delivery, close monitoring should be continued for a minimum of 24 hours. It is important to be vigilant and continue anticonvulsive treatment for first 24–48 hours because eclampsia is likely to occur during this period.

Blood pressure needs to be continuously monitored in the postpartum period. Antihypertensive treatment can then be gradually tapered off depending upon the blood pressure levels.

Mode of delivery

Eclampsia per se is not an indication for cesarean delivery. In case the cervix is not favorable, labor can be induced using vaginal prostaglandins and oxytocin infusion. Indications for cesarean section in cases of eclampsia are listed in table 12.14. If LSCS is decided upon in a case of eclampsia, then the next $MgSO_4$ dose (to be given after 4 hours) may be deferred. This is so because $MgSO_4$ may have a synergistic action with that of muscle relaxants, thereby accentuating the action of muscle relaxants, resulting in uterine atony.

HELLP SYNDROME

About 20% of women with severe preeclampsia may develop a complication called HELLP syndrome (an abbreviation which stands for hemolysis, elevated liver enzymes and low platelet count).

Symptoms

Symptoms may include nausea and vomiting (65%), headache (31%), upper abdominal pain (30%) and general malaise (90%). Since early diagnosis of this syndrome is critical, HELLP syndrome must be suspected in any pregnant woman who presents with malaise, epigastric pain or a viral type illness in presence of preeclampsia. Such women must be evaluated with a complete blood cell count and liver function tests.

Table 12.13: Drugs for controlling PPH in cases with severe preeclampsia

Oxytocin (10 units IV or IM),
Prostaglandin (125 µg or 250 µg IM),
Misoprostol 600 to 1,000 µg (rectal, vaginal, oral)

Table 12.14: Indications for cesarean section in cases with eclampsia

Any obstetric indication (CPD, placenta previa, etc)
Fetal distress
Vaginal delivery is unlikely to occur within a reasonable time frame after the first eclamptic fit

Pathophysiology

The pathophysiology of this multisystem disease can be attributed to abnormal vascular tone, vasospasm and coagulation defects, microvascular endothelial damage and intravascular platelet activation. Activation of platelets can result in the release of thromboxane A_2 and serotonin, causing further vasospasm, platelet agglutination and aggregation and endothelial damage. This cascade is only terminated with delivery.

Diagnosis

The three chief abnormalities found in HELLP syndrome are hemolysis, elevated liver enzyme levels and a low platelet count. Laboratory tests like proteinuria and an increased uric acid concentration, which are usually elevated in cases with preeclampsia, may not be altered in cases with HELLP syndrome.

Platelet count

A low platelet count (<1,00,000/mm^3) is the best indicator of HELLP syndrome. The thrombocytopenia has been attributed to increased consumption and/or destruction of platelets. Platelet counts can drop to as low as 6,000 per mm^3 (6×10^9 per L), but any platelet count less than 150 per mm^3 (150×10^9 per L) warrants attention. Reduction in the values of various clotting parameters, like the prothrombin time, partial thromboplastin time and fibrinogen level (<300 mg per dL) is usually not present in patients with HELLP syndrome, unless there is an associated DIC. Besides the reduction in above mentioned clotting parameters, increase in the levels of D-dimer is a more sensitive indicator of subclinical coagulopathy and may be positive before other coagulation studies become abnormal.

Peripheral smear

The hemolysis in HELLP syndrome results in a microangiopathic hemolytic anemia. Red blood cells become fragmented as they pass through small blood vessels with endothelial damage and fibrin deposits. The peripheral smear may reveal evidence of hemolysis in form of spherocytes, schistocytes, triangular cells and burr cells. Excessive hemolysis may result in increase in serum bilirubin levels ≥ 1.2 mg/dl.

Table 12.15:Classification of HELLP syndrome

Class of HELLP syndrome	*Platelet count*
Class I	Less than 50,000 per mm^3 (50 $x10^9$ per L)
Class II	50,000 to less than 100,000 per mm^3 (50 to 100 x 10^9 per L)
Class III	100,000 to 150,000 per mm^3 (100 to 150 x 10^9 per L)

Liver function tests

Obstruction of hepatic blood flow by fibrin deposits in the sinusoids is thought to result in periportal necrosis and in severe cases, intrahepatic hemorrhage, subcapsular hematoma formation or hepatic rupture. This liver damage manifests in form of elevated liver enzyme levels (AST and ALT ≥ 72 IU/L and LDH > 600 IU/L). Hepatic imaging regardless of the severity of the laboratory abnormalities is useful for assessment of subcapsular hematoma or rupture.

12

Physical examination

The physical examination may be normal in patients with HELLP syndrome. However, right upper quadrant tenderness is present in as many as 90% of affected women. Hypertension and proteinuria may be absent or mild.

Differential Diagnosis

The differential diagnosis of HELLP syndrome includes acute fatty liver of pregnancy, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, viral hepatitis, gall bladder disease, gastroenteritis, kidney stones, pyelonephritis, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, encephalopathy and hyperemesis gravidarum.

Classification

The classification of HELLP syndrome is shown in table 12.15. Patients with class I HELLP syndrome are at a higher risk for maternal morbidity and mortality than patients with class 2 or 3 HELLP syndrome.

Treatment

Management of HELLP syndrome is described in flow chart 12.3. The mainstay of therapy is supportive management, including seizure prophylaxis and blood pressure control in patients with hypertension. Women remote from term should be considered for conservative management, whereas those with period of gestation greater than 34 weeks must be delivered. Some patients may require transfusion of blood products or platelets. Rarely, patients with refractory HELLP syndrome require plasmapheresis.

Previously, when the patients were diagnosed with HELLP syndrome, prompt delivery was recommended. However recent research suggests that morbidity and mortality does not increase when patients with HELLP are treated conservatively. The patient management should be decided on the basis of gestational age and the condition of the mother and fetus. In the past, delivery in patients with HELLP syndrome was routinely accomplished by cesarean section. Patients with severe HELLP syndrome, superimposed DIC or a gestation of less than 32 weeks should be delivered by cesarean section. A trial of labor is appropriate in patients with mild to moderate HELLP syndrome who remain stable, have a favorable cervix and have a period of gestation of 32 weeks of greater. Corticosteroids to achieve pulmonary lung maturity may be administered to women in whom delivery may be required before 32 completed weeks of gestation. The laboratory abnormalities in HELLP syndrome typically worsen after delivery and then begin to resolve by three to four days postpartum.

The various other therapeutic options used in the patients with HELLP syndrome are described below:

Corticosteroids

Patients with HELLP syndrome should be routinely treated with high dose corticosteroids. The antenatal administration of dexamethasone (Decadron) in a high dosage of 10 mg intravenously every 12 hours has been shown to markedly improve the laboratory abnormalities associated with HELLP syndrome. Corticosteroid therapy should be instituted in patients with HELLP syndrome who have a platelet count of less than 100,000 per mm^3 (100 × 10^9 per L) and should be continued until liver function abnormalities have started resolving and the platelet count becomes greater than 100,000 per mm^3 (100 × 10^9 per L).

Magnesium sulfate

Patients with HELLP syndrome should be treated prophylactically with magnesium sulfate to prevent seizures, whether hypertension is present or not.

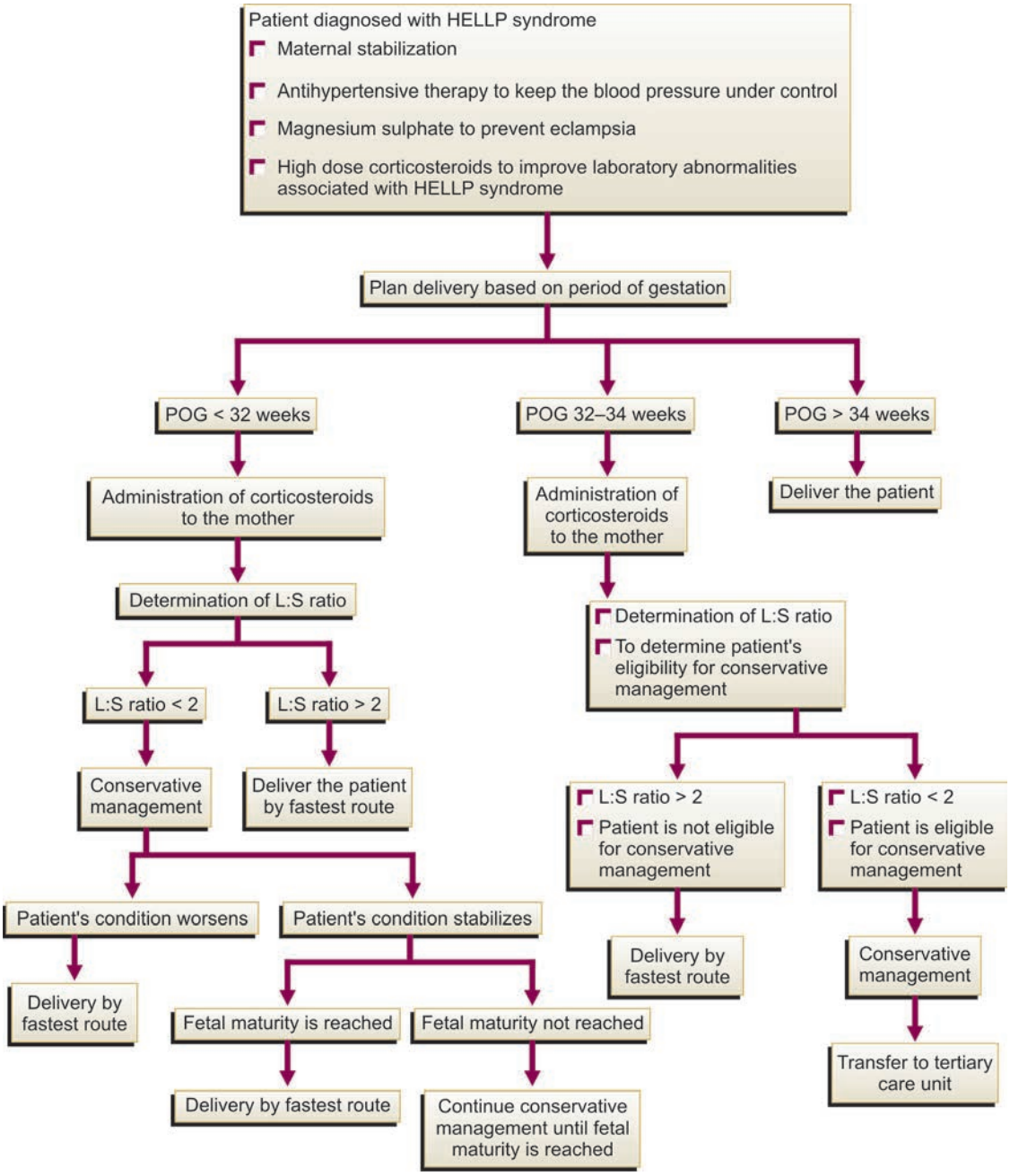
Antihypertensive therapy

Antihypertensive therapy should be initiated if BP remains consistently greater than 160/110 mm Hg despite the use of magnesium sulfate. This reduces the risk of maternal cerebral hemorrhage, placental abruption and seizure. The goal is to maintain diastolic blood pressure between 90 and 100 mm Hg.

Blood transfusion

Nearly half of the patients with HELLP syndrome require transfusion with some form of blood product. Patients with a

Flow chart 12.3: Management of cases with HELLP syndrome



platelet count greater than 40,000 per mm^3 (40×10^9 per L) are unlikely to bleed. These patients do not require transfusion unless the platelet count drops to less than 20,000 per mm^3 (20×10^9 per L). Patients who undergo cesarean section should be transfused if their platelet count is less than 50,000 per mm^3 (50×10^9 per L). Prophylactic transfusion of platelets at delivery does not reduce the incidence of postpartum hemorrhage or hasten normalization of the platelet count. Patients with DIC should be given fresh frozen plasma and packed red blood cells.

Plasmapheresis

Plasmapheresis has been successful in patients with severe laboratory abnormalities i.e., a platelet count of less than 30,000 per mm^3 (30×10^9 per L) and continued elevation of liver function values and those who have required repeat

transfusions to maintain their hematocrit at 72 hours postpartum. In these patients, plasmapheresis has resulted in an increase in the platelet count and a decrease in the lactate dehydrogenase levels.

Complications

HELLP syndrome is associated with high rate of mortality and can cause numerous complications such as DIC, placental abruption, adult respiratory distress syndrome, hepatorenal failure, pulmonary edema, subcapsular hematoma and hepatic rupture. Patients with HELLP syndrome are at an increased risk of developing recurrence in subsequent pregnancies.

Important Questions and Answers

Q.1. How should the patient in above mentioned case study be managed?

Ans. Since the woman appears to be suffering from mild preeclampsia, she should be admitted to hospital for maternal monitoring and fetal assessment (flow chart 12.1). Also, the woman is more than 38 weeks pregnant, therefore she should be delivered as soon as possible.

Q.2. By what method should the woman be delivered?

Ans. In presence of an obstetric indication (fetal malpresentation, placenta previa, etc) or a fetal indication (fetal distress) a cesarean section should be performed. Otherwise, there is no requirement for a cesarean delivery and vaginal route should be the delivery modality of choice. A surgical induction of labor (artificial rupture of membranes) should be performed if the cervix is favorable. If the cervix is not favorable, medical induction of labor using cervical priming with prostaglandin E_2 gel followed by induction with oxytocin may be done.

Q.3. On examining this patient you observe that she has brisk knee jerks. How should this observation alter her management?

Ans. Increased tendon reflexes are a sign of imminent eclampsia. The patient should be considered to be affected with severe preeclampsia, irrespective of the degree of hypertension or the amount of proteinuria. To prevent the development of eclampsia, the patient must be admitted to the hospital and observed. She may be administered magnesium sulfate if required.

Q.4. What is the likely pathophysiology of preeclampsia?

Ans. The exact pathophysiology of preeclampsia is not yet understood. The most likely causes for preeclampsia and their underlying mechanisms are tabulated in table 12.16 and described in flow chart 12.4. Some of these causes are as follows:

Inadequate trophoblastic invasion

Preeclampsia occurs only in the presence of a placenta. Preeclampsia is associated with a failure of the normal invasion of trophoblast cells, resulting in the maladaptation of maternal spiral arterioles (figure 12.4). The maternal arterioles are the source of blood supply to the fetus and inadequate trophoblastic invasion of these spiral vessels, which causes placental insufficiency can interfere with normal villous development. In most cases, poor villous development results in placental insufficiency. Secondary damage, such as fibrin deposition and thrombosis, can then occur within the placenta. These features result in placental insufficiency, which is characteristically present in preeclampsia. These pathological changes may be aggravated due to disorders such as diabetes, hydatidiform mole, multiple pregnancy, etc.

Maternal inflammatory response

Although preeclampsia is a multisystem disorder, the chief pathology underlying preeclampsia is a vascular endothelial dysfunction. This could be related to strong maternal inflammatory response. Cytokines such as tumor necrosis factor (TNF-α) and interleukins are responsible for producing inflammatory damage.

Hereditary factors

Preeclampsia has been considered to be familial, but the exact genetic defect or preeclampsia gene has not yet been identified. A single preeclampsia gene is unlikely; there are probably several modifier genes along with environmental factors. The various genes which have been thought to

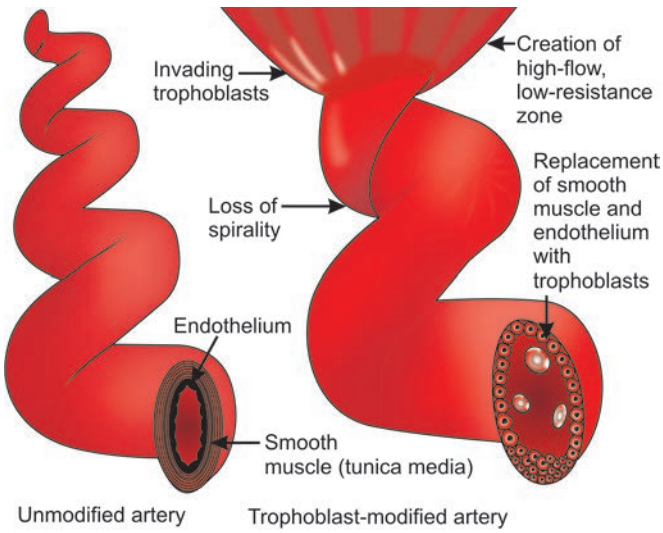


Fig. 12.4: Normal trophoblastic invasion of the spiral vessels

Flow chart 12.4: Pathophysiology of preeclampsia

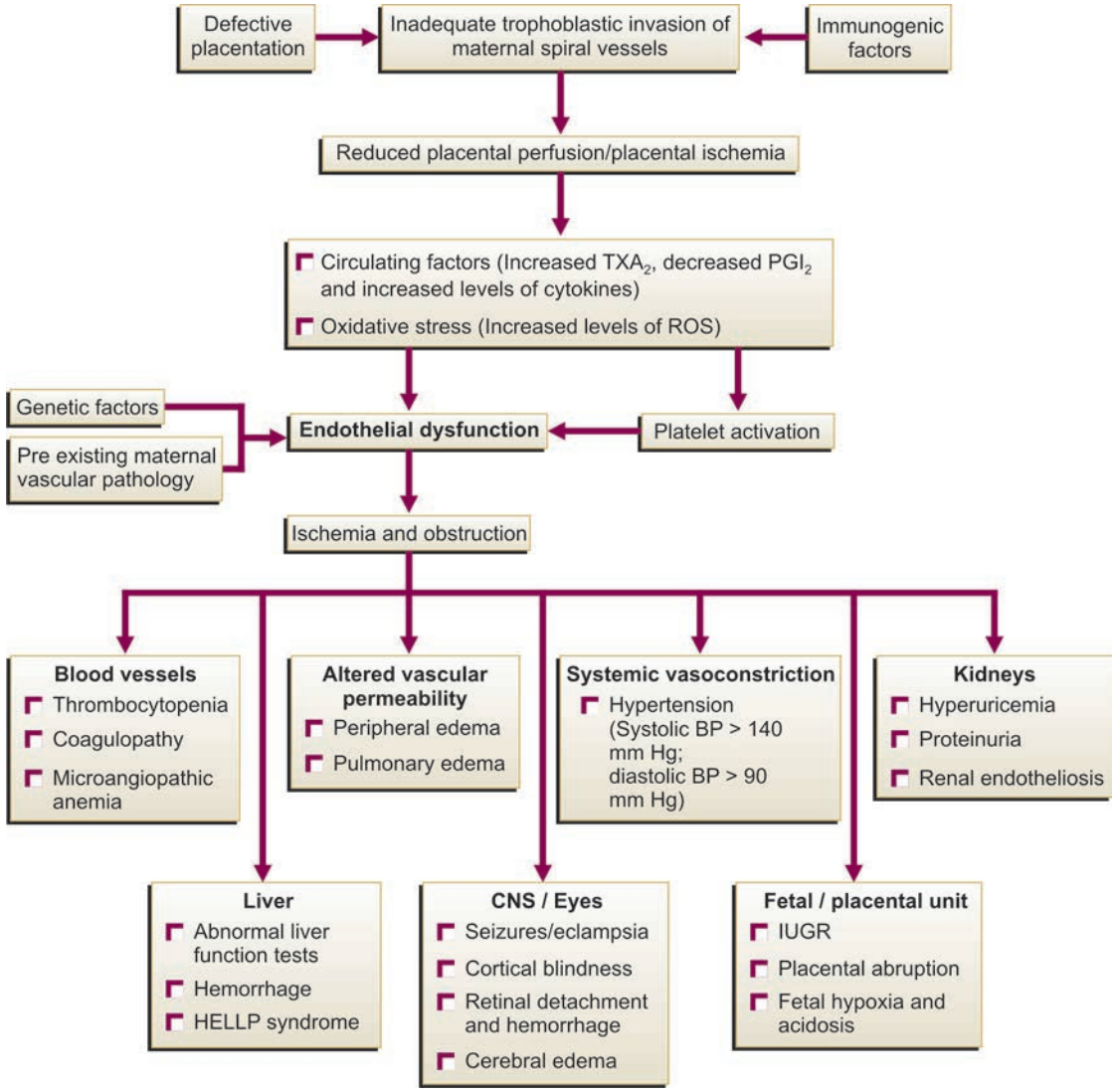


Table 12.16: Pathophysiology of preeclampsia

Likely cause for preeclampsia	*Underlying mechanism*
Inadequate trophoblastic invasion	Insufficient blood flow to the uterus
Prostacyclin/thromboxane imbalance	Disruption of the balance of the hormones that maintain the diameter of the blood vessels.
Endothelial activation and dysfunction	Damage to the endothelial lining of the blood vessels that regulates the diameter of the blood vessels keeping fluid inside and preventing leakage of proteins.
Calcium deficiency, or insufficient magnesium oxide	Calcium helps maintain vasodilation, so a deficiency would impair the function of vasodilation; magnesium stabilizes vascular smooth muscles and helps regulate vascular tone.
Hemodynamic vascular injury	Injury to the blood vessels due to too much blood flow
Immunological activation	The immune system believes that damage has occurred to the endothetial cells and in trying to rectify the problem, it may result in the in the formation of scar tissues, thereby worsening the problem.
Nutritional problems/poor diet	Insufficient protein, excessive protein, not enough fresh fruit and vegetables (antioxidants).
Genetic factors	Exact gene has yet not been identified.

the likely candidates include the genes which encode angiotensinogen, superoxide dismutase, tumor necrosis factor α, methylene-tetrahydrofolate reductase, factor V Leiden and endothelial nitric oxide synthase.

Immunological factors

Risk of development of preeclampsia is especially decreased in when there is impairment in the production of blocking antibodies to various placental antigenic sites. These antigens are responsible for producing damage similar to that occurring in case of acute graft reflection.

Endothelial dysfunction and vasospasm

In the normal pregnancy, the vascular system is refractory to the effect of a potent vasoconstrictor, angiotensin II due to the increased production of an enzyme angiotensinase. This enzyme is produced by the placenta and destroys angiotensin II. In preeclampsia, there is increased vasocontriction due to reduced refractoriness to the action of angiotensin II and due to the imbalance in production of various prostaglandins. There is increased production of vasocontrictors like thromboxane A_2 and reduced production of vasodilatory prostaglandins like prostacyclins.

Q.5. What is the likely cause for proteinuria in cases of preeclampsia?

Ans. Proteinurea is primarily due to the vasospasm and endothelial dysfunction of the endothelial cells lining the afferent glomerular arterioles. This results in an increased permeability of the vessels causing the development of proteinuria. Albumin forms the major component of this proteinurea. However, it is not admissible to use the term albuminuria as small amounts of globulins are also present.

Q.6. What is difference between preeclampsia, toxemia, PET and PIH?

Ans. Toxemia is an older term based on a belief that the condition was the result of toxins (poisons) in the blood. PET (preeclamptic toxemia) is a term used by older physicians in the UK and elsewhere in Europe. PIH, a newer term, stands for pregnancy induced hypertension. The preeclampsia Foundation uses the term "preeclampsia" as an umbrella term to cover all variants of various hypertensive disorders occurring during pregnancy. While to the medical researcher these terms may have subtle differences, they all represent serious conditions that the clinical should not ignore.

Q.7. What is the most common time for occurrence of preeclampsia?

Ans. Preeclampsia develops during pregnancy and so does eclampsia, but 25% of eclampsia cases develop postpartum, most often in the first 4 days. Patients should be evaluated every 1 to 2 week postpartum with periodic BP measurement. If BP remains high even after 8 week postpartum, chronic hypertension should be considered.

Q.8. Is outpatient management appropriate?

Ans. The Working Group reports that hospitalization is frequently recommended for women with new onset preeclampsia. After serial assessment, the setting for continued management can be determined. Hospitalization until delivery, allows rapid intervention for complications.

Q.9. Can anesthesia be used during labor and delivery?

Ans. If required and in the absence of coagulopathy, regional or neuraxial analgesia/anesthesia is preferred.

Q.10. Does invasive hemodynamic monitoring have a role in management?

Ans. Invasive hemodynamic monitoring (e.g., pulmonary artery catheter) may be useful in women with preeclampsia who have severe cardiac or renal disease, pulmonary edema, treatment-refractory hypertension, or unexplained oliguria.

Bibliography

1. ACOG practice bulletin on diagnosing and managing preeclampsia and eclampsia. American Academy of Family Physicians website. Available at: http://www.aafp.org/afp/20020715/practice.html [Accessed April 2009].
2. Brigelius-Flohe R, Kelly FJ, Salonen JT, et al. The European perspective on vitamin E: Current knowledge and future research. Am J Clin Nutr. 2002;76:703-16.
3. Bucher HC, Guyatt GH, Cook RJ, et al. Effect of calcium supplementation on pregnancy induced hypertension and preeclampsia: A metaanalysis of randomized controlled trials. JAMA. 1996;275:1113-7.
4. Caritis S, Sibai B, Hauth J, Lindheimer MD, Klebanoff M, Thom E, et al. Lowdose aspirin to prevent preeclampsia in women at high risk. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. N Engl J Med. 1998;338:701-5.
5. Carroli G, Duley L, Belizan JM, Villar J. Calcium supplementation during pregnancy: A systematic review of randomised controlled trials. Br J Obstet Gynaecol. 1994;101:753-58.
6. Cartis S, Sibai B, Hauth J, et al. Lowdose aspirin to prevent preeclampsia in women at high risk. National institute of child health and human development network of maternal-fetal medicine units. N Engl J Med. 1998;338(11):701-5.
7. Chappell LC, Seed PT, Briley AL, Kelly FJ, Lee R, Hunt BJ, Parmar K, Bewley SJ, Shennan AH, Steer PJ, Poston L. Effect of antioxidants on the occurence of preeclampsia in women at increased risk: A randomised trial. Lancet. 1999;345:810-16.
8. CLASP (Collaborative Lowdose Aspirin Study in Pregnancy). A randomized trial of lowdose aspirin for prevention and treatment of preeclampsia among 9364 pregnant women. Lancet. 1994;343(8898):619-29.

9. Der Simonian R. Metaanalysis in the design and monitoring of clinical trials. Stat Med. 1996;15:1237-48.
10. Duley L, Gulmezoglu AM, Henderson-Smart DJ. Magnesium sulfate and other anticonvulsants for women with preeclampsia (Cochrane Review). The Cochrane Library. 2003:CD000025.
11. Duley L, Gulmezoglu AM. Magnesium sulfate versus lytic cocktail for eclampsia (Cochrane Review). The Cochrane Library. 2003:CD002960.
12. Duley L, Henderson-Smart D, Meher S. Altered dietary salt for preventing preeclampsia, and its complications. Cochrane database of Systematic Reviews. 2005, Issue 4. Art. No. CD005548.
13. Duley L, Henderson-Smart D. Magnesium sulfate versus diazepam for eclampsia (Cochrane Review). The Cochrane Library. 2003:CD000127.
14. Duley L, Henderson-Smart D: Magnesium sulfate versus phenytoin for eclampsia (Cochrane Review). The Cochrane Library. 2003:CD000128.
15. Duley L, Henderson-Smart D. Magnesium sulfate versus diazepam for eclampsia. Cochrane Database Syst Rev. 2000;(2): CD000127.
16. Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the collaborative eclampsia trial. Lancet. 1995;345:1455-63.
17. Gillman MW, Rifas-Shiman SL, Kleinman KP, Rich-Edwards, JW, Lipshultz SE. Maternal Calcium intake and offspring blood pressure. Circulation. 2004;110:1990-5.
18. Gleeson R, Farrell J, Doyle M, Walshe JJ. HELLP syndrome: A condition of varied. presentation. Ir J Med Sci. 1996;165:265-7.
19. Ilekis. J.V., et al. Preeclampsia—A Pressing Problem: An Executive Summary of a National Institute of Child Health and Human Development Workshop. Reproductive Sciences. 2007; 14(6):508-23.
20. Katz VL, Watson WJ, Thorp JM Jr, Hansen W, Bowes WA. Treatment of persistent postpartum HELLP syndrome with plasmapheresis. Am J Perinatol. 1992;9:120-2.
21. Levine RJ, Hauth JC, Curet LB, et al. Trial of calcium to prevent preeclampsia. NJEM. 1997;337:69-77.
22. Lopez-Jaramillo P, Delgado F, Jacome P, Teran E, Ruano C, Rivera J. Calcium supplementation and the risk of preeclampsia in Ecuadorian pregnant teenagers. Obstet Gynecol. 1997; 90:162-7.
23. Magann EF, Chauhan SP, Naef RW, Blake PG, Morrison JC, Martin JN. Standard parameters of preeclampsia: Can the clinician depend upon them to reliably identify the patient with the HELLP syndrome? Aust N Z J Obstet Gynaecol. 1993;33:122-6.
24. Magpie Trial Collaboration Group. Do women with preeclampsia, and their babies, benefit from magnesium sulfate? The Magpie Trial: A randomised placebo controlled trial. Lancet. 2002;359(9321):1877-90.
25. Montan S. Medical prevention of pre-eclampsia. Acta Obstet Gynecol Scand Suppl. 1997;164:111-5.
26. Munday DN, Jones WR. Pregnancy complicated by the antiphospholipid syndrome. Aust N Z J Obstet Gynaecol. 1993; 33:255-8.
27. National high blood pressure education programme: Working group report on high blood pressure in pregnancy. Am J Obstet Gynecol. 2000;183:51.
28. Neiger R, Trofatter MO, Trofatter KF. D-dimer test for early detection of HELLP syndrome. South Med J. 1995;88:416-9.
29. Oslen SF, Secher NJ, Tabor A, et al. Randomised clinical trials of fish oil supplementation in high risk pregnancies. Fish oil trials in pregnancy (FOTIP) team. BJOG. 2000; 107(3):382-95.
30. Podymow T and Phyllis A.Update on the use of antihypertensive drugs in pregnancy. Hypertension. 2008;51:960-69.
31. Rotchell YE, Cruickshank JK, Gay MP, et al. Barbados low dose aspirin study in pregnancy (BLASP): A randomized trial for prevention of preeclampsia and its complications. Br J Obstet Gynaecol. 1998;105(3):286-92.
32. Ruano R, Fontes RS, Zugaib M. Prevention of preeclampsia with lowdose aspirin—A systematic review and metaanalysis of the main randomized controlled trials. Clinics. 2005;60(5): 407-14.
33. Rumbold A, Crowther CA. Vitamin C supplementation in pregnancy. Cochrane Database Syst Rev. 2005;18(2):CD004072.
34. Schroder W, Heyl W. HELLP-syndrome. Difficulties in diagnosis and therapy of a severe form of preeclampsia. Clin Exp Obstet Gynecol. 1993;20:88-94.
35. Sibai BM, Frangieh AY. Management of severe preeclampsia. Curr Opin Obstet Gynecol. 1996;8:110-3.
36. Sibai BM, lipshitz J, Anderson GD, Dilts PV. Reassessment of intravenous MgSO4 therapy in preeclampsia-eclampsia. Obstet Gynecol. 1981;57:199-202.
37. Sibai BM, Mercer BM, Schiff E, Friedman SA. Aggressive versus expectant management of severe preeclampsia at 28 to 32 weeks' gestation: A randomized controlled trial. Am J Obstet Gynecol. 1994;171:818-22.
38. Sibai BM. The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets): Much ado about nothing? Am J Obstet Gynecol. 1990;162:311-6.
39. Villar J, Abdel-Aleem H, Merialdi M, Mathai M, Ali MM, Zavaleta N, Purwar M, Hofmeyr J, Nguyen TN, Campódonico L, Landoulsi S, Carroli G, Lindheimer M. World Health Organization calcium supplementation for the prevention of preeclampsia trial group. World Health Organization randomized trial of calcium supplementation among low calcium intake pregnant women. Am J Obstet Gynecol. 2006;194:639-49.
40. Waisman GD, Mayorga LM, Camera MI, Vignolo CA, Martinotti A. Magnesium plus nifedipine: potentiation of hypotensive effect in preeclampsia? Am J Obstet Gynecol. 1988; 159:308-9.
41. Weinstein L. Syndrome of hemolysis, elevated liver enzymes and low platelet count: A severe consequence of hypertension in pregnancy. Am J Obstet Gynecol. 1982;142:159-67.

Chapter

13

Gestational Diabetes

Case Study

A 30-year-old G2P1L1 with previous history of giving birth to a baby with birth weight of 4.8 kg presented for routine ANC check-up at 20 weeks. The first baby was born by normal vaginal delivery. The diagnosis of gestational diabetes was confirmed in the previous pregnancy. However, the OGTT performed at six weeks postpartum at the time of previous pregnancy was found to be within normal limits.

Introduction

DIABETES MELLITUS

Diabetes mellitus is an endocrine disorder of carbohydrate metabolism, resulting from the lack of action of hormone insulin, produced by the pancreatic β cells, in the body. Due to insulin deficiency, the body is unable to utilize glucose efficiently and is associated with the development of symptoms like polyphagia, polyuria, polydipsia, nocturia, weight loss, exhaustion, electrolyte imbalance, etc. Diabetes can be associated with development of numerous complications related to the disease process and the treatment. This includes complications like diabetic ketoacidosis, hyperosmolar nonketotic diabetic coma, lactic acidosis, hypoglycemia, etc. Longstanding diabetes can result in development of numerous macrovascular and microvascular complications. Macrovascular complications include complications like myocardial infraction, peripheral vascular disease (ischemia, intermittent claudication, etc), stroke, etc. Microvascular complications can include complications like neuropathy, retinopathy, nephropathy, erectile dysfunction, etc.

According to the classification system devised by the WHO and American diabetes Association (ADA), diabetes mellitus has now been classified into two types: Type 1 and type 2 diabetes. The previously used terms NIDDM (non-insulin-dependent diabetes mellitus) and IDDM (insulin-dependent diabetes mellitus) are no longer used. Metabolic changes taking place in diabetes mellitus are shown in the flow chart 13.1 (A and B), whereas different types of diabetes are shown in the table 13.1 below.

Table 13.1: Etiological classification of disorders of diabetes mellitus

Classification	*Criteria*
Type 1	Type 1 A: Due to islet cell autoantibodies Type 1 B: Idiopathic
Type 2	Predominantly due to insulin resistance with relative insulin deficiency.
Other kspecific types	Genetic defects of β-cell function, genetic defect of insulin action, diseases of exocrine pancreas, endocrinopathies, drug or chemical-induced diabetes, diabetes associated with genetic syndromes, immune mediated diabetes, etc.
Gestational diabetes	Diabetes associated with pregnancy.

About 2% to 5% of the total pregnancies may be affected by diabetes. Among pregnancies complicated by diabetes, about 65% cases involve gestational diabetes, whereas 35% cases are associated with preexisting diabetes, of which 25% of cases may be associated with preexisting type 1 diabetes; and 10% may involve preexisting type 2 diabetes.

Depending on the time of onset of diabetes, women can be classified into two types:

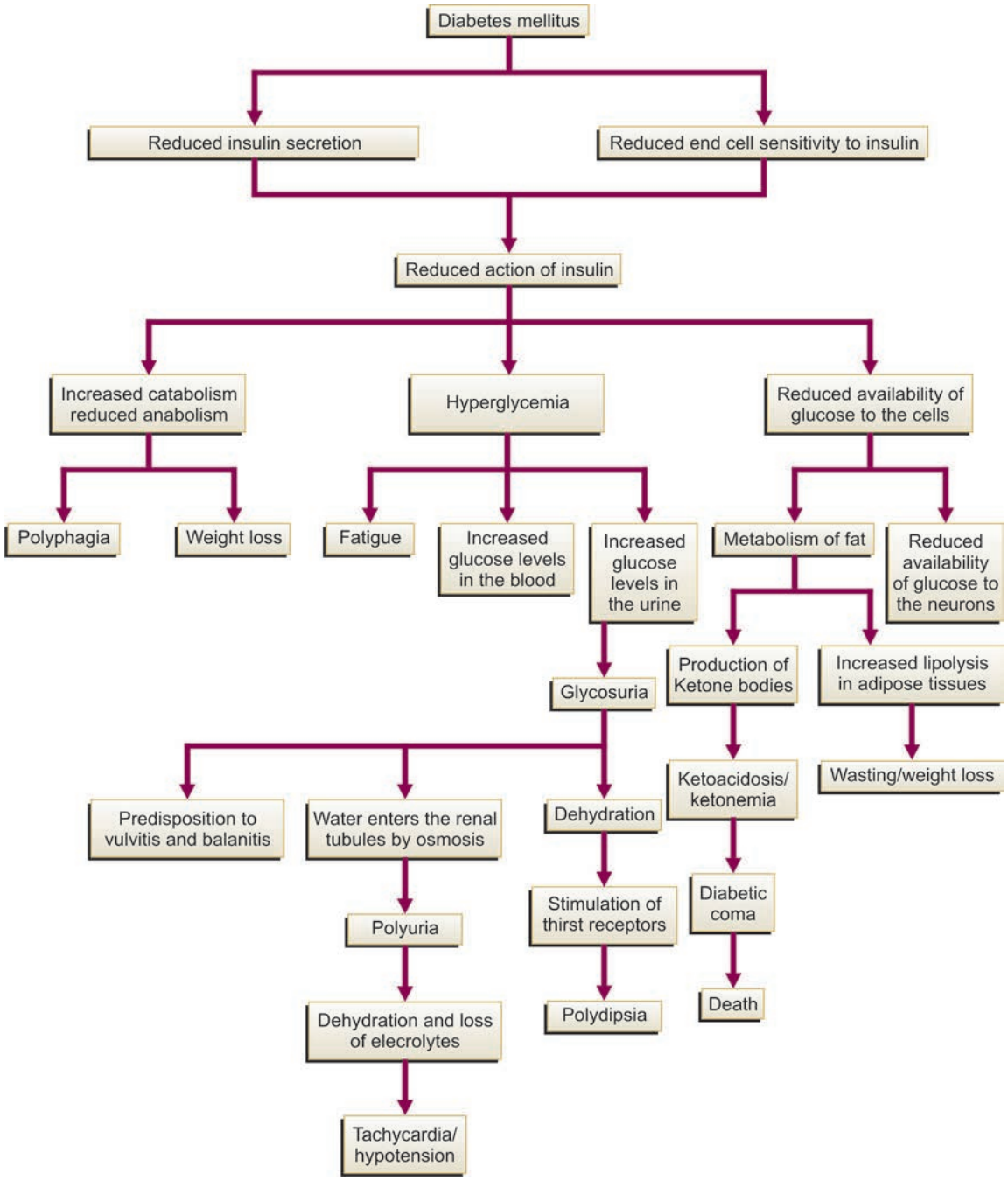
Women with pre-gestational diabetes: Pregnant women in whom diabetes had been diagnosed before pregnancy.

Women with gestational diabetes: Pregnant women in whom diabetes is diagnosed for the first time during pregnancy.

Gestational Diabetes

Women who develop diabetes during pregnancy are said to have gestational diabetes. Gestational diabetes is defined by the world health organization (WHO) as "carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy." Gestational diabetes now includes both gestational impaired glucose tolerance and gestational diabetes mellitus. Some women with gestational diabetes may remain diabetic after delivery of the fetus, while others may revert to apparent normality. Early diagnosis and treatment of gestational diabetes is especially important as it can result in high rates of perinatal mortality and morbidity.

Flow chart 13.1A: Immediate metabolic consequences of diabetes mellitus

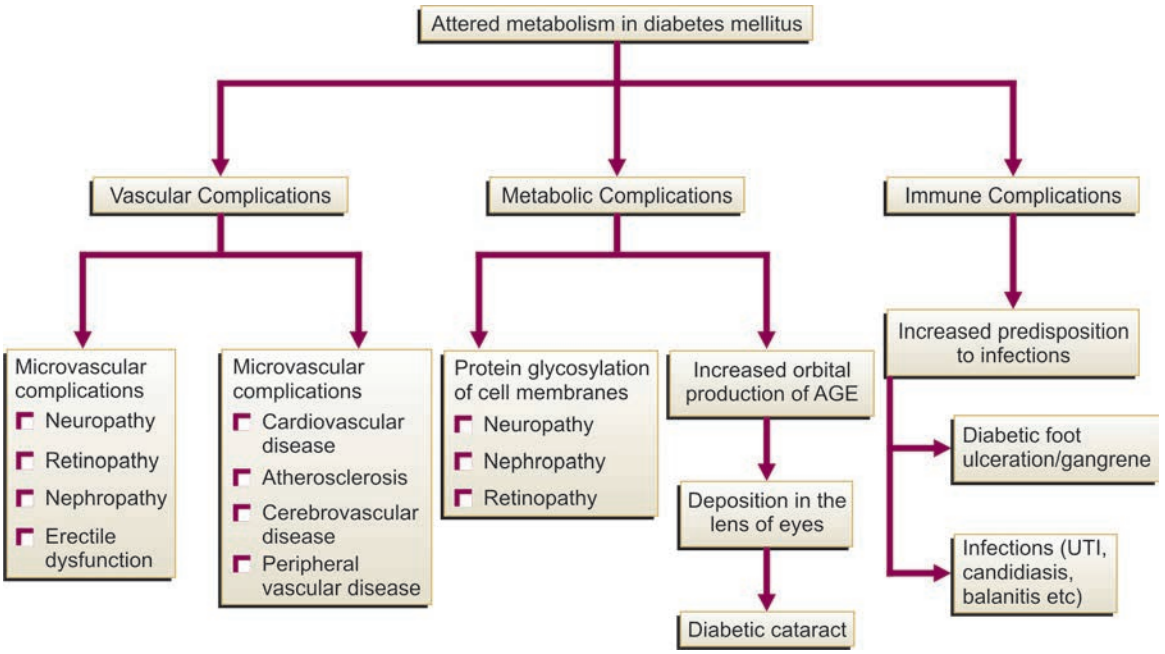


Physiological Effects of Pregnancy on Glucose Metabolism

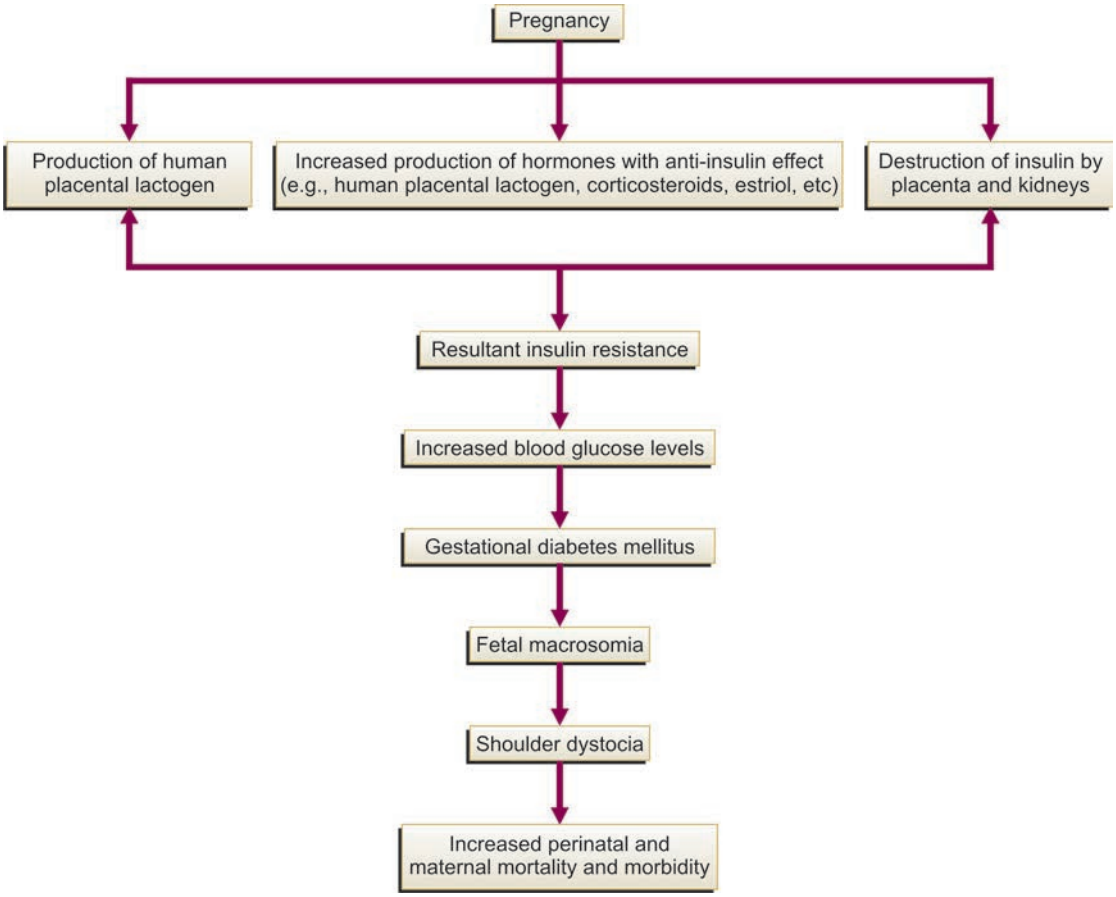
Pregnancy is a diabetogenic state, resulting in development of insulin resistance. In the first half of pregnancy there is an increased sensitivity to insulin and therefore there is a tendency towards development of hypoglycemia. On the other hand, the second half of pregnancy (especially after 24 weeks of gestation) is related with development of insulin resistance. This insulin resistance is thought to be the cause for pathogenesis of gestational diabetes (flow chart 13.2). As a result, insulin requirements decrease during the first trimester and increase progressively from the 2nd trimester until the last month of gestation. Some of these physiological changes are:

- Human placental lactogen, which has antiinsulin and lipolytic effects, is produced late in pregnancy. As a result, the glucose levels in maternal plasma are increased.

Flow chart 13.1B: Delayed complications of diabetes mellitus



Flow chart 13.2: Pathogenesis of gestational diabetes



- Steroid hormones (especially corticosteroids, estriol and progesterone), which are produced late in pregnancy show an anti-insulin effect.
- Some insulin may be destroyed by the placenta and kidneys.
- The diabetogenic effects of pregnancy are increased in presence of maternal obesity and history of gestational diabetes in previous pregnancy.

History

RISK FACTORS

The risk factors which predispose a woman to develop gestational diabetes and need to be elicited while taking the history are described in table 13.2.

Table 13.2: Risk factors for development of diabetes

Body mass index above 30 kg/m^2
Previous macrosomic baby weighing 4.5 kg or above
Previous history of gestational diabetes
Family history of diabetes
Ethnic origin with a high prevalence of diabetes:
– South Asian (specifically women whose country of family origin is India, Pakistan or Bangladesh)
– Black caribbean
– Middle Eastern (specifically women whose country of family origin is Saudi Arabia, United Arab Emirates, Iraq, Jordan, Syria, Oman, Qatar, Kuwait, Lebanon or Egypt)

General Physical Examination

There are no specific findings related to gestational diabetes on general physical examination. However signs suggestive of preeclampsia must be looked for as the women with GDM are especially prone to develop preeclampsia.

Specific Systemic Examination

ABDOMINAL EXAMINATION

Women with GDM are especially prone to develop polyhydramnios. Some signs suggestive of polyhdramnios on abdominal examination are as follows:

- Abdomen is markedly enlarged, along with fullness of flanks. The skin of the abdominal wall appears to be tense, shiny and may show appearance of large stria.
- The patients have a fundal height greater than the period of amenorrhea and fetal parts may not be easily palpable.
- Fetal heart sounds may appear muffled as if coming from a distance.
- A fluid thrill may be commonly present.
- It may be difficult to palpate the uterus or the fetal presenting parts due to presence of excessive fluid.

Since women with GDM are prone to develop macrosomic or IUGR fetuses, signs for both these features must be observed on clinical abdominal examination.

Features suggestive of IUGR are described in chapter 11.

Macrosomic fetus is suggested, in case expected fetal weight on Lepold's maneuver appears to be more than 4.0 kg. However, estimation of fetal weight on Lepold's maneuver has been observed to be grossly inaccurate.

Management

Management comprising of investigations and definitive obstetric management is discussed below.

Investigations

The investigations which need to be done during pregnancy in order to make a diagnosis of gestational diabetes include the following:

Glucose Challenge Test (GCT)

Glucose challenge test is a screening test for gestational diabetes, in which plasma blood glucose levels are measured one hour after giving a 50 gram glucose load to the woman, irrespective of the time of the day or last meals. It is not necessary for the woman to follow a special diet before test or to be in the fasting stage. The timing for this test depends on the woman's likely risk of developing gestational diabetes during her pregnancy. This test need not be routinely performed in women at low risk for diabetes; must be performed at 24–28 weeks in women with average risk of diabetes and as soon as possible in women at high risk for diabetes (table 13.3 and flow chart 13.3). A value of 140 mg/dl or higher indicates high risk for development of gestational diabetes. Some people prefer to use 130 mg/dl as a cutoff threshold, but the number of false positive screening results would be much higher with the 130 mg/dl threshold. An abnormal result on glucose challenge test must be followed by a 100 g oral glucose tolerance test. This is also known as a two step procedure. However, if one hour screening test shows plasma glucose values larger than 200 mg/dl, there is no need for glucose tolerance test. Such large plasma glucose values indicate that the woman is definitely diabetic and her treatment can be started without further testing.

Flow chart 13.3: Screening for diabetes

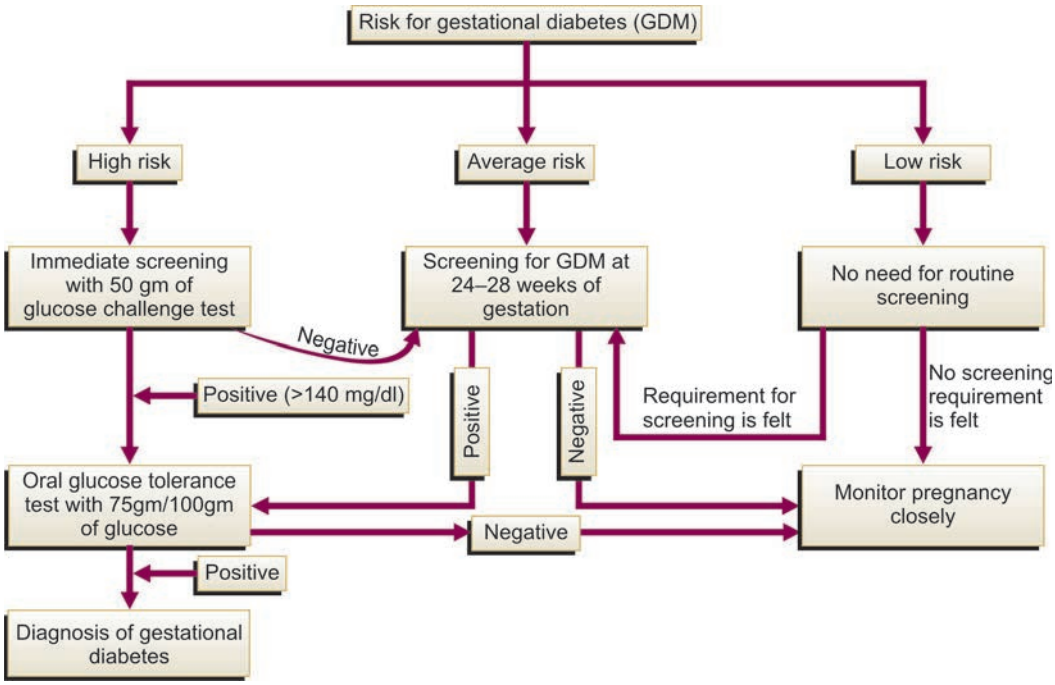


Table 13.3: Timing for GCT based on the woman's likely risk of developing gestational diabetes during pregnancy

Low risk	*Average risk*	*High risk*
Member of an ethnic group with a low prevalence of GDM	Member of an ethnic group with a high prevalence of GDM	Marked obesity
No known history of diabetes in first degree relatives	Overweight before pregnancy	Strong family history of type II DM
Age < 25 years	Diabetes in first degree relatives	Previous history of GDM
Normal weight before pregnancy	Age > 25 years	Previous history of impaired glucose metabolism or glucosuria
No history of abnormal glucose metabolism.		
No previous history of poor obstetrical outcome		
Blood Glucose screening not routinely required	**Blood Glucose testing at 24 – 28 weeks (one or two-step procedure)**	**Perform Glucose testing as soon as possible**

Source: Metzger BE and Coustan DR. Summary and recommendations of the fourth internal workshop-conference on gestational diabetes mellitus. Diabetes Care 1998;21(2):B161.

Oral Glucose Tolerance Test (OGTT)

An abnormal result on glucose challenge test should be followed by an OGTT. This test involves measurement of blood glucose levels at fixed time intervals following the intake of prefixed quantities of glucose. While a 100 grams, 3 hour GTT is a standard in the US, in the UK a 75 grams, two hour GTT is preferred. If the 100 grams 3 hour GTT is used, the diagnosis can be made either using the Carpenter and Coustan criteria (table 13.4) or criteria defined by the National Diabetes Data Group (table 13.5). On the other

Table 13.4: 100 grams glucose load by O'Sullivan and Mahan: Criteria modified by Carpenter and Coustar

Status	*Plasma/serum glucose (mmol/liter)*	*Plasma/serum glucose levels (mg/dl)*
Fasting	≥ 5.8 mol/L	95
One hour	≥ 10.0	180
Two hour	≥ 9.1	155
Three hours	≥ 8.0	140

Source: Carpenter MW & Coustan DR. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol 1982; 144: 768-73.

Table 13.5: National Diabetes Data Group criteria for 100 grams OGTT

Status	*Plasma/serum glucose levels (mmol/liter)*	*Plasma/serum glucose levels (mg/dl)*
Fasting	≥ 5.3 mol/L	105
One hour	≥ 10.0	190
Two hour	≥ 8.6	165
Three hours	≥ 7.8	145

hand, if the 2 hour 75 g oral glucose tolerance test is used, the diagnosis must be made using the criteria defined by the World Health Organization (table 13.6). 75 grams OGTT is performed in the morning after the patient has had at least three days of unrestricted diet comprising of greater than 150 g of carbohydrates. Firstly a fasting blood sample is taken, following which the patient is advised to drink 75 grams of anhydrous glucose in 150–300 ml of water over the course of five minutes. The second blood sample is taken two hours following the glucose load. If two or more of these values on GTT are abnormal, the patient has gestational diabetes (table 13.6). The patient cannot be diagnosed as being a gestational diabetic, if only one value is abnormal. However, she is at an increased risk for developing complications, such as macrosomia (18%) and preeclampsia-eclampsia (7.9%). Even patients who show no abnormal values in their 3-hour GTT have risks of 6.6% and 3.3% for development of macrosomia and preeclampsia-eclampsia respectively. This shows that even small alteration in maternal carbohydrate metabolism may have a significant impact on the fetus. Thus the obstetrician needs to maintain strict glycemic control in order to decrease the frequency of the abnormal outcomes to both the mother and fetus at the time of pregnancy.

Rx Treatment/Obstetric Management

Diagnosis and treatment of gestational diabetes is of extreme importance. If gestational diabetes is not detected and controlled on time, it can result in high rates of perinatal morbidity and mortality, primarily related to the development of complications such as macrosomia and shoulder dystocia. These complications may be associated with an increased risk of birth trauma, induction of labor and cesarean section. Gestational diabetes also increases the risk of the baby developing obesity and/or diabetes in later life. Controlling the patient's blood sugar level is the best way for preventing various diabetes related complications, including the risk of miscarriage, stillbirth and congenital malformations, particularly those affecting the brain, spine and heart, etc. The definitive management of the pregnant diabetic patient is best undertaken using a multidisciplinary team approach involving an obstetrician, midwife, physician, endocrinologist, diabetologist, neonatalogist, etc. The two main aims for management of diabetic patient during pregnancy are as follows:

- Maintenance of blood glucose levels
- Regular fetal monitoring.

Monitoring in the Preconceptional Period

For women with pregestational diabetes, the blood glucose levels need to be controlled right since the preconceptional period. The following steps need to be taken to monitor the women during the preconceptional period:

Measurement of HbA1c levels: Monthly measurement of the glycosylated hemoglobin levels give an idea about the patient's blood glucose levels over past few months. The clinician's aim must be to maintain the levels of HbA1c below 6.1%. Increased level of glycosylated hemoglobin is associated with higher rates of complications at the time of pregnancy. Thus the women whose HbA1c is above 10% should be strongly advised to avoid pregnancy and use contraception until their glycosylated hemoglobin levels come within the normal limits.

Self-monitoring of blood glucose levels: Self-monitoring of blood glucose levels using a glucose meter must be offered to all diabetic women planning for pregnancy. These women need to be educated regarding the importance of maintaining adequate levels of glucose in their body. These women should be advised to test their blood glucose levels at least four times a day, including fasting blood glucose levels and blood glucose levels one hour after every meal.

Testing for blood and urine ketone levels: Women with type 1 diabetes who are planning pregnancy should be advised to use ketone testing strips and test for ketonuria in their urine samples, especially if their blood glucose levels show hyperglycemia.

Discontinuation of various drugs during pregnancy: Lipid lowering drugs including statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin, etc) should

Table 13.6: World Health criteria for 75 grams OGTT

	Whole blood venous	*Whole blood capillary*	*Plasma venous*	*Plasma capillary*
Fasting	≥ 6.1 mmol/L	≥ 6.1 mmol/L	≥ 7.0 mmol/L (126 mg/dl)	≥ 7.0 mmol/L
2 hours	≥ 6.7 mmol/L	≥ 6.7 mmol/L	≥ 7.8 mmol/L (140 mg/dl)	≥ 8.9 mmol/L

be discontinued before pregnancy or as soon as the pregnancy is confirmed.

If the woman has been using antihypertensive agents like angiotensin converting enzyme inhibitors and angiotensin-II receptor antagonists, they should be discontinued before conception or as soon as pregnancy is confirmed because of the possible risk of congenital malformations (skull defects and oligohydramnios). She should be prescribed safer alternative antihypertensive drugs, suitable for use during pregnancy. Calcium channel blockers should be avoided throughout pregnancy because of the risk of disruption to labor and fetal hypoxia. However, in case the clinicians feel that the risk of uncontrolled maternal hypertension is greater than the fetal risk, nifedipene may be continued.

Whereas all the oral hypoglycemic drugs need to be discontinued before pregnancy, women with diabetes may be advised to use metformin as an adjunct or alternative to insulin in the preconception period and during pregnancy. There is strong evidence for the effectiveness and safety of metformin.

Retinal assessment in the preconception period: Women with pregestational diabetes planning pregnancy must be offered retinal assessment at the time of their first preconception appointment. This may not be required if an annual retinal assessment has taken place within the last six months. If no changes related to diabetic retinopathy are found at the time of initial examination, annual retinal assessment is required.

Renal assessment in the preconception period: Women with diabetes should be offered a renal assessment, including a measure of microalbuminuria, before planning pregnancy. She should be referred to a nephrologists, if serum creatinine is abnormal (≥ 120 µmol/liter) or the estimated glomerular filtration rate (eGFR) is less than 45 ml/minute/1.73 m^2.

Maintenance of adequate body weight: Women with diabetes who are planning to become pregnant and who have a body mass index above 27 kg/m^2 should be offered advice on how to lose weight.

Regular intake of folic acid: Women with diabetes who are planning to become pregnant should be advised to take folic acid in the dose of 5 mg/day, starting right from the periconceptional period and through out the period of gestation. This would help in reducing the risk of having a baby with neural tube defects.

MANAGEMENT DURING THE ANTENATAL PERIOD

The following advice needs to be given to the woman with GDM during the antenatal period (table 13.7):

- Antenatal care in patients with GDM should preferably be hospital-based, involving a multi-disciplinary team approach comprising of an endocrinologist, obstetrician and pediatrician. The blood glucose levels need to be assessed every 1 to 2 weeks throughout pregnancy.
- *Requirement for hypoglycemic therapy:* The clinician needs to substitute oral hypoglycemic drugs with insulin. The insulin regimen need to be individualized and the patient must be advised to check their blood glucose levels at least four times a day. The women must be encouraged to monitor their blood glucose regularly and to adjust their insulin dosage in order to maintain their blood glucose levels within the normal (non-diabetic) range. The aim should be to maintain her HbA1c levels below 7.0% and glucose levels within 4–7 mmol/L. HbA1c should not be used routinely for assessing glycemic control in the second and third trimesters of pregnancy. Diabetic ketoacidosis is a serious complication which can cause fetal death at any stage. All diabetic women should also test their urine for ketones, especially if their blood glucose levels are high, if vomiting occurs or if they are unwell.
- *Retinal assessment during pregnancy:* Pregnant women with preexisting diabetes should be offered retinal assessment by digital imaging with mydriasis using tropicamide. This can be offered following their first antenatal clinic appointment and again at 28 weeks if the first assessment is normal. If any diabetic retinopathy is present, an additional retinal assessment should be performed at 16–20 weeks. Women, in whom preproliferative diabetic retinopathy has been diagnosed during pregnancy, should have ophthalmological follow up for at least 6 months following the birth of the baby. Diabetic retinopathy should not be considered a contraindication to vaginal birth.
- *Renal assessment during pregnancy:* Diabetic nephropathy is a progressive disease that can be divided into the following stages:
  - Microalbuminuria (incipient nephropathy), which can be defined as albumin: Creatinine ratio of ≥ 3.5 mg/mmol or albumin concentration of ≥ 20 mg/liter.

Table 13.7: Specific antenatal care for women with pregestational diabetes and GDM

Education and information regarding diabetes, hypoglycemia, self-monitoring of blood glucose levels, etc.
Advice and support in relation to optimizing glycemic control.
If case of previously diabetic women, oral diabetes medication needs to be changed to insulin. In case of women with gestational diabetes, initial control of blood glucose levels must be through diet and nutritional advice. If these options do not work, insulin may be advised.
Retinal and/or renal assessment must be offered if these have not been undertaken in the previous 12 months.

- Macroalbuminuria or proteinuria (overt nephropathy), which is defined as albumin: Creatinine ratio of ≥ 30 mg/mmol or albumin concentration of ≥ 200 mg/liter as a result of widespread glomerular sclerosis;
- End-stage renal disease, which is associated with decreasing creatinine clearance, increasing serum creatinine levels and uremia.

Women with diabetic nephropathy are at increased risk of adverse pregnancy outcomes, in particular IUGR, chronic hypertension, preeclampsia and preterm birth. If renal assessment has not been undertaken in the preceding 12 months in women with preexisting diabetes, it should be arranged at the time of first contact in pregnancy. If serum creatinine is abnormal (≥120 micromol/liter) or if total protein excretion exceeds 2 g/day, referral to a nephrologist should be considered (eGFR as used during the preconceptional period should not be used during pregnancy).

Diabetes education and information: The obstetrician needs to discuss information regarding the effect of diabetes on pregnancy; importance of blood glucose control at the time of pregnancy; changes in the hypoglycemic therapy during and after birth; complications related to use of insulin therapy (e.g. hypoglycemia); advice regarding timing, mode of delivery and management of birth; management of the baby after birth; and advice related to early parenting (including breastfeeding and initial care of the baby); contraception and follow up.

Exercise and Diet Therapy in the Antenatal Period

The first line therapy for the women with gestational diabetes is exercise and diet therapy. The women must be advised to take moderate exercise for at least 30 minutes daily.

Proper nutritional advice is one of the most important components of the care of women with GDM. The objective of nutritional treatment is to provide a healthy diet, which contains the necessary calories and nutrients, to both mother and the fetus without causing postprandial hyperglycemia. Since the carbohydrate content of the food is likely to increase the blood glucose levels, women with gestational diabetes should be preferably advised to choose carbohydrates having low glycemic index. The amount of calorie consumption per day based on the woman's body mass index, (calculated by dividing an individual's weight in kilograms by the square of her height in meters), is shown in the table 13.8. Women with gestational diabetes whose prepregnancy body mass index was between 25.9–29.9 kg/m² should be advised to restrict their calorie intake to 25 kcal/kg/day or less; women with the normal body weight (BMI between 18.5–24.9 Kg/m^2 must consume approximately 30 Kcal/Kg/day; calorie consumption must be approximately 35–40 Kcal/kg/day for women who are underweight (BMI < 18.5); 20 Kcal/kg/day per day for women with moderate and severe obesity (BMI between 30.0–49.9) and 12 Kcal/kg/day for morbidly obese women (BMI ≥ 50).

Table 13.8: Calorie intake in diabetic women based on their BMI

BMI	*Interpretation*	*Calorie intake*
BMI ≤ 18.5	Underweight	35–40 Kcal/kg/day
BMI of 18.5–24.9	Normal	30 Kcal/kg/day
BMI of 25.0–29.9	Overweight	25 Kcal/kg/day
BMI of 30.0–39.9	Moderate obesity	20 Kcal/kg/day
BMI of 40–49.9	Severe obesity	20 Kcal/kg/day
BMI ≥ 50	Very severe obesity	12 Kcal/kg/day

This total calorie intake must be distributed in form of multiple small evenly spaced meals and snacks throughout the day, e.g. three small meals in morning, afternoon and night and three snacks in mid-morning, mid-afternoon and a bedtime snack. The bedtime snack is particularly important as it helps in avoiding overnight hypoglycemia and ketosis. Of the total calorie intake, 40% to 50% must come from carbohydrates; 30% to 40% from fats (two thirds of which should be unsaturated fats and remaining one third should be saturated fats); and 15% to 20% must come from proteins. The woman must be advised to consume lean proteins including oily fish and avoid red meat (beef, pork, etc) and also must increase her consumption of polyunsaturated fats in comparison to the monounsaturated or saturated fats. She must also be advised to restrict her intake of refine sugars and increase her daily consumption of fibers.

Diabetic food pyramid

The meal plan for a diabetic individual can be based on the "Diabetes Food Pyramid" which is shown in figure 13.1A. This has been designed by the American Diabetes Association and the American Dietetic Association. This diabetes meal plan looks very much like the US department of agriculture's food guide pyramid. Similar to the USDA's Food Guide Pyramid, the diabetes food pyramid suggests that the individual must try to obtain the bulk of calories from fruits, vegetables, whole grains and low-fat dairy products. The food must be low in saturated fats, transfats, cholesterol, salt and added sugars. The diabetes food pyramid differs from the standard food guide pyramid in the way it groups different foods together. For example, in the standard pyramid, beans and legumes are grouped with meats, due to their protein content. In the diabetes pyramid, however, beans are grouped with starches, because they affect blood glucose in the same way that starchy foods do. Since blood glucose levels are of

primary concern to people with diabetes, the Diabetes Food Pyramid focuses on the way in which certain foods affect blood glucose levels. Under this plan, 60% to 70% of the total daily calories should come from grains, beans and starchy vegetables, with the rest coming from meat, cheese, fish and other proteins. Fats, oils and sweets should be used sparingly. The women should be advised to eat more from the groups at the bottom of the pyramid and less from the groups at the top. The healthy meal of a diabetic individual should comprise of one third carbohydrates (grains, beans, etc), one third vegetables and one third should be in form of proteins, fats, low fat dairy products and refined sugars (figure 13.1B).

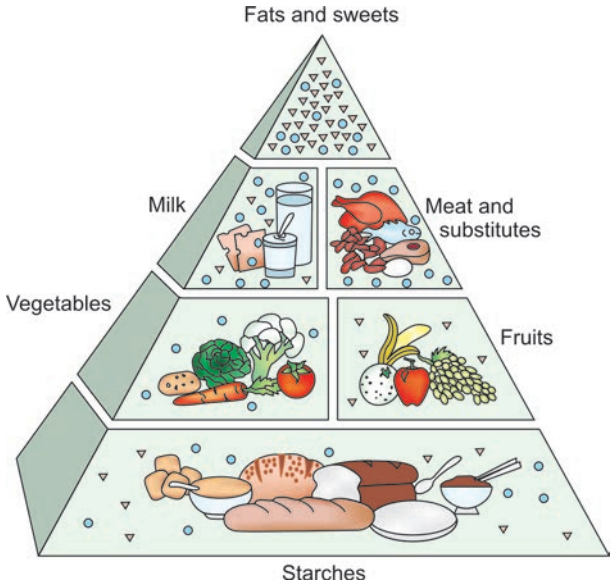


Fig. 13.1A: Diabetes food pyramid

Antihypoglycemic Therapy in the Antenatal Period

Most cases of gestational diabetes will respond to changes in diet and exercise. Hypoglycemic therapy should be considered for women with gestational diabetes if diet and exercise fail to maintain blood glucose targets during a period of 1–2 weeks. ACOG does not recommend the use of oral hypoglycemic agents during pregnancy. This is so as most of the oral hypoglycemic agents are capable of crossing placenta and can therefore cause fetal hypoglycemia. If the women with pregestational type 2 diabetes had been taking oral hypoglycemic drugs, these need to be substituted with insulin. The objective of the treatment is to maintain the fasting capillary glucose (FCG) values under 95 mg/dl and 1 or 2 hour postprandial values under 140 mg/dl and 120 mg/dl, respectively.

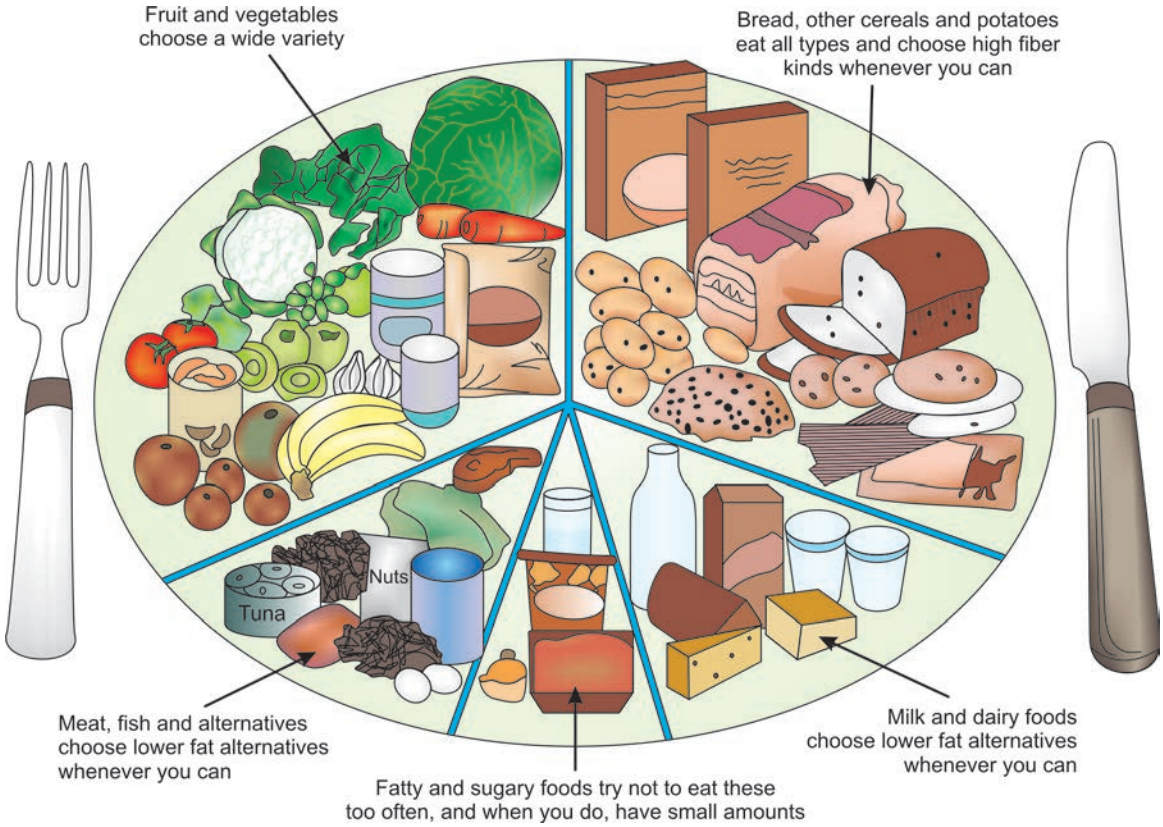


Fig. 13.1B: Components of a healthy diet for a diabetic patient

Insulin therapy

Insulin therapy may include regular insulin, or rapid-acting insulin analogues (aspart and lispro). Presently, there is insufficient evidence regarding the use of long-acting insulin analogues (insulin glargine, protamine zinc insulin, etc) during pregnancy. Therefore isophane insulin (intermediate-acting insulin) is used during pregnancy. The National Service Framework for Diabetes (NSF for diabetes, 2002) recommends that women with type 2 diabetes who require treatment with oral hypoglycemic agents and are planning to become pregnant or are already pregnant should be transferred to insulin therapy because of the theoretical risk associated with these drugs crossing the placenta. Clinicians must be aware that the rapid acting insulin analogues (aspart and lispro) have advantages over soluble regular human insulin during pregnancy and therefore should be preferred over regular insulin.

Hypoglycemia and loss of hypoglycemic awareness is common during early pregnancy. The women with insulin treated diabetes are especially at risk of developing hypoglycemia and hypoglycemia-unawareness in pregnancy, particularly in the first trimester. The women must be educated about dealing with hypoglycemia. She must be advised to carry sugar candies or glucose tablets with her all the time. The women, her partner or other family members should be educated regarding the use of glucagon injections. The moment she experiences any symptoms related to hypoglycemia, she should eat the candies. In case of severe symptoms related to hypoglycemia, intramuscular glucagon injection may be required.

During pregnancy, women are usually prescribed four-daily insulin injections (three injections of regular insulin to be taken before each meal and one injection of isophane insulin to be taken at night time). In case adequate blood glucose control in not achieved with insulin injections, the woman should be offered continuous subcutaneous insulin infusion (CSII). Presently, there are no randomized controlled trials, which show advantage or disadvantage of using CSII pumps over intermittent insulin injections during pregnancy. Insulin should be commenced if the blood glucose criteria mentioned in table 13.9 are met.

If it is safely achievable, women with diabetes should aim to keep fasting blood glucose between 3.5 and 5.9 mmol/ liter and 1 hour postprandial blood glucose below 7.8 mmol/liter during pregnancy (table 13.10).

Sites for insulin injections

The common sites in the body (figure 13.2) for injecting insulin include the following:

- The upper lateral area of the thighs.

Table 13.9: Indications for starting insulin therapy

Capillary blood glucose levels	*Plasma blood glucose levels*
Fasting whole blood glucose is >5.3 mmol/L	Plasma glucose >5.8mmol/L
1-hourly postprandial whole blood glucose is >7.8 mmol/L	Plasma glucose >8.6 mmol/L

Table 13.10: Target ranges for blood glucose during pregnancy

Fasting blood glucose between 3.5 and 5.9 mmol/liter
1-hour postprandial blood glucose below 7.8 mmol/liter

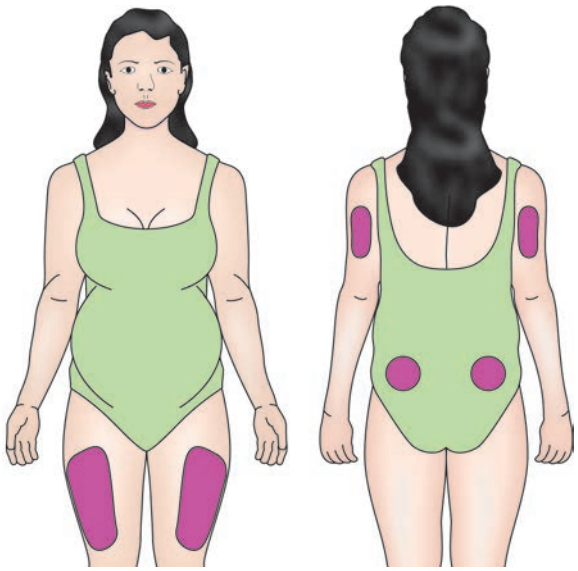


Fig. 13.2: Sites of insulin injection

- The upper outer area of the back of the arms.
- The buttocks.

Education Regarding Diabetes

Women with diabetes who are planning to become pregnant should be informed that establishing good glycemic control before conception and continuing this throughout pregnancy will help in reducing the risk of miscarriage, congenital malformation, stillbirth and neonatal deaths. The importance of avoiding unplanned pregnancy should be an essential component of education for diabetic women, starting right from adolescence. The women must be advised to use contraception, until pregnancy is planned. Women with diabetes who are planning to become pregnant and their families should be offered information regarding how diabetes affects pregnancy (table 13.11) and how pregnancy affects diabetes (table 13.12). The information should cover:

- The role of diet, body weight and exercise.

Table 13.11: The effect of diabetes on pregnancy

Need for strict glycemic control during pregnancy.
Need for pregnancy planning.
Risk for increased fetal complications including the risk for congenital malformations, macrosomia, shoulder dystocia, birth injuries, etc.
Increased risk for maternal complications including miscarriage, preeclampsia, hydramnios, preterm labor, increased rate of cesarean section, etc.
Requirement for strict fetal surveillance.
General anesthesia in women with diabetes can increase the risk of hypoglycemia.

Table 13.12: The effect of pregnancy on diabetes

Changes in the eating pattern.
Decreased insulin requirement during the first half of pregnancy followed by increased insulin requirement during the second half of pregnancy.
Increased risk for hypoglycemia and decreased hypoglycemia awareness during pregnancy.
Deterioration of retinopathy and nephropathy in patients with pregestational diabetes.
Reduced renal threshold for glycosuria.
Disrupted blood glucose control due to nausea and vomiting during pregnancy.
Hyperemesis gravidarum in women with diabetes can lead to ketoacidosis.

- The risks of hypoglycemia and hypoglycemia-unawareness during pregnancy.
- How nausea and vomiting in pregnancy can affect glycemic control.
- The increased risk of having a baby who is large for gestational age, which increases the likelihood of birth trauma, induction of labor and cesarean section.
- The need for assessment of diabetic retinopathy and nephropathy before and during pregnancy (especially in women with pregestational diabetes).
- The women should be explained about the importance of maternal glycemic control during labor and birth and early feeding of the baby in order to reduce the risk of neonatal hypoglycemia.
- The patient must be instructed not to skip doses of insulin. She should be advised not to smoke, or drink alcohol or abuse illicit drugs.
- Monthly measurement of HbA1c levels in the preconceptional period and the third trimester of pregnancy must be advised.

Fetal Monitoring During the Antenatal Period

The schedule of various tests for fetal surveillance during the antenatal period is described in table 13.13.

Screening for congenital malformations

Since the fetuses of diabetic women are at a particularly high risk of congenital malformations, screening for these malformations must be started as soon as possible. First trimester ultrasound scan at 11–13 weeks must be done to look for nuchal translucency as there is an increased risk of neural tube defects. Maternal serum screening for α-fetal proteins at 16–18 weeks must be done to rule out the risk for neural tube defects. Second trimester ultrasound scan for detailed scanning for fetal congenital anomalies including four-chamber view of the fetal heart and outflow tracts must be done at 18–20 weeks.

The methods of fetal surveillance for monitoring fetal wellbeing depend on whether the patients are low risk or high risk, both of which are described below:

Low-risk patients

Low-risk gestational diabetic patients who have achieved adequate glycemic control with diet and exercise and do not develop any of the complications related to gestational diabetes including macrosomia, polyhydramnios, or preeclampsia need not be admitted to the hospital. They must be seen in

Table 13.13: Fetal surveillance during the antenatal period

Period of gestation	*Test for fetal surveillance*	*Parameter observed*
28, 32, 36 weeks	Third trimester ultrasound scan Daily fetal movement count	Fetal growth assessment and amniotic fluid volume. Less that 10 movements in one hour suggestive of fetal distress.
Twice weekly, starting from 28 weeks onwards	Non-stress test	Presence of two or more accelerations that peak 15 beats per minute above the baseline, each lasting for 15 seconds or more and all occurring within a 20 minutes period from beginning the test.
To be done on weekly basis starting from 28 weeks onwards	Fetal biophysical profile/or at least amniotic fluid volume	A BPP test score of at least 8 out of 10 is considered reassuring. A score of 6 or 7 out of 10 is equivocal and must be repeated within 24 hours. A score of 4 or less is a positive test and strongly suggests preparing the patient for delivery.
Monthly ultrasound starting at 32–36 weeks	Ultrasound	Estimation of fetal weight

the clinic on biweekly basis from 36 weeks onwards. In these cases, NST must be done during each visit.

High-risk patients

High-risk gestational diabetics and patients on oral antihypoglycemic therapy and/or insulin should have antepartum fetal surveillance testing starting at 28–32 weeks of the gestation (table 13.3). Biweekly non-stress tests are most commonly performed starting from 28 weeks onwards. Ultrasound monitoring of fetal growth, estimated fetal weight and amniotic fluid volume needs to be done on monthly basis, starting from 28 to 36 weeks. The biophysical profile (BPP) or at least the amniotic volume is performed on weekly basis from 28 weeks onwards. Women with diabetes and a risk of intrauterine growth restriction (macrovascular disease and/or nephropathy) require an individualised approach for monitoring fetal growth and wellbeing. Umbilical artery Doppler ultrasound can be done every 3 to 4 weekly in IUGR fetuses.

Timing and Mode of Birth

- *Low-risk patients:* There is no need to deliver low risk gestational diabetic patients before term. These women may be allowed to develop spontaneous labor and to deliver by 38–40 weeks of gestation.However, there is no need to wait beyond forty completed weeks of gestation. Once the uncomplicated gestational diabetic patient reaches 40 weeks, labor should be induced. Cesarean delivery may be required, if the estimated fetal weight is greater than 4000 g or some other obstetrical indication for cesarean delivery is present.
- *High-risk patients:* High risk gestational diabetic patients should have their labor induced when they reach 38 weeks. Cesarean delivery may be required, if the estimated fetal weight is greater than 4000 g (macrosomia) or some other obstetrical indication for cesarean delivery is present. If delivered vaginally, macrosomic babies are at an increased risk of shoulder dystocia.

Diabetes should not in itself be considered a contraindication for attempting vaginal birth after a previous cesarean section. Pregnant women with diabetes who have an ultrasound-diagnosed macrosomic fetus should be informed of the risks and benefits of vaginal birth, induction of labor and cesarean section. The final decision regarding the mode of delivery depends on the patient's wishes and the obstetrician's judgement. The ACOG recommends an elective cesarean section in women with sonographically estimated fetal weight of 4.5 kg.

Management During the Intrapartum Period

The two main goals of intrapartum management include avoidance of shoulder dystocia and maintenance of blood glucose levels. The following precautions should be taken during the intrapartum period:

- During the time of labor and birth, capillary blood glucose should be monitored on an hourly basis in women with diabetes and maintained at the levels between 4–7 mmol/liter by using intravenous dextrose and insulin infusion.
- Babies born with gestational diabetes are particularly at risk of developing neonatal hypoglycemia. Early feeding of the neonate is recommended for reducing the risk of neonatal hypoglycemia.
- The use of corticosteroids for pulmonary maturity in diabetic women, in whom preterm delivery may be required, is considered controversial as the administration of steroids in diabetic women may cause significant worsening of glycemic control requiring an increase in insulin dose. However diabetes should not be considered a contraindication for administration of antenatal steroids in order to achieve fetal pulmonary maturation. Insulin-treated diabetic individuals who are receiving steroids for fetal lung maturation should be closely monitored for their blood glucose levels and can be given additional insulin according to a pre-agreed protocol.
- Anesthetic assessment must be offered to women with diabetes and comorbidities such as obesity or autonomic neuropathy during the third trimester of pregnancy. If general anesthesia is used at the time of cesarean section in women with diabetes, blood glucose levels should be monitored regularly, preferably at every half hourly interval, starting right from the induction of general anesthesia until after the baby is born and the woman becomes fully conscious. General anesthesia in women is associated with high risk of hypoglycemia. These women also have a high rate of Mendelson syndrome due to the higher resting gastric volume compared to women without diabetes.
- Betamimetic drugs should not be used for tocolysis in women with diabetes due to the tendency of betamimetics to cause hyperglycemia and ketoacidosis.
- Delivery should be by the vaginal route unless there are obstetric contraindications.
- Since fetal distress is more common in diabetic women, continuous external or internal CTG monitoring is required at the time of labor. Fetal scalp blood may also be analysed in case of non-reassuring fetal heart trace.
- Capillary blood glucose levels must be checked frequently using finger stick at every one-two hourly intervals and regular insulin must be administered accordingly (table 13.14). The target range for glucose concentration is 4.0–8.0 mMol /L. Insulin requirement during labor may fall due to uterine contractions. Two separate intravenous lines must be started: One for IV infusion of short-acting insulin (50 units human actrapid in 50 ml of normal saline

Table 13.14: Low dose insulin infusion for diabetic women during the intrapartum period

Blood glucose (g/dl)	*Insulin dosage (U/hr)*	*Intravenous fluids (125 ml/hr)*
< 100	0	D_5 lactated ringer
100–140	1.0	D_5 lactated ringer
141–180	1.5	Normal saline
181–220	2.0	Normal saline
>220	2.5	Normal saline

Table 13.15: Insulin requirements at the time of labor

Day before induction	*Day of induction*
Normal diet to be given	Administration of half the morning dose of regular insulin before a light breakfast
Normal insulin dose, an evening before induction	IV infusion to be started once the labor establishes.
No overnight fasting	

to produce insulin concentration of one unit/ml) and second for dextrose with potassium (500 ml of 10% dextrose and 20mmol/L of KCl at the rate of 100 ml/hr). Potassium is added as insulin drives extracellular K^+ into the cells.

- Insulin requirements at the time of labor in diabetic women are shown in table 13.15. It is important to reduce or omit the dose of long acting insulin given on the day of delivery. Since the insulin requirements drop markedly after delivery, regular insulin must be used to meet most or all the insulin requirements of the mother. In cases of vaginal delivery, prostaglandin gel should be used as early as possible in the morning. In case of elective cesarean delivery, the diabetic woman must be taken up as the first case in the morning. In these cases the usual insulin dosage and meal must be given an evening before surgery. The woman must be put on fast from 12 midnight onwards.

Neonatal Care

- Women with diabetes should preferably be advised to give birth in hospitals where advanced neonatal resuscitation skills are available 24 hours a day.
- Routine admission of these babies to the neonatal unit is not required unless conditions mentioned in table 13.16 are fulfilled. Normal babies of women with diabetes should be kept with their mothers. Women should be encouraged to have skin-to-skin contact with their babies as soon as possible after birth. They should be advised to start breastfeeding as soon as possible after birth and ideally within an hour.

Table 13.16: Indications for admission to the neonatal units

Hypoglycemia associated with abnormal clinical signs.
Respiratory distress.
Cardiac decompensation due to congenital heart disease or cardiomyopathy.
Signs of neonatal encephalopathy.
Signs of polycythemia.
Requirement for intravenous fluids and tube feeding.
Jaundice requiring intense phototherapy and frequent monitoring of bilirubinemia.

- Blood glucose testing should be carried out routinely at birth in babies of women with diabetes after birth. This should be repeated at every 2–4 hours intervals.
- Since these babies are particularly prone to develop hypoglycemia, i.e. (blood glucose less than 2.6 mmol/liter), they should be fed as soon as possible after birth (within 30 minutes) and then at frequent intervals (every 2–3 hours) in order to maintain blood glucose concentration of at least 2.0 mmol/liter.
- In case the blood glucose values remain below 2.0 mmol/liter on two consecutive occasions despite maximal maternal feeding, additional measures such as tube feeding or intravenous dextrose may be required.
- Blood tests for polycythemia, hyperbilirubinemia, hypocalcemia and hypomagnesemia should be carried out in babies with clinical signs.
- An echocardiogram may be performed if the baby shows clinical signs associated with congenital heart disease or cardiomyopathy.
- These babies should be discharged only when the healthcare professionals are satisfied that the babies are maintaining blood glucose levels and are feeding well.

Postnatal Care

- Immediately after birth, the insulin requirements may fall, therefore insulin doses must be reduced immediately to prepregnancy levels, in order to avoid hypoglycemia. In case of patients with pregestational diabetes, the prepregnancy dose of insulin may be administered. In women with gestational diabetes, no insulin may be required post delivery. However blood glucose monitoring needs to be continued for two hours post delivery and then post prandially for next 48 hours.
- Women with preexisting type 2 diabetes who are breastfeeding can resume or continue to take metformin and glibenclamide immediately following birth, but other oral hypoglycemic agents should be avoided while breastfeeding.

- These women are also at an increased risk of hypoglycemia in the postnatal period, especially when breastfeeding. Thus they should be advised to have a meal or snack before or during each feed.
- Women with diabetes who are breastfeeding should continue to avoid any drugs for the treatment of diabetes and its complications that were discontinued for safety reasons in the preconception period. The safety of oral hypoglycemic agents, ACE inhibitors, angiotensin II receptor blockers (ARBs), statins, calcium-channel blockers and antiobesity drugs in women who are breastfeeding has not been established. However, according to the NICE guidelines, women with preexisting type 2 diabetes who are breastfeeding can start taking metformin and glibenclamide immediately following birth.
- Women who were diagnosed with gestational diabetes (including those with ongoing impaired glucose regulation) should be informed about the risks of gestational diabetes in future pregnancies. They should be offered screening with 75 grams OGTT (as recommended by Diabetes UK) or fasting plasma glucose (as recommended by NICE) for diabetes at six weeks postpartum check-up and annually thereafter and while planning future pregnancies. The blood glucose values for postpartum evaluation for glucose intolerance in women with gestational diabetes are shown in table 13.17. According to NICE guidelines (2008), the women who were diagnosed with gestational diabetes should also be offered lifestyle advice (including weight control, diet and exercise) at the time of discharge. The women who are found to have diabetes even at six weeks follow up should be managed accordingly.
- These women should also be offered contraceptive advice and the need for preconception care when planning future pregnancies.

Table 13.17: Postpartum evaluation for glucose intolerance in women with gestational diabetes

Blood glucose levels	*Normal*	*Impaired fasting blood*	*Diabetes mellitus glucose/IGT*
Fasting	< 110 mg/dl	110–125 mg/dl	≥126 mg/dl
Two hours post-prandial	< 140 mg/dl	140–199 mg/dl	≥ 200 mg/dl

Antenatal banking of colostrum

Babies of women with diabetes are at increased risk of neonatal hypoglycemia and may require frequent early feeding for maintenance of normal blood glucose levels. The women with diabetes are encouraged to express and store colostrum before birth. Antenatal expression and storage of colostrum may be of benefit to babies of women with diabetes. This is especially so because increased risk of neonatal complications in the babies born to diabetic women may require admission to intensive/special care units. This may prevent opportunities for early skin-to-skin contact and initiation of breastfeeding. Presently, there is no good evidence to support the effectiveness of antenatal banking of colostrum in women with diabetes. Future randomized controlled trials are required in order to determine the safety and cost-effectiveness of this practice. Until that time it is better that the practice of antenatal colostrum banking is not strongly encouraged.

Complications

Diabetes in pregnancy is associated with numerous risks to the mother and the developing fetus which are enumerated in table 13.18.

Table 13.18: Maternal and fetal complications related to gestational diabetes

Maternal complications	*Fetal complications*
Miscarriage	Fetal distress and birth asphyxia
Preeclampsia	Brachial plexus injuries
Preterm labor	Cephalohematoma, resulting in more pronounced neonatal jaundice
Prolonged labor	Stillbirth, congenital malformations, macrosomia, birth injury, perinatal mortality
Polyhydramnios (could be associated with fetal polyuria)	Hypoxia and sudden intrauterine death after 36 weeks gestation
35% to 50% risk of developing type II diabetes later in the life	Congenital maformations
Increased risk of traumatic damage during labor	Fetal hypoglycemia, polycythemia, hyperbilirubinemia and renal vein thrombosis
Increased risk of shoulder dystocia	Stillbirths
Diabetic retinopathy and nephropathy can worsen rapidly during pregnancy.	

Effect of Diabetes on the Fetus

Fetal hyperinsulinemia is likely to result in the following:

- An overgrowth of insulin-sensitive tissues such as adipose tissues, especially around the chest, shoulders and abdomen, which increases the risk of shoulder dystocia.
- Increased risk for perinatal death, birth trauma and rates of cesarean section.
- Neonatal metabolic complications such as hypoglycemia.
- Fetal hypoxia which may increase the risk of intrauterine fetal death.
- Fetal polycythemia, hyperbilirubinemia and renal vein thrombosis.
- An increased longterm risk of obesity and diabetes in the child.

FETAL COMPLICATIONS

Some of the fetal complications are described below:

Congenital Malformations

Infants of women with established insulin dependent diabetes mellitus have more than ten times the risk in comparison to the general population for development of congenital malformations. They also have five times the risk for stillbirth. Some of the congenital abnormalities commonly encountered in the babies of diabetic mothers are listed in table 13.19.

Intrauterine fetal death

According to the American Diabetes Association (1999) a fasting hyperglycemia of more than 105 mg/dl may be associated with an increased risk of fetal death during the last 4–8 weeks of gestation.

Macrosomia

The term macrosomia is often used to describe birth weight more than 4000 g or birthweight ≥ 90th percentile for gestational age. This is also referred to as large for gestational age or LGA fetuses (ACOG, 2000). Fetal macrosomia occurs in 17% to 30% of the pregnancies with gestational diabetes (figure 13.3) as compared with 10% in nondiabetic population. There are two types of macrosomia: Symmetric and Asymmetric. Symmetric macrosomia accounts for about 70% of cases. Asymmetric macrosomia is characterized by thoracic and abdominal circumference that is relatively larger than the head circumference. In symmetric macrosomia, the baby is symmetrically large on the whole. Symmetric macrosomia may also occur in women without diabetes. Some other causes of symmetric fetal macrosomia are listed in table 13.20. Macrosomia is usually indicated by the presence of an abdominal circumference larger than other measurements, resulting in abnormally elevated head to abdomen and femur to abdomen ratio. The baby is at an increased risk of shoulder dystocia, clavicular fracture and brachial palsy and, overall increased rates of cesarean section. It has also been suggested that babies with asymmetric macrosomia may be at an increased risk of developing obesity, coronary heart disease, hypertension and type 2 diabetes, later in life. The pathogenesis of macrosomia is shown in flow chart 13.4.

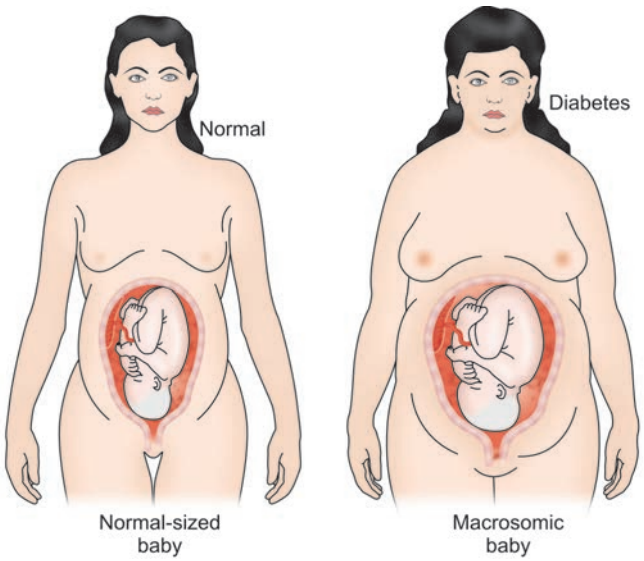


Fig. 13.3: Risk of development of macrosomia in diabetic patients

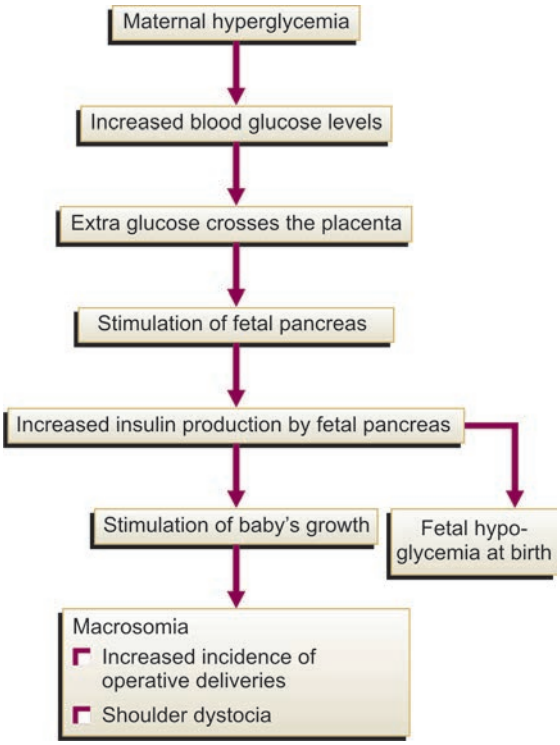
Table 13.19: Various types of congenital malformations associated with gestational diabetes

Caudal regression sequence.
Congenital heart disease: Ventricular septal defect, coarctation of the aorta and transposition of the great arteries, situs inversus etc.
Congenital microcolon.
Renal defects: Agenesis, cystic kidney, duplex ureter, etc.
Neural tube defects: Anencephaly, spina bifida, hydrocephaly, etc.
Cystic fibrosis, in association with meconium ileus.
GI abnormalities: Ileal atresia, rectal/anal atresia, Hirschprung's disease, etc.

Table 13.20: Causes of macrosomia

Inaccurate dating of last menstrual period
Familial, i.e. everyone in the family is large
Chromosomal defects
Hydrops fetalis
Beckwith Wiedemann syndrome

Flow chart 13.4: Pathogenesis of fetal macrosomia



Management

The management of macrosomia is controversial. The ACOG recommends a primary cesarean section if the expected fetal weight (EFW) at the end of pregnancy is 4500 g or more. The controversy arises when the EFW is between 4000 and 4500 g. Some investigators argue that a cesarean section must be performed in these cases as the shoulder and the trunk pads of these fetuses are relatively larger than the head, thereby favoring shoulder dystocia at the time of the birth. However if trial of vaginal delivery is being performed, the clinician must remain extremely vigilant and must immediately perform a cesarean delivery, with the development of any abnormality of labor such as delayed active phase or failure of descent or secondary arrest of cervical dilatation. Assisted vaginal delivery in form of vacuum or forceps application should not be used in these patients.

Gestational diabetes may reoccur in future pregnancies and approximately 55% of the patients, usually those are obese or with prior macrosomic infants, will show glucose intolerance in subsequent pregnancies. Gestational diabetics should be informed that they are at high risk for becoming type 2 diabetics later in their lives. Roughly 40% to 60 % will be overt diabetics when they are in their fifth decade. Lifestyle changes like weight loss, dietary control and exercise will help in preventing overt diabetes later in life.

IUGR

Women with diabetes are also at risk of having an IUGR baby especially in presence of accompanying preeclampsia. In these cases, fetal surveillance must be done using techniques like umbilical artery Doppler ultrasound, fetal cardiotocography and biophysical profile.

Shoulder Dystocia

Shoulder dystocia can be defined as the inability to deliver the fetal shoulders after the delivery of the fetal head without the aid of specific maneuvers (other than the gentle downward traction on the head). Shoulder dystocia usually results when the diameter of the fetal shoulders (bisacromial diameter) is relatively larger than the biparietal diameter. Shoulder dystocia can be of two types: High shoulder dystocia and the low shoulder dystocia. Low shoulder dystocia results due to the failure of engagement of the anterior shoulder and impaction of anterior shoulder over the maternal symphysis pubis. This type of the shoulder dystocia is also known as unilateral shoulder dystocia. This is the commoner type and is easily dealt with using standard techniques. There can be a high perinatal mortality and morbidity associated with the complication and needs to be managed appropriately.

There are two main signs that indicate the presence of shoulder dystocia:

- The baby's body does not emerge out even after the application of routine traction (figure 13.4) and maternal pushing after delivery of the fetal head. Routine traction is defined as "that traction required for delivery of the shoulders in a normal vaginal delivery where there is no

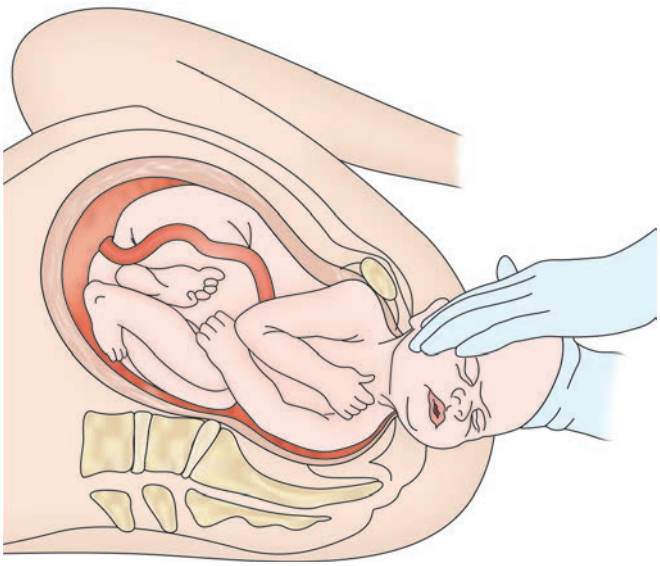


Fig. 13.4: Application of routine traction

difficulty with the shoulders". There is also difficulty with delivery of the fetal face and chin.

- The "Turtle sign": The fetal head suddenly retracts back against the mother's perineum after it emerges from the vagina. The baby's anterior shoulder is caught on the back of the maternal pubic bone, causing retraction of the fetal head and preventing delivery of the remainder of the baby. The baby's cheeks bulge out, resembling a turtle pulling its head back into its shell. There is failure of restitution of the fetal head and the descent of shoulders.

Prediction of shoulder dystocia

Shoulder dystocia is a largely unpredictable and unpreventable event as a large majority of cases occur in the children of women with no risk factors. Clinicians should be aware of existing risk factors but must always be alert to the possibility of shoulder dystocia with any delivery.

The American College of Obstetricians and Gynecologists (ACOG) has recommended that an estimated fetal weight of over 4.5 kg should be considered as an indication for delivery by cesarean section in order to reduce the potential morbidity and mortality in pregnancies complicated with maternal diabetes mellitus. Shoulder dystocia has been observed to recur in about 1% to 16% cases. Other risk factors associated with occurrence of shoulder dystocia are listed in table 13.21.

Table 13.21: Risk factors for shoulder dystocia

Prelabor factors	*Intrapartum factors*
Previous history of shoulder dystocia	Prolonged first stage of labor
Macrosomia	Secondary arrest
Diabetes mellitus	Prolonged second stage of labor
Maternal body mass index > 30 kg/m^2	Oxytocin augmentation
Multiparity	Failure of descent of the head Increased rate of assisted vaginal delivery

Management

The immediate steps which need to be taken in case of an anticipated or a recognized case of shoulder dystocia include the following (flow chart 13.5):

- Shoulder dystocia drill should form an important part of training for the junior doctor and the nurses.
- Immediately after recognition of shoulder dystocia, help should be summoned immediately. This should include further midwifery assistance, an obstetrician, a pediatric resuscitation team and an anesthetist.
- Maternal pushing and fetal pulling and pivoting should be discouraged, as this may lead to further impaction of the shoulders.
- The woman should be maneuvered to bring the buttocks to the edge of the bed.
- Fundal pressure should not be employed. It is associated with a high rate of neonatal complications and may sometimes even result in uterine rupture.
- Routine use of episiotomy is not necessary for all cases. The clinicians should apply their own discretion regarding whether an episiotomy needs to be given or not.
- Management of shoulder dystocia needs to be done within 5–7 minutes of the delivery of the fetal head.
- After delivery, the clinicians should be alert regarding the possibility of postpartum hemorrhage and third and fourth-degree perineal tears.

McRoberts maneuver: If the above mentioned steps do not prove to be useful, the McRoberts maneuver is the single most effective intervention, which is associated with success rates as high as 90% and should be performed first. Prophylactic McRoberts position may also be recommended in cases where shoulder dystocia is anticipated. The McRoberts' maneuver (figures 13.5A and B) involves sharp flexion and abduction of the maternal hips and positioning the maternal thighs on her abdomen. This maneuver helps in cephalad rotation of the symphysis pubis and the straightening of lumbosacral angle. This maneuver, by straightening the sacrum tends to free the impacted anterior shoulder. In a large number of cases, this maneuver by itself helps to free the impacted anterior shoulder.

Suprapubic pressure: Suprapubic pressure in conjunction with McRoberts maneuver is often all that is needed to resolve 50% to 60% cases of shoulder dystocias. Suprapubic pressure is the attempt to manually dislodge the anterior shoulder from behind the symphysis pubis during a shoulder dystocia. In this maneuver the attendant makes a fist and places it just above the maternal pubic bone and pushes in a downward and lateral direction to push the posterior aspect of the anterior shoulder towards the fetal chest for a period of at least 30 seconds (figure 13.6). Since shoulder dystocias are caused by an infant's shoulders entering the pelvis in a direct anterior posterior orientation instead of the more physiologic oblique diameter, pushing the baby's anterior shoulder to one side or the other from above often helps in changing its position to the oblique, which would facilitate its delivery.

The initial management in the cases of shoulder dystocia has also been summarized by the mnemonic HELPERR, which is described in table 13.22.

If these simple measures (the McRoberts maneuver and suprapubic pressure) fail, then there is a choice to be made

Flow chart 13.5: Management of shoulder dystocia

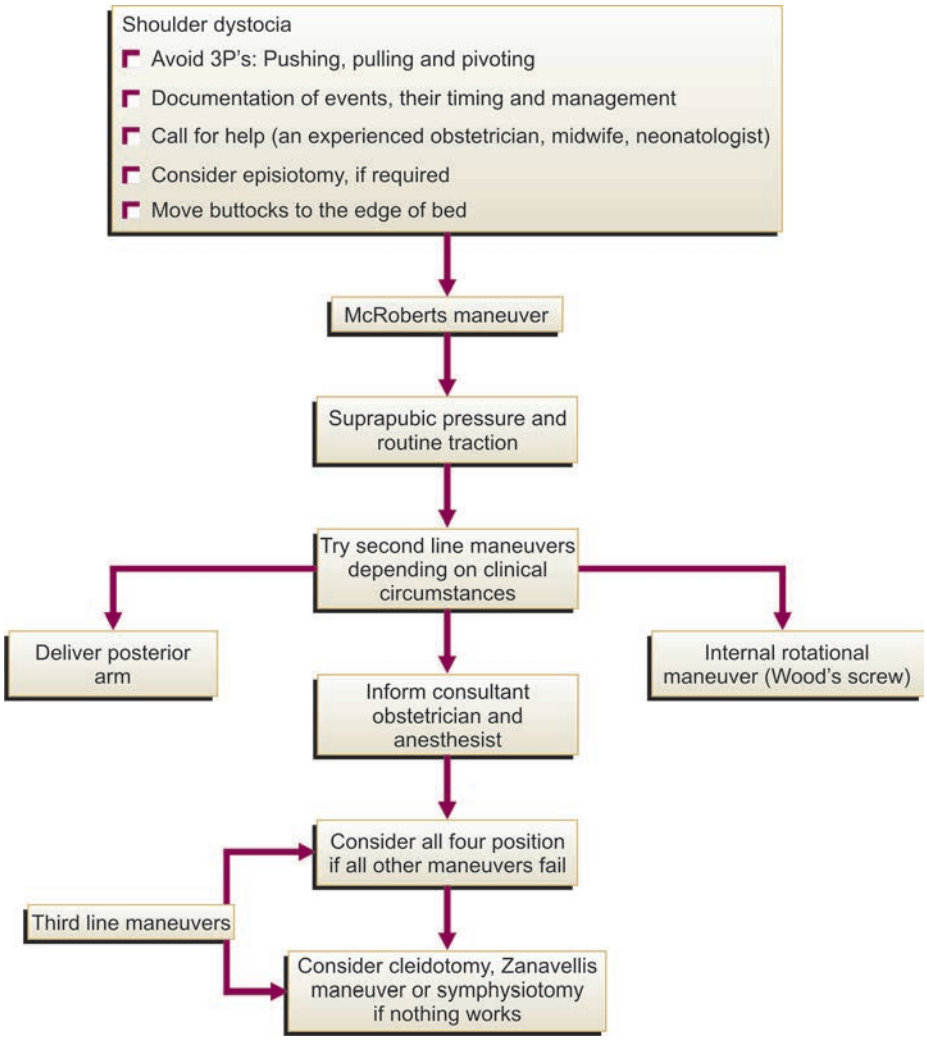


Table 13.22: Mnemonic for describing initial management in the cases of shoulder dystocia

H	Call for help
E	Evaluate for episiotomy
L	Legs (the McRoberts maneuver)
P	Suprapubic pressure
E	Enter maneuvers (internal rotation)
R	Remove the posterior arm
R	Roll the patient

between the all-fours-position and internal manipulation. Some of the maneuvers for internal manipulation include Wood's Screw maneuver and delivery of posterior arm. These maneuvers are more commonly used in comparison to the All-fours position.

Wood's Screw maneuver: In this maneuver, the hand is placed behind the posterior shoulder of the fetus (figure 13.7). The shoulder is rotated progressively by 180% in a corkscrew manner so that the impacted anterior shoulder is released.

A variation of this is the Rubin's maneuver which involves pushing on the posterior surface of the posterior shoulder. In addition to the corkscrew effect, pressure on the posterior shoulder has the advantage of flexing the shoulders across the chest. This decreases the distance between the shoulders, thus decreasing the dimension that must fit out through the pelvis.

Delivery of the posterior arm: Another effective maneuver for resolving shoulder dystocias is the delivery of the posterior arm. In this maneuver, the obstetrician places his or her hand behind the posterior shoulder of the fetus and locates the arm. This arm is then swept across the fetal chest and delivered (figures 13.8A to C). With the posterior arm and shoulder now delivered, it is relatively easy to rotate the baby, dislodge the anterior shoulder and allow delivery of the remainder of the baby.

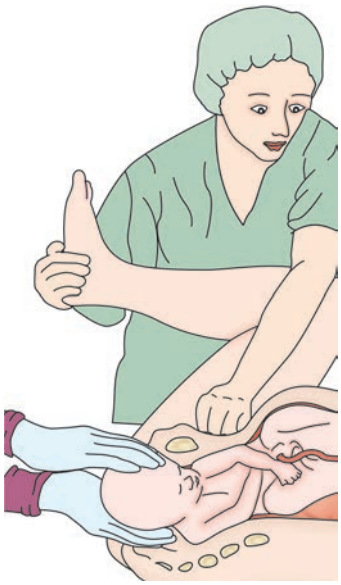


Fig. 13.5A: McRoberts maneuver (exaggerated hyper-flexion of the thighs upon the maternal abdomen) and application of suprapubic pressure

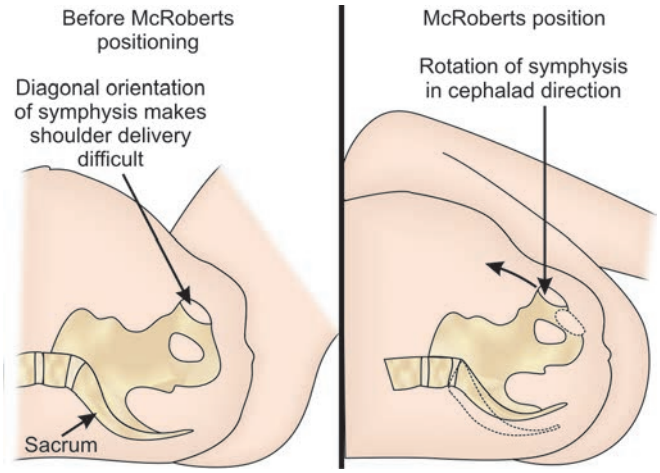


Fig. 13.5B: McRoberts maneuver causes the pubic symphysis to rotate in cephalad direction and straightening of lumbosacral angle

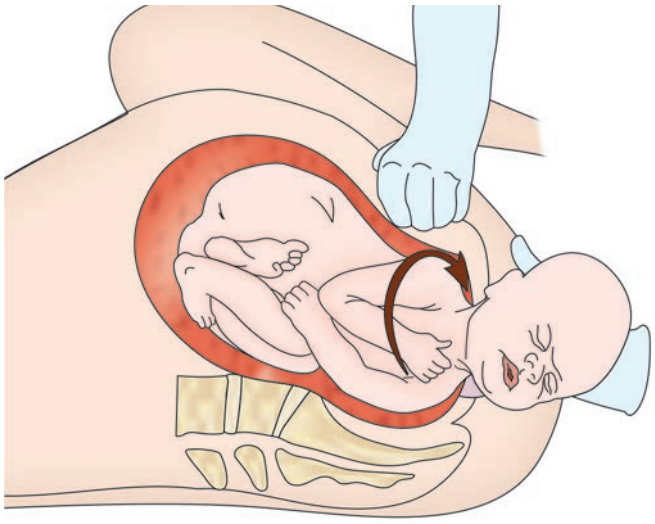


Fig. 13.6: Application of suprapubic pressure in the direction of fetal face

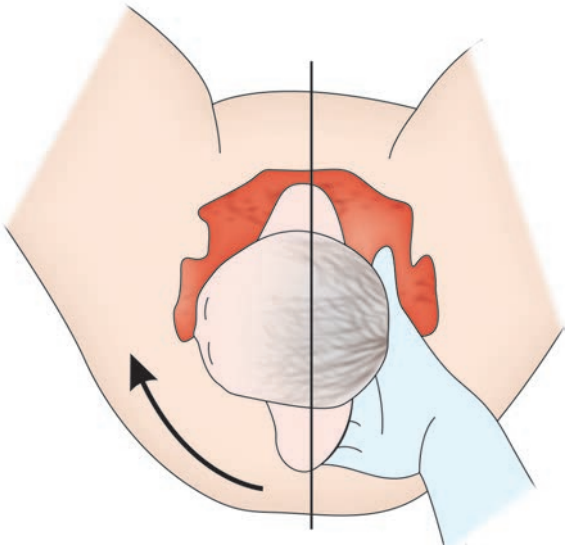
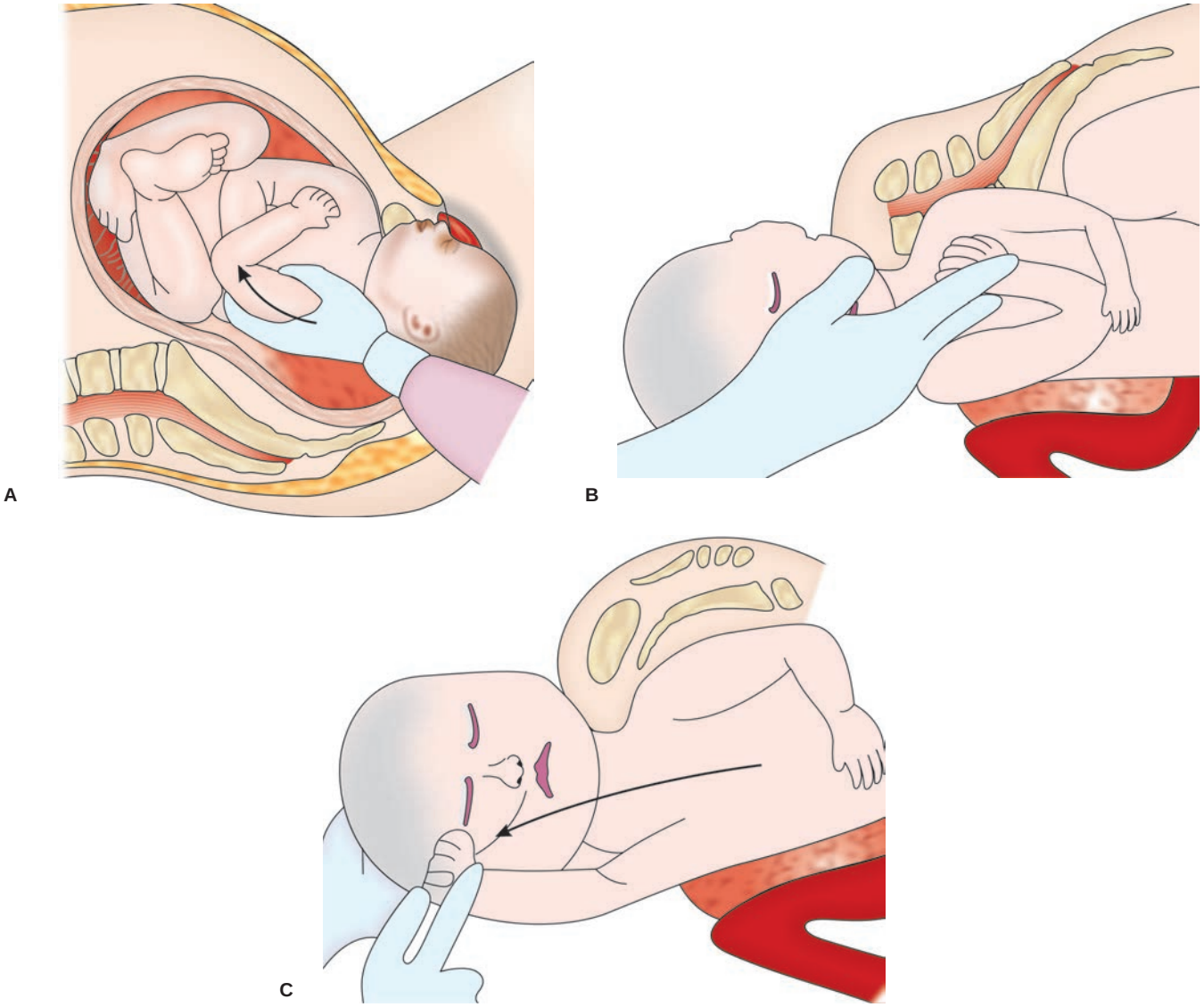


Fig. 13.7: Wood's screw maneuver: The hand is placed behind the posterior shoulder of the fetus. The shoulder is rotated progressively by 180° in a corkscrew manner so that the impacted anterior shoulder is released

All-four maneuver: In this maneuver the patient is instructed to roll over from her existing position and to take a knee chest position on all her four limbs. This allows rotational movement of the sacroiliac joints, resulting in a 1–2 cm increase in the sagittal diameter of the pelvic outlet. It disimpacts the shoulders, allowing them to slide over the sacral promontory.

Third line maneuvers: Several third line methods have been described for cases which are resistant to all simple measures. Some of these maneuvers include cleidotomy (bending the clavicle with a finger or its surgical division), symphysiotomy (dividing the symphyseal ligament) and the Zavanelli maneuver (cephalic replacement of the head followed by cesarean section). These maneuvers are rarely employed in modern obstetric practice.

Zavanelli maneuver: The Zavanelli maneuver involves the rotation of fetal head back into its pre-restitution position, that is, occiput anterior (figure 13.9A). Following this, the head is flexed and pushed back up into the vagina (figure 13.9B). Once the fetal head gets back into the pelvis, an emergency cesarean section is performed to deliver a live baby.



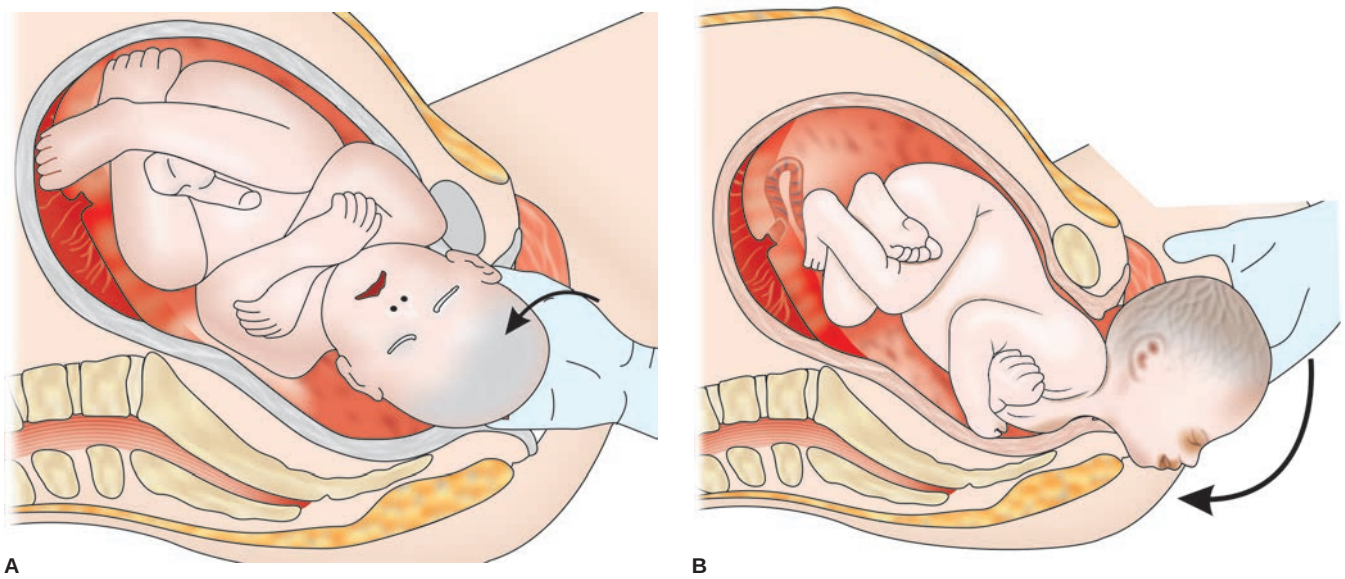
Figs 13.8A to C: Delivery of posterior arm (A) The clinician's hand is introduced into the vagina along the posterior shoulder. Keeping the arm flexed at the elbow, it is swept across the fetal chest (B) The fetal hand is grasped and the arm is extended out along the side of the face (C) The posterior arm and shoulder are delivered from the vagina

Complications of shoulder dystocia

Following shoulder dystocia deliveries, 20% of babies will suffer some sort of injury, either temporary or permanent. The most common of these injuries are damage to the brachial plexus nerves, fracture of clavicles, fracture of humerus, contusions and lacerations and birth asphyxia.

Some of the complications resulting due to shoulder dystocia are described below:

Brachial plexus injuries: The brachial plexus consists of the nerve roots of spinal cord segments C5, C6, C7, C8 and T1 (figure 13.10A). These nerve roots form three trunks, upper, middle and lower, which further divide into anterior and posterior divisions. The upper trunk is made up of nerves from C5 and C6, the middle trunk from undivided fibers of C7 and the lower most trunk is made up of nerves from C8 and T1. Injury to the upper part of the brachial plexus is called Erb palsy (C5 to C7) while injury to the lower nerves of the plexus is called Klumpke palsy (C8 to T1) (figure 13.10B). Both can cause significant, lifelong disability. Erb's palsy affects the muscles of the upper arm and shoulders causing "winging" of scapula. This type of injury also causes adduction and internal rotation of humerus with the forearm extended. This has also been described as the "waiters tip" position.



Figs 13.9A and B: Zanavelli's maneuver (A) The head is manually rotated to occipitoanterior position (B) Flexion of the fetal head and returning it into the vagina while applying constant pressure. This is followed by an immediate cesarean section

13

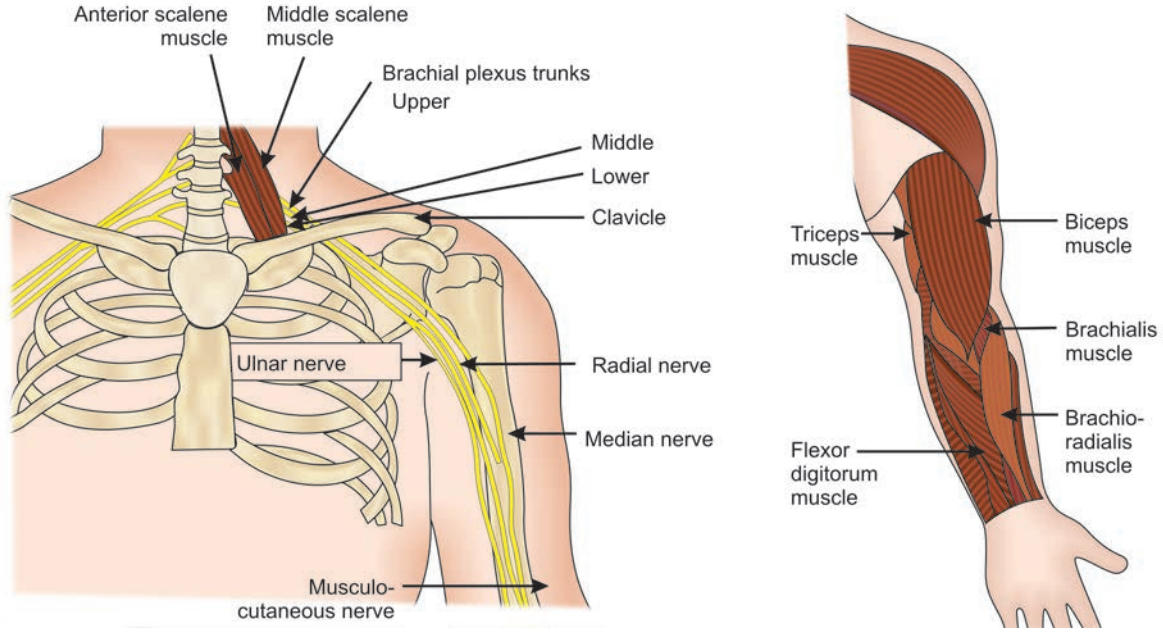


Fig. 13.10A: Anatomy of brachial pleuxes

Klumpke palsy involves lower trunk lesions from nerve roots C7, C8 and T1. In this injury the elbow becomes flexed and the forearm supinated (opened up, palm upwards) with a characteristic clawlike deformity of the hand.

Fractured clavicle: The second most common type of injury suffered by infants following shoulder dystocia deliveries is a fracture of clavicle, having an incidence rate of nearly 10%.

Contusions: The force with which the infant's shoulder is compressed against the maternal pubic bone and the pressure applied by the clinician's hands on the fetus while performing various maneuvers to facilitate delivery may often result in bruises over the baby's body.

Neurological injury: If the head-shoulder delivery interval is greater than seven minutes, chances of the brain injury are high.

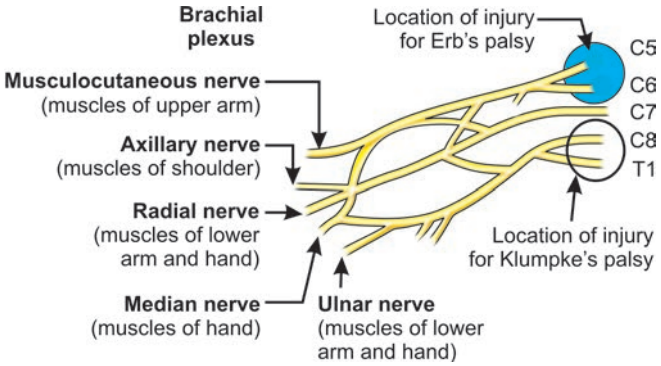


Fig. 13.10B: Areas of brachial plexus injury due to shoulder dystocia

MATERNAL COMPLICATIONS

Besides the fetal complications, shoulder dystocia can also produce some complications in the mother. The most common maternal complications include postpartum hemorrhage, second and third degree perineal tears, cervical lacerations and vaginal and vulvar lacerations.

Important Questions and Answers

Q.1. What is the likely diagnosis in the above mentioned case?

Ans. This case is at high risk of development of gestational diabetes (table 13.3). A glucose challenge test must be performed as soon as possible.

Q.2. At what blood glucose levels is diabetes defined?

Ans. The new diagnostic cutoff value for overt diabetes is taken as fasting plasma glucose values of 126 mg/dl or higher.

Q.3. Can oral hypoglycemic agents be used in diabetic women at the time of pregnancy?

Ans. The ACOG recommends that all oral hypoglycemic drugs should be replaced by insulin during pregnancy. However, Glyburide is a sulphonylurea drug which enhances insulin secretion and does not cross the placenta. It can sometimes be used as an alternative to insulin for treatment of GDM with similar perinatal outcomes. However its use must be avoided in the first trimester. Presently there is limited evidence regarding the use of glyburide during pregnancy.

Q.4. What is the risk for subsequent development of type 2 diabetes in the women with gestational diabetes?

Ans. There is a significant risk that women who develop gestational diabetes will subsequently develop Type 2 diabetes.

Q.5. When will you label the women with gestational diabetes as being a high risk patient?

Ans. Presence of the following conditions in a patient with gestational diabetes places her at high risk:

- History of previous stillbirth or neonatal death.
- History of fetal macrosomia.
- Concomitant obesity and/or hypertension.
- Development of oligohydramnios, polyhydramnios.
- History of preeclampsia.
- Inadequate metabolic control with diet alone.

Bibliography

1. American College of Obstetricians and Gynecologists: Gestational Diabetes. Practice Bulletin No 30, September 2001.
2. American College of Obstericians and Gynecologists: Gestational Diabetes: Practice Bulletin No 22, November 2000.
3. American Diabetes Association : Report of the Expert Committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 2004; 27 (suppl): 5.
4. American Diabetes Association: Clinical practice recommendations. Diabetes Care. 1999;23:S10.
5. American Diabetes Association: Gestational Diabetes Mellitus. Diabetes Care. 2003;26:S103.
6. Carpenter MW & Coustan DR. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol. 1982;144:768-73.
7. Department of Health. National Service Framework for Diabetes: Standards. London: Department of Health; 2002.
8. Key TC, Giuffrida R, Moore TR. Predictive value of early pregnancy glycohemoglobin in the insulin-treated diabetic patient. Am J Obstet Gynecol. 1987;156:273-80.
9. Lemons JA, Vargas P, Delaney JJ. Infant of the diabetic mother. Review of 225 cases. Obstet Gynecol. 1981;57:187-92.
10. Metzger BE and Coustan DR. Summary and recommendations of the fourth internal workshop-conference on gestational diabetes mellitus. Diabetes Care. 1998;21(2):B161.
11. Miller E, Hare JW, Cloherty JP, Dunn PJ, Gleason RE, Soeldner JS et al. Elevated maternal hemoglobin A1c in early pregnancy and major congenital anomalies in infants of diabetic mothers. N Engl J Med. 1981;304:1331-4.
12. National Institute for Health and Clinical Excellence. (March 2008). Diabetes in pregnancy: Management of diabetes and its complications from preconception to the postnatal period. RCOG Press: London.

Chapter

14

Anemia in Pregnancy

Case Study

A 28-year-old G4P3L3 with 28 weeks period of gestation presents with complaints of easy fatigability and dyspnea since last 2 weeks. On general physical examination, pallor was observed on the lower palpebral conjunctiva, tongue and palmar surface of hands. Pedal edema of pitting type was present. No other significant finding was observed on systemic examination. Abdominal examination revealed presence of pregnancy of about 28 weeks period of gestation with cephalic presentation.

Introduction

DEFINITION

Anemia is one of the commonest medical disorder present globally. Anemia can be defined as reduction in circulating hemoglobin mass below the critical level. WHO defines anemia as presence of hemoglobin of less than 11 gm/dl and hematocrit of less than 0.33 gm/dl. Center of Disease Control [CDC, 1990] have defined anemia as hemoglobin levels below 11 gm/dl in the pregnant woman in 1st and 3rd trimester and less than 10.5 gm/dl in second trimester. However in India and most of the other developing countries, the lower limit is often accepted as 10 gms percent.

Hemoglobin is the iron containing biomolecule present in the red blood cells in the human blood vessels. It is responsible for transporting oxygen from the lungs to the various body organs and at the same time transporting carbon dioxide from various body tissues back to lungs (figure 14.1). Each hemoglobin molecule is composed of heme group and four globin chains. Heme group consists of an iron ion held in the heterocyclic porphyrin ring. Iron is essential for carriage of oxygen by hemoglobin, for oxidative metabolism and normal growth.

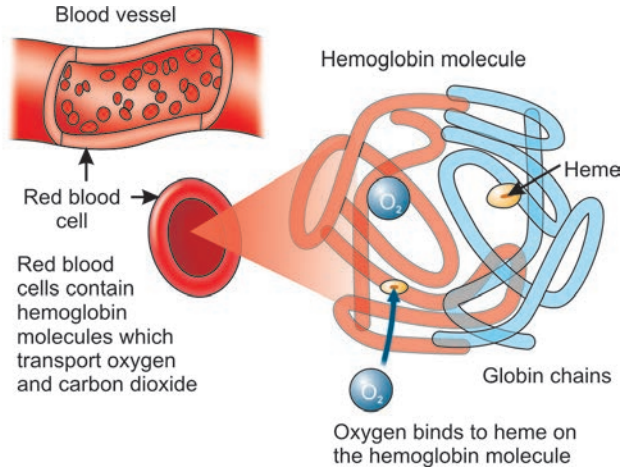


Fig. 14.1: Role of hemoglobin molecules in transportation of oxygen and carbon dioxide

Grading of Anemia

Depending on the levels of circulating hemoglobin in the body, WHO has graded anemia as mild, moderate and severe (table 14.1).

Based on the findings of the peripheral smear and the results of various blood indices (explained later in the

Table 14.1: Grading of anemia according to its severity

Hemoglobin concentration	*AIDS clinical trial group*	*World Health Organization*	*National Cancer Institute*
Mild	8.0–9.4	9.5–10.9	10 to > normal*
Moderate	7.0–7.9	8.0–9.4	8.0–10.0
Severe	6.5–6.9	6.5–7.9	6.5–7.9
Very severe/life threatening	< 6.5	< 6.5	< 6.5

*Normal is defined as 13.7–17.5 g/dl for men and 12–16 g/dl for women

Source: Brokering, KL, Qaqish, RB. Management of Anemia of Chronic Disease in Patients With the Human Immunodeficiency Virus. Pharmacotherapy 2003;23(11):1475-85.

chapter), anemia can be classified into three types as shown in the table 14.2.

Physiological Changes Taking Place in Anemia

1. Decreased hemoglobin oxygen affinity

In a normal person, when oxygen gets bound to hemoglobin, beta chains are pulled close together. On the other hand, when oxygen is released, beta chains move apart, permitting the entry of 2, 3 DPG (2, 3 diphosphoglycerate) molecules, resulting in lower affinity of hemoglobin for oxygen and improved delivery of oxygen to the tissues. These complex interactions are responsible for the sigmoid shape of oxygen dissociation curve. Increased levels of 2, 3 DPG shift the curve to right and help to release more oxygen readily. In anemic individuals, there occurs an adaptive mechanism which increases the tissue levels of 2, 3 DPG, thereby favoring increased availability of oxygen from red cells. Increased levels of 2, 3 DPG also shift the hemoglobin-oxygen dissociation curve to the right (figure 14.2), thus allowing the tissues to more easily extract oxygen from the hemoglobin molecules.

2. Redistribution of blood flow

In anemia, selective vasoconstriction of blood vessels help in redistributing the blood from certain nonvital areas into critical areas. The blood flow is increased to areas like brain, heart and adrenals and reduced to the skin and kidneys. Shunting of blood away from cutaneous sites is responsible for producing clinical finding of pallor, which can be considered as a cardinal sign of anemia.

3. Increased cardiac output

The heart tries to respond to tissue hypoxia by increasing the cardiac output. The increased output is associated with reduced peripheral vascular resistance and reduced blood viscosity, so that cardiac output can rise without an increase in blood pressure. Generally, anemia must be fairly severe (hemoglobin < 7 g/dL) before cardiac output rises.

Table 14.2: Cytometric classification of anemia

Type	*Lab value*	*Causes*
Macrocytic normochromic anemia	Increased MCV, normal MCHC MCV> 100fl MCHC 34	Vitamin B12 deficiency; folate deficiency
Microcytic hypochromic anemia	low MCHC; low MCV MCV< 80fl MCHC < 30	Thalassemias; iron deficiency anemia; anemia of chronic disease (rare cases)
Normocytic normochromic anemia	normal MCHC; normal MCV MCV> 80–99fl MCHC 34	Anemia due to chronic disease, anemia of acute hemorrhage; aplastic anemias; hemolytic anemias

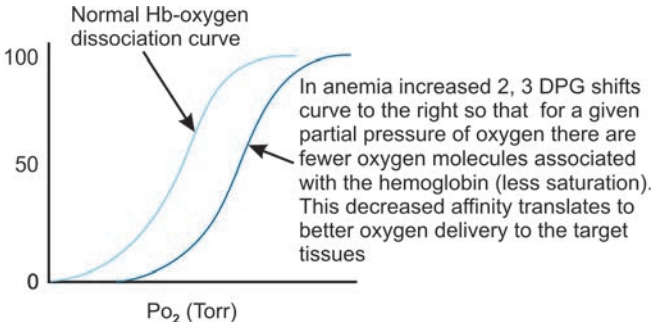


Fig. 14.2: Oxygen dissociation curve in anemic patients

History

SYMPTOMS

In the beginning, the pregnant women with mild anemia may not have any symptom as the body systems try to get adjusted to reduced hemoglobin mass. The symptoms are usually proportional to the severity of anemia. An acute hemorrhagic condition may produce symptoms with loss of as little as 20% of the total blood volume. On the other hand, anemia developing over long periods would allow compensatory mechanisms to operate which would help in masking symptoms until the anemia becomes severe. In developing countries, it is not uncommon to see a patient with hemoglobin of 4 g/dL being reluctantly brought into a clinic by relatives with the complaint that she has been just looking a bit unwell.

With mild anemia, the woman may present with vague complaints of ill health, fatigue, loss of appetite, digestive upset, breathlessness, palpitation, dyspnea on exertion, easy fatigability, fainting, lightheadedness, tinnitus, headache etc. Fatigue is one of the most common complaints of anemic patients. In anemic patients, lack of circulating hemoglobin results in development of fatigue and diminished capability to perform hard labor. As a result, the woman may complain of reduced work performance, tiredness or reduced energy, severe fatigue, restlessness, tiredness or exhaustion, nocturnal leg cramps etc. The woman may also experience headache, paresthesias and numbness in the extremities; oral and nasopharyngeal symptoms (e.g. burning of tongue), dysphagia (due to mucosal atrophy in the laryngopharynx); pica; hair loss etc.

The points in history which are important and should be elicited in these patients in order to know the etiology of anemia include the following:

Dietary History

- A detailed dietary history is important. Vegetarians are more likely to develop iron deficiency. In developing countries due to poor socioeconomic conditions, patients may not be able to afford good nutritious diet rich in iron and proteins.
- History of pica: Pica can be the etiology of iron deficiency among people who habitually eat either clay or laundry starch. One half of patients with moderate iron deficiency anemia may develop pagophagia, in which they develop strong craving to suck ice.

History of Hemorrhage

- Blood loss in any form from the body is an important cause of anemia. Two thirds of body iron is present in circulating red blood cells as hemoglobin. Each gram of hemoglobin contains 3.47 mg of iron, thus, each mL of blood lost from the body (hemoglobin 14 g/dL) results in a loss of 0.5 mg of iron. The clinician needs to enquire about a history of bleeding from any of the orifices (hematuria, hematemesis, hemoptysis, malena, excessive menstrual loss, etc). Since occult bleeding from the gastrointestinal tract often goes unrecognized, the patient needs to be specifically asked if she ever had ulcers in the gastrointestinal tract. History of chronic ingestion of aspirin or other NSAIDS needs to be elicited as this is commonly associated with occult gastric ulcerations.
- History of melanotic stools can be elicited by asking the patient if she has ever passed black colored stools (provided that she is not taking iron). The patient may not be able to give the correct estimate of menstrual blood loss, thus she should be specifically asked about the number of tampons or pads she needs to use in a day during the time of her periods and whether her menstrual flow is associated with passage of clots. Frequent pad changes and passage of clots signify greater blood loss.

Obstetric History

Obstetrical factors such as gravidity, parity and history of previous preterm or small for gestational age deliveries and multifetal pregnancy is important. History of giving birth to babies at frequent intervals before the women has a chance to replenish her depleted iron stores is an important reason for development of anemia in women with low socioeconomic status, especially in developing countries. It is important to ask the woman if she had experienced excessive blood loss at the time of delivery or during the antenatal period in her previous pregnancies. It is also important to ask if she took iron supplements during her previous pregnancies. Under-nourished and anemic women are often observed to give birth to preterm or small for gestational age babies.

Socio-economic History

History regarding various social and demographic factors including age, level of formal education, marital status, area of residence (areas with hook worm infestation, malaria, etc) needs to be elicited.

Behavioral History

Behavioral factors (smoking or tobacco usage, alcohol usage, utilization of prenatal care services, etc)

Medical History

Medical conditions (diabetes, renal or cardio-respiratory diseases, chronic hypertension, etc) can further aggravate the development of anemia during pregnancy.

Menstrual History

It is important to take a detailed history of previous menstrual cycles including the amount of blood loss and the number of days the blood loss occurs. Small amount of menstrual blood loss occurring over a long period of time can also result in the development of anemia.

Treatment History

It is important to ask the woman if she has been taking iron supplements during this pregnancy. An easy way of assessing whether the woman is speaking truth regarding the intake of iron tablets is to ask her the color of the stools. Due to continuous ingestion of iron tablets, the color of stools invariably turns black.

General Physical Examination

The following signs can be observed on general physical examination:

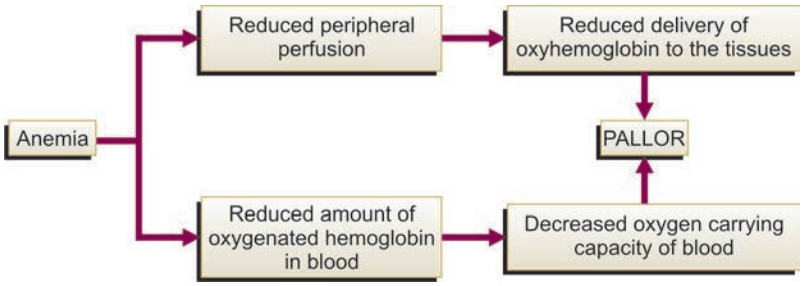
Pallor (figure 14.3)

Reduced amount of oxygenated hemoglobin in anemic individuals results in development of nonspecific pallor of the mucous membranes. Clinical examination may reveal pallor in lower palpebral conjunctiva (figure 14.4), pale nails, pale palmar surface of hands, pale tongue (figure 14.5), lips, nail beds etc. Mechanism of development of pallor is illustrated in the flow chart 14.1

Epithelial changes

The epithelial tissues of nails, tongue, mouth, hypopharynx and stomach are affected resulting in development of brittle,

Flow chart 14.1: Mechanism of development of pallor



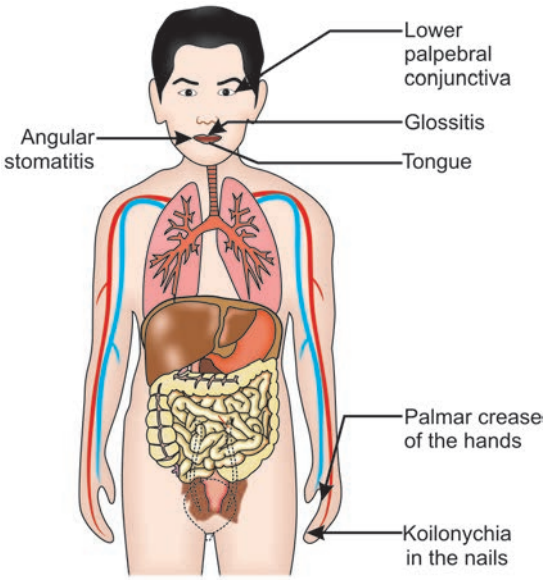


Fig. 14.3: Areas to look for pallor in the human body

Fig. 14.4: Pallor in the lower palpebral conjunctiva

fragile, spoon-shaped nails, glossitis, angular stomatitis and atrophic gastritis, etc.

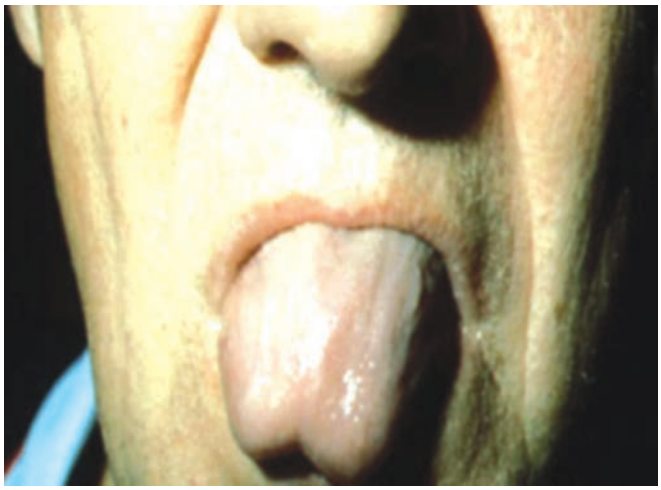


Fig. 14.5: Pale tongue

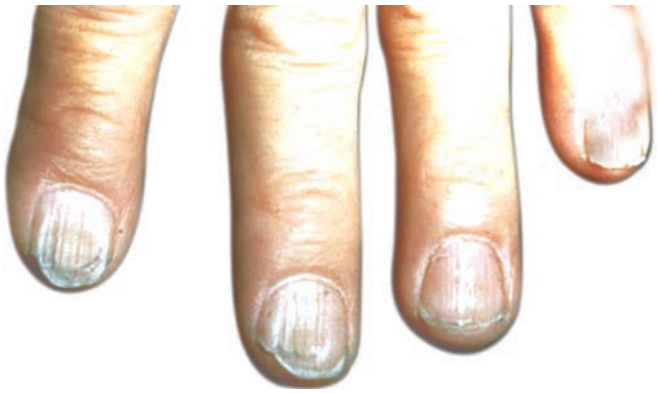


Fig. 14.6: Koilonychia

Nail changes

Thinning, flattening and finally development of concave "spoon shaped nails", also known as koilonychias (figure 14.6).

Changes in the tongue or mouth

There may be atrophy of lingual papilla accompanied by soreness or burning of the tongue. Glossitis and stomatitis

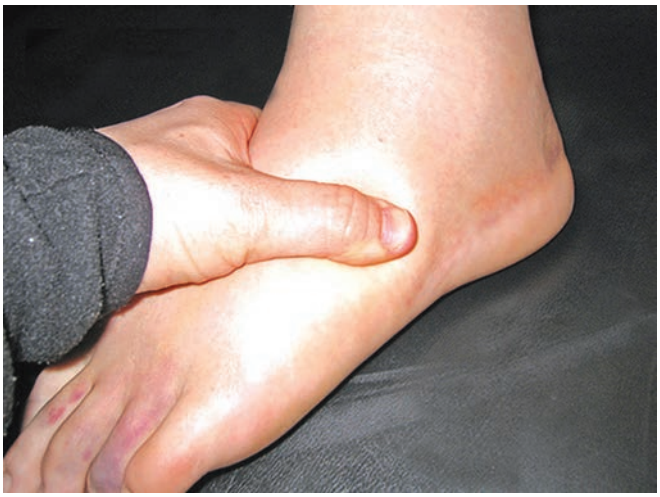


Fig. 14.7: Pedal edema

can also develop. Angular stomatitis, characterized by development of ulcerations or fissures at the corners of the mouth is a less specific sign of anemia. It is commonly associated with deficiency of riboflavin or pyrixodine.

Pedal edema

In severely anemic cases, there may be pedal edema (figure 14.7).

Plummer Vinson Syndrome

This syndrome is also known as Paterson Kelly Syndrome after the names of its discoverers. This is a rare condition characterized by presence of iron deficiency anemia, nail abnormalities and dysphagia. Some of the symptoms for Plummer Vinson syndrome include the following: Pain in the throat during swallowing, burning sensation during swallowing, sensation of food being stuck in larynx, fatigue, pallor, difficulty in swallowing, development of mucosal webs in esophagus, etc.

Specific Systemic Examination

ABDOMINAL EXAMINATION

Splenomegaly may occur with severe, persistent, untreated iron deficiency anemia.

CARDIOVASCULAR SYSTEM

In cases of severe anemia, increased blood flow to the heart results in the development of tachycardia and a systolic ejection murmur. In rapidly developing anemia (e.g. from hemorrhage), additional symptoms and signs may be noted e.g. syncope on rising from bed, orthostatic hypotension (i.e., the blood pressure falls when the patient is raised from the supine to the sitting or standing positions) and orthostatic tachycardia.

Differential Diagnosis

Normocytic Anemia

The most important cause of normocytic anemia during pregnancy is physiological anemia due to hemodilution.

Physiological anemia due to pregnancy

The two main reasons for development of physiological anemia due to pregnancy are:

- Physiological hemodilution resulting in disproportionate increase in plasma volume.
- Negative iron balance during pregnancy.

Physiological hemodilution: Pregnancy causes a disproportionate increase in plasma volume leading to an apparent reduction of red blood cell mass, hemoglobin and hematocrit value. A normochromic normocytic anemia is produced as a result of this physiological dilution which starts at 8–10 weeks of gestation and reaches a maximum during the second trimester of pregnancy. Maternal blood volume expands most rapidly during the second trimester, whereas in the third trimester the rate of rise considerably slows down, ultimately plateauing towards the last weeks of pregnancy. Blood volume expansion occurs both due to an increase in plasma volume and erythrocyte volume. Initially, the increase in plasma volume is larger than the red cell volume. Thus there is a drop in the hematocrit of approximately five units for a normal singleton pregnancy. Hemoglobin concentration at term averages to about 12.5 gm% in normal women. Therefore, in most women hemoglobin concentration below 11.0 g/dl should be considered abnormal.

Negative iron balance during pregnancy

There is an increased iron requirement during pregnancy amounting to about 1000 mg (table 14.3). This increase is due to the following reasons:

- 270 mg of iron is actively transferred to fetus. Fetus utilizes maternal iron for building up hemoglobin molecules.
- 170 mg is lost through various routes of excretion, primarily the gastrointestinal tract.
- Total amount of iron transferred to placenta and cord is 90 mg.
- 450–500 mg of iron is utilized due to expansion in the total volume of circulating maternal erythrocytes.

Table 14.3: Iron requirements during pregnancy

Reason for iron requirement	*Amount of iron required*
Iron actively transferred to the fetus	270 mg
Iron lost though various routes of excretion	170 mg
Iron transferred to placenta and cord	90 mg
Iron utilized due to expansion in the maternal volume of circulating erythrocytes	400–500 mg
Total iron requirements	**980–1000 mg**

Added to this increased physiological requirement of pregnancy, is depleted iron stores and deficient dietary intake.

All these above mentioned factors in table 14.3 amount to a total of about 980–1000 mg of iron requirement during pregnancy. This requirement of iron occurs in every woman during pregnancy, irrespective of her prior iron status. Since pregnancy results in amenorrhea, this leads to a saving of nearly 240–300 mg of iron in form of menstrual blood. Thus total iron requirements during pregnancy are 600–700 mg (6–7 mg of daily requirement of elemental iron for about 100 days). Average diet in the US provides 5–14 mg of elemental iron per day, out of which nearly one–tenth is absorbed (0.5–1.5 mg). During pregnancy, there is an additional requirement of about 2 to 5 mg iron every day. If the woman wants to fulfill these iron requirements solely from diet, she needs to consume about 20–50 mg of dietary iron as 10% of elemental iron is absorbed from the diet. This is practically impossible in India and other developing countries because an average vegetarian diet contains not more than 5–14 mg of iron. Also in developing countries, majority of women enter pregnancy in an already iron depleted condition and may be consuming an iron deficient diet. Iron depletion can be attributed to young age of child bearing and frequent occurrence of pregnancies in a woman without allowing the recovery of iron stores in the body.

Due to the above mentioned reasons, in most parts of the developing world including India, there is a need for routine iron supplementation to all pregnant women because the amount of iron absorbed from the diet, together with that mobilized from the stores is usually insufficient to meet the maternal demands imposed by pregnancy. Thus during pregnancy, there is daily requirement for additional 20–30 mg of elemental iron. Even though the absorption of iron is increased from 1–2 mg per day to about 6 mg per day in the later part of pregnancy, in the absence of exogenous supplemental iron, the hemoglobin concentration and the hematocrit would fall appreciably as the maternal blood volume increases. For these reasons, the supplementation with exogenous iron during pregnancy becomes essential. Hemoglobin

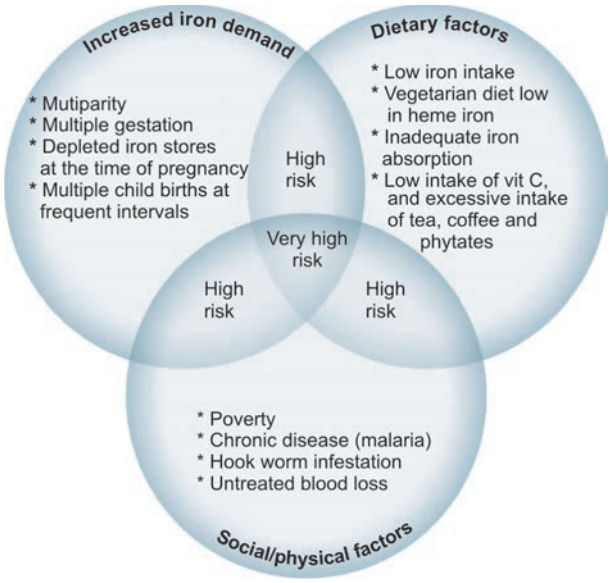


Fig. 14.8: Multifactorial etiology of anemia

production in the fetus is not impaired because placenta obtains iron from the mother, even when the mother has severe iron deficiency anemia. If iron supplements are not given to pregnant women, her serum iron and ferritin levels may decline, especially during the second half of pregnancy. Therefore, it is essential that patient's hematocrit or hemoglobin during routine pregnancy be checked at 28–32 weeks to detect any significant decrease in hemoglobin levels.

The above mentioned obligate iron requirements during pregnancy and physiological hemodilution constitute an important cause of anemia during pregnancy. Due to this and the acute blood loss accompanying child birth and labor, prevalence of iron deficiency anemia during the pregnancy is quite high and has far reaching consequences, especially with severe degrees of anemia. Though exact data on the prevalence of anemia in woman is not available, it is estimated that 60 million pregnant women worldwide are anemic. Out of these, only 4 million are in developed countries, rest of them belong to the developing countries. Prevalence rate of anemia in US is about 1.29%. Anemia in pregnancy has a multifactorial etiology (figure 14.8). Various other factors responsible for anemia during pregnancy include the following:

- Prior history of menorrhagia (loss of more than 80 ml of blood per month)
- Multiple gestations
- Vegetarian diet, low in meat.
- Increased frequency of blood donation
- Chronic blood loss due to hookworm infestation, schistosomiasis etc.
- Chronic infection (e.g. malaria)
- Chronic aspirin use.

Majority of women in child bearing age have deficient iron stores due to blood loss from menstruation, repeated child birth and chronic hookworm infection especially in the developing countries. In multigravidas, repeated child bearing does not give time to replenish the iron stores in between the pregnancies, thereby perpetuating anemia. Deficient or defective intake of iron, folic acid and other hematopoetic factors due to poverty, ignorance or absorption disorders may lead to nutritional deficiency during pregnancy. Deficiency of other micronutrients (folic acid, zinc etc) is also commonly seen accompanying iron deficiency anemia. Infants born to a mother suffering from iron deficiency anemia may have deficient iron stores during infancy, childhood and adolescence. This child during the period of her pregnancy may develop manifest anemia, thereby setting up a vicious cycle.

Malaria which is endemic in certain parts of the world causes anemia by hemolysis. Presence of chronic infections may cause anemia by impairing hematopoiesis. Genetic factors like thalassemia, sickle cell anemia, G6PD deficiency etc can also result in anemia. With the exception of thalassemia major, which is associated with iron overload, other genetic disorders usually have concomitant iron deficiency during pregnancy. Deficiency of vitamin B12, although a rare cause of anemia during pregnancy, is sometimes seen in strict vegetarians or those eating fad diets.

Microcytic Anemia

The three most common causes of microcytic anemia are iron deficiency anemia, thalassemia and anemia due to chronic infection.

Iron deficiency anemia

Causes for iron deficiency anemia are listed in table 14.4.

Iron deficiency anemia has been defined as microcytic hypochromic type. This type of anemia usually develops, when body iron stores become inadequate for the need of normal erythropoesis. Body iron stores must be reduced before red cell production is reduced. Therefore anemia occurs at a later stage of iron deficiency. Serum ferritin less than 20 ng/ml is associated with iron deficiency anemia. The various stages involved in the development of anemia during pregnancy are as follows:

- *Depletion of iron stores:* This stage is associated with low serum ferritin levels.
- *Impaired hemoglobin production:* In this stage, there is deficiency of iron without manifest anemia. This stage is associated with low ratio of serum iron to total iron binding capacity (iron/TIBC), low MCV and elevated erythrocyte protoporphyrin levels. However, hemoglobin levels remain within the normal range.
- *Manifest iron deficiency:* This stage is associated with low hemoglobin levels along with additional evidence of iron deficiency including low serum ferritin levels, low ratio of serum iron to TIBC levels, low MCV, MCH and MCHC and elevated erythrocyte protoporphyrin.

Iron is absorbed mainly from duodenum and jejunum in the ferrous form and is transported in the blood in form of transferrin.

Table 14.4: Causes of iron deficiency anemia

Nutritional causes
Iron deficiency anemia (60%)
Dimorphic anemia both due to deficiency of iron and folic acid
Hemolytic anemia
Hemoglobinopathies
Anemia due to blood loss
Acute
Acute blood loss (antepartum hemorrhage, postpartum hemorrhage)
Chronic
Hookworm infestation, bleeding piles, malarial infestation

Thalassemia

Thalassemia includes a group of genetically inherited disorders, which are characterized by impaired or defective production of one or more normal globin peptide chains. Abnormal synthesis of globin chains can result in ineffective erythropoiesis, hemolysis and varying degrees of anemia. Depending on whether the synthesis of α or β-chains is affected, thalassemia can be classified into two types: α-thalassemia or β-thalassemia.

Iron deficiency anemia has to be differentiated from other causes of hypochromic anemia including thalassemia (table 14.5) and anemia due to chronic diseases (table 14.6).

Anemia due to thalassemia can be differentiated on the basis of erythrocyte indices. Although MCV may be reduced in thalassemia to values as low as 60–70 fl, values this low are rarely encountered in cases with iron deficiency anemia. Serum iron concentration is usually normal or increased in thalassemic syndromes, while it is usually low in iron deficiency anemia. Marrow examination and hemoglobin electrophoresis also help in differentiating between iron deficiency anemia and thalassemia by respectively showing normal bone marrow iron stores and increased proportions of Hb F & Hb A_2 in cases with thalassemia.

Chronic iron deficiency anemia

Anemia can be produced due to the diseases like chronic renal insufficiency, hypothyroidism, malignancies (hematologic

Table 14.5: Differentiation between iron deficiency anemia and thalassemia

Blood index	*Iron deficiency anemia*	*Thalassemia*
Peripheral smear	Microcytic hypochromic anemia	Microcytic hypochromic anemia
Serum iron	Reduced	Normal or high
TIBC	High	Normal
Percentage saturation	Reduced	Normal or high
Serum ferritin	Reduced	High
Hemoglobin pattern	Normal	Abnormal
Hb F & Hb A_2	Normal	High
Red cell width	High	Normal
Free erythrocyte porphyrin (normal < 35)	> 50	Normal
MCV, MCHC, MCH	All reduced proportionally to the severity of anemia	All reduced to very low levels in relation to the severity of anemia
Bone marrow iron stores	Absent	Present

Table 14.6: Differentiation between iron deficiency anemia and anemia due to chronic diseases

Blood index	*Iron deficiency anemia*	*Anemia due to chronic diseases*
Peripheral smear	Microcytic hypochromic anemia	Microcytic hypochromic anemia (20–30%)
Serum iron	Reduced	Normal
TIBC	High	Reduced
Percentage saturation	< 16%	> 16%
Serum ferritin	Reduced	Normal
MCV, MCHC, MCH	All reduced proportionally to the severity of anemia	Low/normal
Bone marrow iron stores	Absent	Present

malignancies, leukemia, lymphoma, myeloma, etc). Anemia due to chronic disease is caused by a reduction in both the lifespan of existing RBCs and in the number of new RBCs produced to replace dying RBCs. Cytokines, such as interleukin (IL-I), IL-6 and tumor necrosis factor (TNF-α), may directly reduce RBC production and survival. For example, in anemia of chronic renal failure, the kidneys do not produce sufficient erythropoietin in response to hypoxia.

The anemia due to chronic disease is usually normocytic normochromic type, but hypochromic microcytic anemia may also occur in 20% to 30% of patients with chronic diseases or malignancy. The differentiation between iron deficiency anemia and anemia due to chronic diseases is shown in table 14.6. Sometimes, it may not be possible to differentiate between the two types of anemia, just by the examination of the blood film. Furthermore, the serum iron concentration is usually decreased in IDA, whereas it may be normal in anemia due to chronic diseases. Also, the TIBC is usually increased in IDA, whereas it is decreased in cases of anemia due to chronic disease. In IDA, transferrin saturation is usually less than 16%, where as in anemia due to chronic diseases, it is usually greater than 16%.

Management

Management comprising of investigations and definitive obstetric management is discussed below.

Investigations

The algorithm for diagnosis of anemia during pregnancy is described in flow chart 14.2. The following investigations need to be done:

Hemoglobin and Hematocrit

Hemoglobin concentration reflects the capacity of blood to distribute oxygen from the lungs to tissues in the body. Hematocrit on the other hand reflects the measurement of the percentage of red blood cells found in a specific volume of blood. Hematocrit is sometimes also known as packed cell volume (PCV). A low hematocrit indicates a decrease in number or size of red blood cell mass or an increase in plasma volume.

Blood Cellular Indices

Abnormalities in various blood indices with iron deficiency anemia are described in table 14.7 below. Some of these indices are as follows:

Table 14.7: Abnormalities in blood indices with iron iron deficiency anemia

Blood index	*Normal value*	*Value in iron deficiency anemia*
MCH	26.7 to 33.7 pg/cell (average 30.6 pg/cell)	< 26.7 pg/cell
MCHC	32–36% (average 33.9%)	< 30 gm%
MCV	83–97 fl (average 90 fl)	< 76 fl
Hemoglobin	12.1 to 14.1 gm/dl	< 11 gm/dl in 1st and 3rd trimesters and less than 10.5 gm/dl in second trimester
Hematocrit	36.1 to 44.3%	< 36.1%
Red cell count	3.9 to 5.0 × 10^6 cells/μL (average 4.42 × 10^6 cells/μL)	< 3.9 × 10^6 cells/μL or normal
Red cell distribution index	31–36%	< 31%

MCV (mean corpuscular volume)

This index indicates the morphology of the RBCs which could be microcytic, normocytic or macrocytic.

$$\text{MCV} = \frac{\text{Packed cell volume}}{\text{Red cell count per liter}} \times 10^{15}\,\text{fl}$$

MCH (mean corpuscular hemoglobin)

This index indicates average weight of hemoglobin in RBC. MCH is reduced in cases of microcytosis and hypochromia. MCH alone however cannot distinguish between microcytosis and hypochromia.

$$\text{MCH} = \frac{\text{Hb in gm\%}}{\text{Red cell count per liter}} \times 10^{13}\,\text{pg}$$

MCHC (mean corpuscular hemoglobin concentration

This index represents weight of hemoglobin/volume of cells. Since this index is independent of cell size, it is more useful than MCH in distinguishing between microcytosis and hypochromia. A low MCHC always indicates hypochromia, as a microcyte with a normal hemoglobin concentration will have a low MCH but a normal MCHC.

$$\text{MCHC} = \frac{\text{Hb in gm\%}}{\text{PCV}} \times \text{gm per cent}$$

Out of the various indices used, mean corpuscular volume and mean corpuscular hemoglobin concentration are the two most sensitive indices of iron deficiency.

Red cell distribution width (RDW)

This indicates the variation in the size of RBCs. Thus, RDW is elevated in anemias resulting from iron deficiency.

Reticulocyte Count

This test helps in measuring the percentage of reticulocytes, which are slightly immature red blood cells, in blood. Normally, the development and maturation of the reticulocytes takes place in the red bone marrow and then they circulate for about a day in the blood stream before developing into mature red blood cells. Thus by measuring the reticulocyte count, clinician gets an idea regarding the rate of synthesis of reticulocytes by the marrow and their release into the blood stream. Normally, about 1% to 2% of the red blood cells in the blood are reticulocytes. The reticulocyte count may rise when there is an excessive blood loss or in certain diseases like hemolytic anemia in which red blood cells are destroyed prematurely.

Peripheral Smear

Peripheral smear examination is another simple method for diagnosis of anemia. Examination of the peripheral smear is an important part of the workup of patients with anemia.

Peripheral smear in iron deficiency anemia

Peripheral smear of blood shows microcytic and hypochromic picture. There is presence of pale looking RBCs with large central vacuoles (hypochromic RBCs). The peripheral smear (figure 14.9) shows the following:

- *Anisocytosis (abnormal size of cells):* The RBCs are small and deformed (microcytosis). The microcytosis is

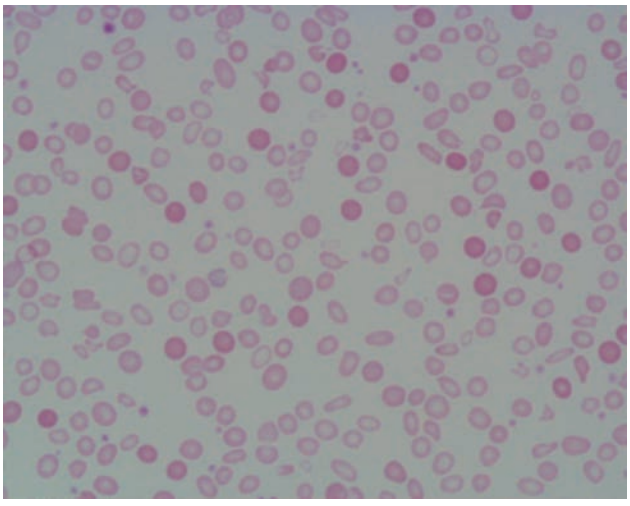
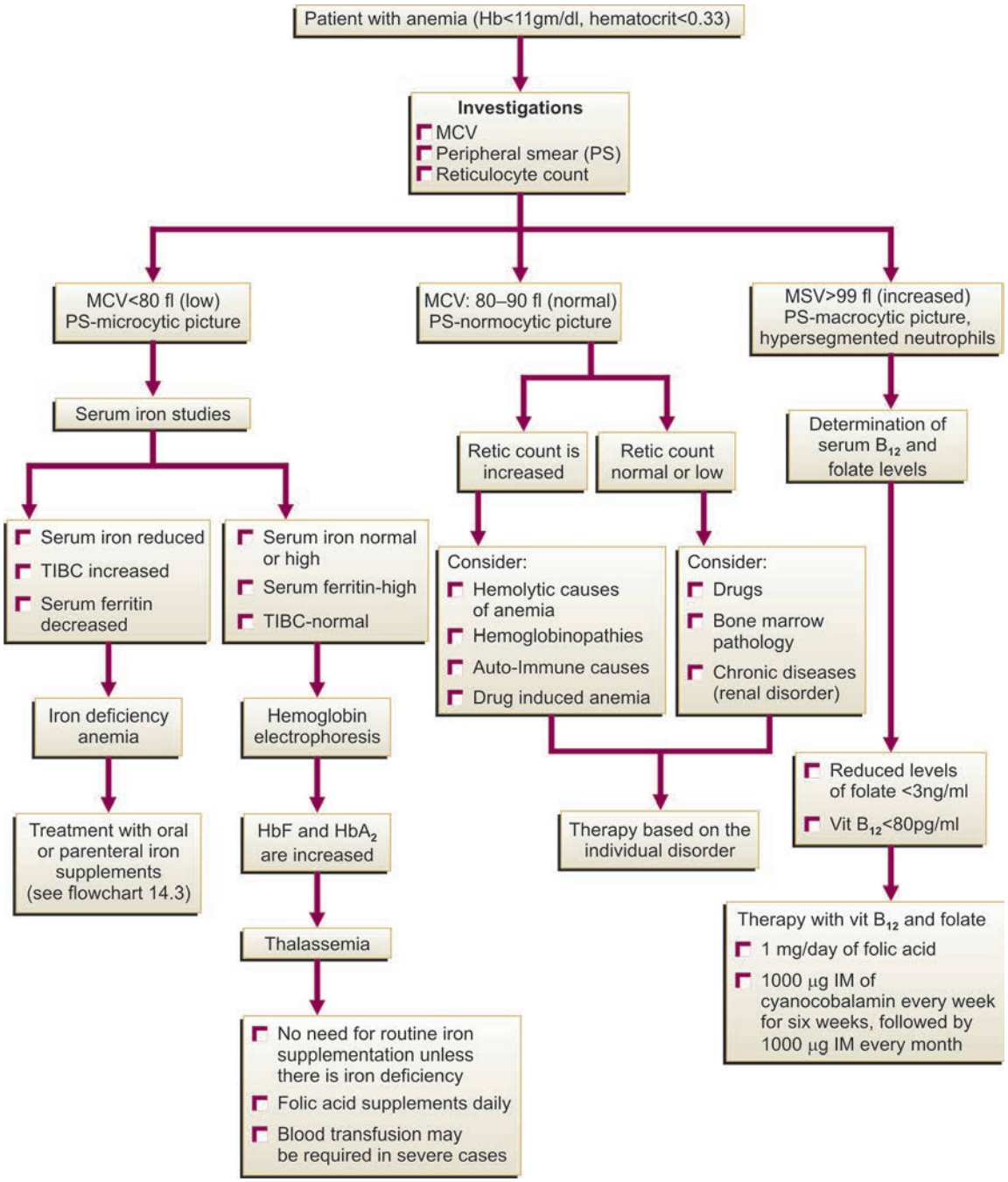


Fig. 14.9: Peripheral smear in case of iron deficiency anemia

Flow chart 14.2: Diagnosis of anemia during pregnancy

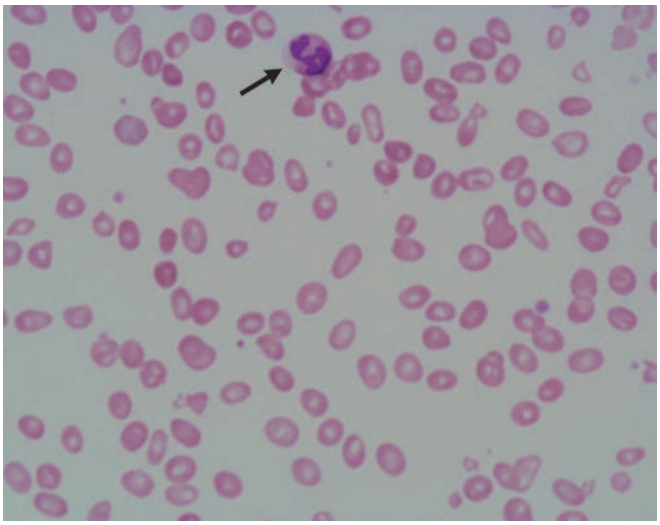


apparent in the smear long before the MCV is decreased after an event producing iron deficiency.

- *Poikilocytosis (abnormal shape of cells):* Presence of pencil cells and target cells.
- Presence of ring or pessary cells with central hypochromia (large central vacuoles).
- RBC osmotic fragility is slightly reduced.
- Radiochromium-51cr studies show reduced RBC life span.

Peripheral smear in megaloblastic anemia

- Presence of macrocytes and megaloblasts
- Hypersegmentation of neutrophils (figure 14.10)
- Fully hemoglobinized red blood cells.



The arrow is pointing towards hypersegmented neutrophil

Fig. 14.10: Peripheral smear in case of megaloblastic anemia

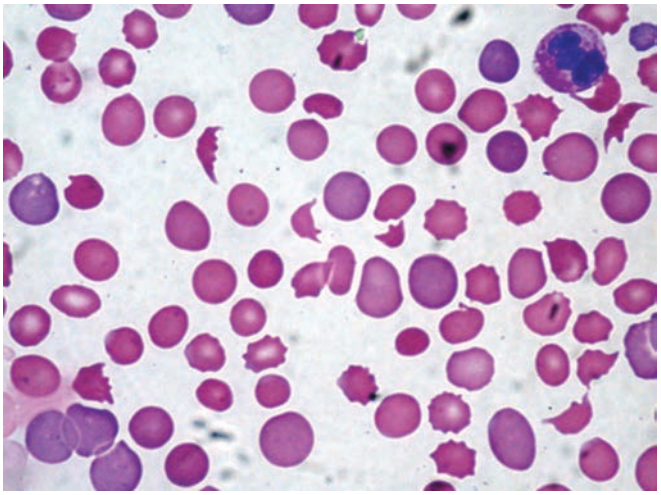


Fig. 14.11: Peripheral smear in case of hemolytic anemia

Peripheral smear in hemolytic anemia (thalassemia)

Presence of polychromatic, stippled and target cells (figure 14.11). Platelets usually are increased in this disorder.

Peripheral smear in combined folate and iron deficiency

The peripheral smear in these cases reveals a population of macrocytes mixed among the microcytic hypochromic cells. This combination can normalize the mean corpuscular volume (MCV).

Serum Iron Studies (Table 14.8)

A low serum iron and ferritin with an elevated total iron binding capacity (TIBC) is diagnostic of iron deficiency.

Table 14.8: Changes in serum iron studies with iron deficiency anemia

Blood parameter	*Normal value*	*Value in iron deficiency anemia*
Serum transferrin levels	200–360 mg/dl	>360 mg/dl
Serum iron concentration	60–175 µgm/dl	< 60 µgm/dl
Transferrin saturation	25%–60%	< 25%
Ferritin levels	50–145 ng/ml	< 20 ng/ml
Serum protoporphyrin	30–70 µgm/dl	> 70 µgm/dl

Transferrin delivers iron to bone marrow and storage sites. Circulating transferrin is normally only about 30% saturated with iron. The remaining 70% is unbound and represents the TIBC. The finding of a low serum iron and a high TIBC is highly indicative of iron deficiency anemia.

Ferritin is storage form of iron, whose concentration in the serum is proportional to total iron stores. Low serum ferritin levels are virtually diagnostic of iron deficiency as they are decreased only in iron deficiency anemia. In iron deficiency anemia, iron stores are depleted prior to anemia; therefore, the earliest change usually observed is reduced ferritin levels (< 20 ng/ml).

Iron deficiency anemia is also associated with the elevation of erythrocyte protoporphyrin levels as there is no iron available to form hemoglobin.

Stool Examination

Stool examination for ova and cysts (three consecutive samples) can help in determining if the cause of anemia can be attributed to parasitic infestation. Testing the stools for the presence of hemoglobin is useful in establishing gastrointestinal bleeding as the etiology of iron deficiency anemia. Usually, chemical testing that detects more than 20 mL of blood loss daily from the upper gastrointestinal tract is employed. Severe iron deficiency anemia can occur in patients with a persistent loss of less than 20 mL/d.

Urine Routine/Microscopy

Urine routine/microscopy help in detecting the presence of pus cells/occult blood or schistosomes.

Hemoglobin Electrophoresis

Hemoglobin electrophoresis and measurement of hemoglobin A_2 and fetal hemoglobin are useful in establishing either beta-thalassemia or hemoglobin C or D as the etiology of the microcytic anemia. Unfortunately, simple tests do not exist for alpha-thalassemia in most laboratories and it is a diagnosis of exclusion.

Table 14.9: Indications of bone marrow examination
No response to any treatment even after 4 weeks
Suspected aplastic anemia
Kala-azar
Sideroblastic anemias

Table 14.10: Bone marrow findings in iron deficiency anemia
Micronormoblastic erythroid hyperplasia.
Bone marrow iron is reduced or absent.
Intermediate normoblasts are predominantly seen.
Cytoplasm of the normoblasts is reduced and shows differential staining.
Cytoplasm matures slowly in comparison to the nucleus, such that the cytoplasm is still polychromatic, while the nucleus has become pyknotic.

Bone Marrow Examination

A bone marrow aspirate stained for iron (Perls stain) can be diagnostic of iron deficiency. While the performance of bone marrow examination for the diagnosis of iron deficiency has largely been displaced by the performance of serum iron, TIBC and serum ferritin, the absence of stainable iron in a bone marrow aspirate reflects absent iron stores. The indications of bone marrow examination have been enumerated in table 14.9. It is diagnostic in identifying the sideroblastic anemias by showing presence of ringed sideroblasts (table 14.10). Occasionally, it is useful in differentiating patients with the anemia of chronic disorders or alpha-thalassemia from patients with iron deficiency. It also serves as the investigation of choice in cases where anemia is related to aplastic anemia.

℞ Treatment/Obstetric Management

The algorithm for treatment of patients diagnosed with iron deficiency anemia is shown in flow chart 14.3. Treatment of the patient diagnosed with iron deficiency basically depends on the period of gestation as described in flow chart 14.3. If the period of gestation is less than 30 completed weeks of gestation, oral iron preparations (containing 200–300 mg of elemental iron with 500 µg of folic acid) must be prescribed in divided doses. If the patient is not compliant with oral therapy or other causes for ineffective oral treatment are present, parenteral therapy may be considered. If period of gestation is between 30–36 weeks, parenteral therapy must be administered. The rise in hemoglobin levels by the parenteral route is same as that with oral route, but this route is preferred during 30–36 weeks of pregnancy as it guarantees certainty of administration. If the patient presents with severe anemia beyond 36 weeks and there is not enough time to achieve a reasonable hemoglobin level before delivery, blood transfusion may be required.

Patient presenting with severe anemia in late pregnancy (after 36 weeks)

Women with severe anemia presenting late in pregnancy should ideally be managed in hospital settings. They may or may not present with heart failure. However, they all need urgent admission and require complete rest with sedation and oxygen. In case of CCF, patients should be given digitalis, diuretics and packed red cells. Packed red cells are the preferred choice for severe anemia in later part of pregnancy. This should be infused along with diuretics. Once the patient is stabilized, total dose infusion of iron dextran may be considered.

Blood transfusion

Indications for blood transfusion for correction of anemia during pregnancy are as follows:

- There is not enough time to achieve a reasonable hemoglobin level before delivery, for e.g. patient presents with severe anemia beyond 36 weeks.
- There is acute blood loss or associated infections.
- Anemia is refractory to iron therapy.

In all the above mentioned cases, packed red cell transfusion must be given with meticulous care so as to prevent severe circulatory overload, pulmonary edema and development of any transfusion related reactions.

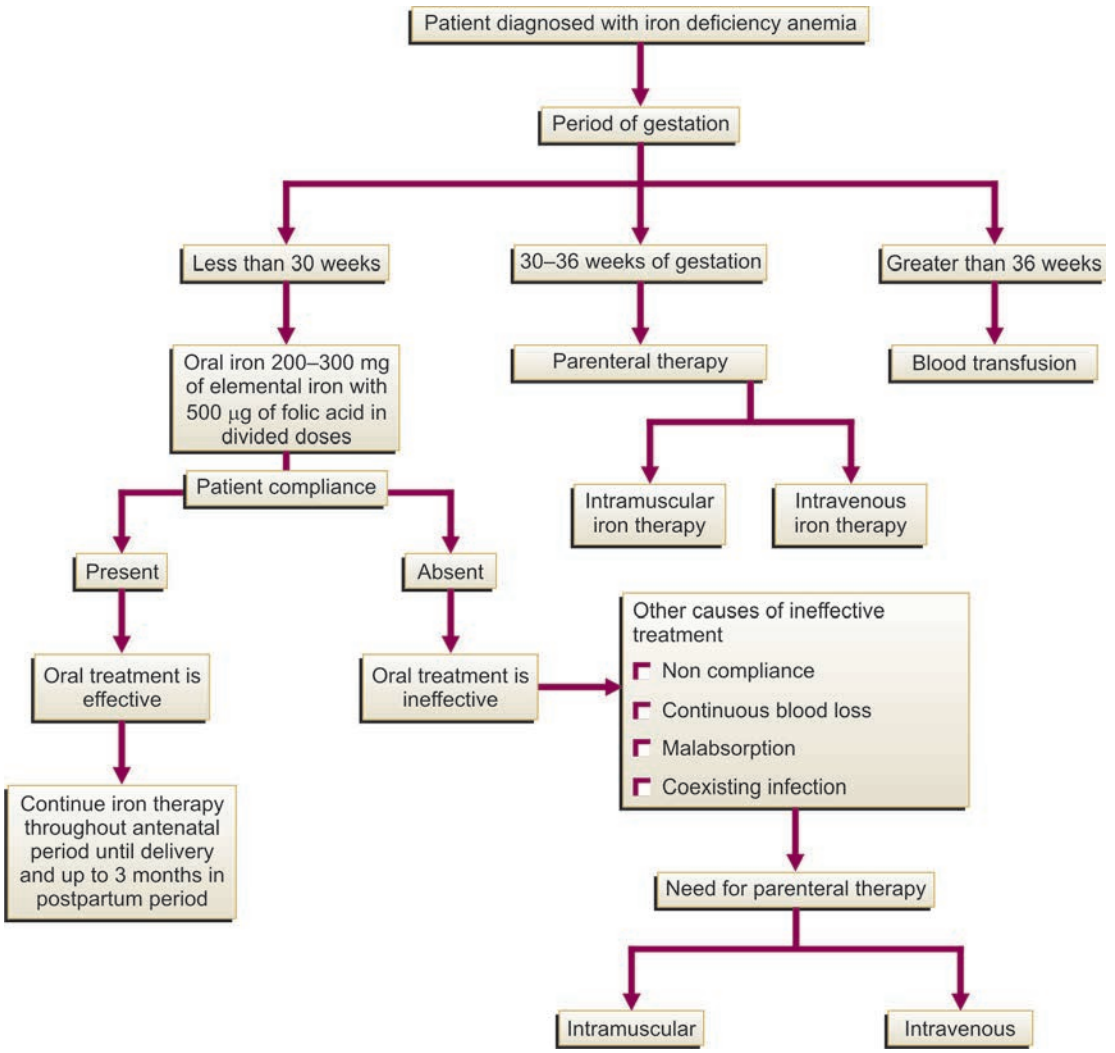
Response to iron therapy

Much before the treatment causes an improvement in the degree of anemia and hematological indices, there occurs an improvement in subjective symptoms such as fatigue, lassitude, etc. Epithelial changes may also revert to normal. Response to treatment is shown by the indicators mentioned in table 14.11.

The earliest hematological response to treatment is reticulocytosis. Initially, there is an increase in reticulocytes by 4–6 days, which peaks by 9–12 days. Hemoglobin levels usually start rising at the rate of 2 g/dl after 3 weeks. The plasma iron will gradually increase and the initially elevated TIBC will return to normal in about one month. Blood ferritin levels

Table 14.11: Indicators for showing response to iron therapy
Increase in the reticulocyte count (2% to 16%)
Increase in hemoglobin levels
Epithelial changes (especially in tongue and nails) revert to normal

Flow chart 14.3: Treatment of iron deficiency anemia in pregnancy



return to normal in about 4–6 months. If the predictable rise in hemoglobin does not occur after oral iron therapy, the clinician must try to find out the possible reasons. Some of the reasons are listed in table 14.12.

Table 14.12: Causes of failure to oral iron therapy

Incorrect diagnosis (presence of non-iron deficiency microcytic anemia)
Faulty absorption of iron
Presence of chronic infection
Loss of iron from the body
Lack of patient compliance
Persistent blood loss (hookworm, bleeding piles, etc)
Ineffective release of iron from a particular preparation
Concomitant folate deficiency

PREVENTION

Prevention of Iron Deficiency Anemia

As previously explained, in most parts of the developing world including India, there is a need for routine iron supplementation to all pregnant women in order to build up their iron stores. It is also advisable to build up iron store before a woman marries and becomes pregnant. This can be achieved by taking the following steps:

- Routine determination of hemoglobin or hematocrit, starting from the time of adolescence.
- Routine screening for anemia and provision of supplements to adolescent girls, starting right from the school days.
- Encouraging consumption of diet containing iron rich foods.
- Fortification of widely consumed food with iron.
- Management of endemic infection (e.g. malaria).

Table 14.13: Factors reducing the absorption of dietary iron
Phytates present in whole-grain cereals; legumes, nuts, seeds, etc
Calcium and phosphorus in milk;
Tannins in tea
Polyphenols present in many vegetables
Increased gastric pH due to presence of antacids or reduced gastric acidity

Table 14.14: Methods for improving iron absorption in the diet
Adding lime juice, which is a good source of vitamin C, to one's food
Avoiding the intake of substances like tea, coffee and milk with the meals
Cooking food in iron vessels
Taking iron tablets with orange juice or water rather than with milk, tea or coffee.
Avoiding the use of antacids with iron as lower gastric acidity reduces absorption of iron

Routine determination of hemoglobin or hematocrit

Hemoglobin or hematocrit should be routinely determined at the time of first prenatal visit in order to detect any preexisting anemia. Anemia accompanied by ferritin levels less than 20 ng/ml can also be presumed to be due to iron deficiency.

Even when the woman does take iron supplements, her hemoglobin and hematocrit should be monitored every two to three monthly.

Dietary changes

Improving nutritional status of women through dietary changes is one of the most important strategies for reducing the prevalence of iron deficiency anemia during pregnancy. Eating a healthy and a well-balanced diet during pregnancy helps in maintaining the iron stores. A good quality diet should not only contain sufficient proteins for hemoglobin synthesis but also various micronutrients, including vitamin A, zinc, calcium, riboflavin, vitamin B12 etc. Since the absorption of dietary iron can be affected by numerous factors (mentioned in table 14.13), iron absorption in the body can be improved by observing some simple precautions related to dietary habits. Some of them are listed in table 14.14.

Phytates present in whole-grain cereals; calcium and phosphorus in milk; tannins in tea; and polyphenols in many vegetables inhibit iron absorption by decreasing the intestinal solubility of non-heme iron from the meals. Adding lime juice or orange juice, both of which are rich in vitamin C would help in increasing the absorption of non-heme iron. On the other hand, drinking excessive tea or coffee may interfere with iron absorption. All iron preparations inhibit the absorption of tetracyclines, sulphonamides and trimethoprim. Thus, iron should not be given together with these agents.

Fig 14.12: Sources of heme iron

Examples of iron rich foods

Two types of iron are present in food: Heme iron which is principally found in animal products and non-heme iron which is found mainly in the plant products. Heme iron is mainly derived from myoglobin and hemoglobin present in meat (beef, lamb, etc), poultry, fish etc (figure 14.12). Heme iron is better absorbed (upto 35%) than non-heme iron, but heme iron forms smaller fraction of the diet. During the course of pregnancy as the iron stores decrease, the absorption of dietary non-heme iron increases. Non-heme iron is mostly in ferric form, and needs to be reduced to ferrous form for absorption. Sources of heme iron include animal blood, flesh and viscera. Non-heme iron includes cereals, seeds, vegetables, milk and eggs.

Animal products

- Red meat: Beef, pork, lamb (liver should be avoided due to high content of vitamin A)
- Poultry: Chicken, duck, turkey
- Fish: Shellfish (Clams, mussels, sardines, anchovies and oysters)
- Eggs: One large egg (70–80 mg) contains about 1 mg of iron.

Plant products

- Dried fruits: Half a cup of walnuts (125 mg) contain approximately 3.75 mg of iron; half a cup of cashew nuts approximately 2.65 mg; 1/2 cup of raisins 2.55 mg; and half cup of peanuts approximately 1.55 mg of iron.
- Green leafy vegetables: Such as spinach, broccoli, kale, turnip greens and collard greens are a good sources of iron. Half cup spinach contains nearly 2.4 mg iron.
- Pulses, cereals, jaggery
- Legumes, such as lima beans and green peas, dry beans and peas.
- Yeast-leavened whole-wheat bread and rolls.
- Iron-enriched white bread, pasta, rice and cereals.

Since folate deficiency has been found to commonly coexist with that of iron deficiency, diet rich in both iron and folic acid must be encouraged. Dietary sources of folate include the following:

- Leafy, dark green vegetables
- Dried beans and peas
- Citrus fruits and juices and most berries
- Fortified breakfast cereals
- Enriched grain products.

Fortification of food with iron

Fortification of the food with iron and folic acid is being tried in some countries and has been found to be one of the most effective, inexpensive and simple strategy for ensuring adequate supply of iron to large segments of the population in both developed and developing countries. Fortification of cereal grain products was introduced in 1941 in the US when iron and three vitamins, thiamin, riboflavin and niacin, were added to flour and bread. Ready-to-eat cereals were fortified at about the same time. These fortifications have contributed to increased dietary iron intake and reductions in iron deficiency anemia in the US. Fortification of food has been tried in other countries as well, e.g. fortification of rice in Philippines with ferrous sulfate; fortification of wheat flour with metallic iron in European countries including Sweden, UK, etc.

Management of endemic infection

Malaria and hookworm infection are the major factors responsible for causing anemia in pregnancy by causing hemolysis and chronic blood loss respectively. The preferred drug for treating malaria in pregnancy is chloroquine. Malaria prophylaxis should also be given to pregnant women in areas where malaria is endemic. Also, antihelmenthic drugs like albendazole or mebendazole are recommended to all pregnant women after the first trimester of pregnancy. This drug would help in treating hookworm infestation. To prevent recurrence of infection, patients should be advised to take certain precautions including use of proper footwear, improvement of sanitation and personal hygiene.

Exogenous iron supplementation

Iron supplementation has presently become the most common strategy currently used for controlling iron deficiency in developing countries. As described previously, pregnancy results in development of a physiological anemia. Also, in order to fulfill the iron requirement related to pregnancy, there is requirement for exogenous iron supplementation. The WHO recommends universal iron supplementation comprising of 60 mg elemental iron and 400 µg of folic acid once or twice daily for 6 months in pregnancy, in countries with prevalence of anemia less than 40% and an additional 3 months postpartum in countries where prevalence is greater than 40%. However, since women in developing countries including India may often start pregnancy with low or absent iron stores due to poor nutrition and frequent infection like hookworm and malaria, the clinicians often prescribe double the dose, which is 120 mg of elemental iron and 1 mg folic acid. Oral iron is usually continued up to 3–6 months after hemoglobin levels has come within normal limits.

Along with this, iron rich diets and diets which enhance iron absorption must be encouraged as well. Iron supplementation leads to increased hemoglobin concentration resulting in improved oxygen carrying capacity which acts as a buffer against increased blood loss that might occur during delivery.

In developing countries, routine iron supplementation during pregnancy is practiced, regardless of the fact, whether the mother is anemic or not. In India, Ministry of Health and Family Welfare, Government of India has recently recommended that all pregnant ladies must be given iron supplements amounting to 199 mg of elemental iron and 300 µgms of folic acid starting from second trimester, for a period of 100 days. Now the trend is moving towards supplementation for a total of 200 days including the postpartum period. When the hemoglobin concentration becomes normal in accordance with period of gestation, dose can be reduced to 30 mg/day. In a woman seen late in pregnancy, 120 mg of elemental iron daily is recommended during pregnancy and puerperium. However, presently there is not enough evidence to demonstrate with certainty that routine daily or intermittent iron or iron-folic acid supplementation in pregnancy improves functional and health outcomes for women and babies. Also, the routine iron supplementation during pregnancy to all women (regardless of their iron status) in developed countries where anemia is not prevalent is still debatable.

TREATMENT

Treatment with Iron Supplements

Oral preparations

Oral iron supplements are most commonly used for the treatment of iron deficiency anemia. Some forms are time-released, while others must be taken several times each day. Use of iron supplements helps in improving the iron status of the mother during pregnancy and during the postpartum period, even in women who enter pregnancy with reasonable iron stores. The main problems associated with the use of iron supplements is occurrence of side effects (table 14.15) including anorexia, diarrhea, epigastric discomfort, nausea, vomiting and constipation, passage of dark greenish or black

Table 14.15: Possible side effects associated with iron medication

Epigastric discomfort, nausea, diarrhea or constipation
Feces may turn black
Interaction with various drugs e.g. inhibition of absorption of antibiotics like tetracyclines, sulphonamides, trimethoprim, etc
Temporary staining of teeth
Epigastric pain is likely to result from a combination of high-dose vitamin C supplements with iron tablets

colored stools, temporary staining of teeth etc. The enteric coated and prolonged-release preparations are not favored as these preparations dissolve poorly in the acidic milieu of the duodenum, where maximum absorption of iron occurs. Since iron is absorbed in ferrous form, only ferrous salts must be used. Iron must be taken orally in 3–4 doses, one hour prior to meals. Oral iron therapy must be continued for at least 12 months after the anemia has been corrected in order to replenish the depleted iron stores.

Although associated with gastrointestinal side effects, oral iron supplements are not associated with the anaphylaxis that can occur with parenteral iron preparations.

The amount of element iron present in different types of oral preparations varies from one another. While prescribing a dose of iron supplements to a patient, it is important to distinguish between the amount of iron compound and the equivalent amount of elemental iron in the preparation. Thus, 300 mg of hydrated ferrous sulphate, which contains 20% iron by weight, would provide 60 mg of element iron, while 300 mg of ferrous gluconate, which contains 12% iron by weight, would provide 36 mg of elemental iron and 200 mg of ferrous fumerate, would provide 64 mg of elemental iron (table 14.16). Since the oral iron preparations are associated with numerous previously mentioned side effects, slow release supplements were introduced with the objective of reducing the occurrence of side effects. However, the efficacy of some of these slow release preparations in terms of amount of iron absorbed is still not known for sure. Thus only those slow release preparations whose absorption efficacy is known, should be used. Moreover, iron tablets are absorbed more completely when given in between rather than with meals.

How to select the oral iron salt?

There are many iron preparations available in the market and a clinician is often confused as to which iron preparation should be advised to the patient. Ferrous sulphate is the least expensive and best absorbed form of iron. If for some reasons this is not tolerated, then ferrous gluconate, or fumarate are the next choice for iron therapy. Newer iron formulations like carbonyl iron and polymaltose iron are claimed to produce fewer side effects. Carbonyl iron has been proposed as an alternative to other commonly used iron salts, on the assumption that it can be administered in large doses with minimal side effects. This iron preparation is composed of metallic iron powder, having a particle size of less than 5 μm. Since it is insoluble, it is not absorbed until it is converted into ionic form. The bioavailability of carbonyl iron has been estimated to be about 70% of that of an equivalent amount of ferrous sulphate. Oral doses as high as 600 mg three times a day have not been found to be associated with any side effects. However, presently there is no good evidence available to prove this fact. Besides, these newer iron formulations are much more costly than the previously available ones.

Table 14.16: Amount of elemental iron in different iron formulations

Molecular iron formulation	*Dose of the salt (mg)*	*Elemental iron per tablet (mg tablet)*
Hydrated ferrous sulphate	300	60
Ferrous fumerate	200	64
Ferrous gluconate	300	60
Ferrous glycine sulphate	225	45
Ferrous glycine sulphate	100	35
Ferrous sulphate (dry)	200	65
Iron polysaccharide	140	140

Table 14.17: Methods of reducing side effects associated with oral iron therapy

Starting with one tablet daily and increasing the dosage every 3–5 days can sometimes help patients tolerate oral iron better than immediately starting with three times daily dosing.
Avoiding the use of high-dose vitamin C supplements with iron tablets, as this would result in increased epigastric pain.
Taking iron supplements with meals, even though this results in reduced iron absorption, the frequency of side effects is also reduced as well.
Administration of iron supplements at bed time.
Use of iron formulations containing reduced amount of elemental iron.

The iron salt to be prescribed to the patient should be selected on the basis of patient compliance, tolerance, side effects, clinical situation of the patient and availability of a particular salt. In order to build up the iron stores, oral iron must be continued for 3–6 months after hemoglobin has come to normal levels. Some of the methods of reducing side effects associated with oral iron therapy are listed in table 14.17.

Though intake of iron with food would result in reduction of side effect related to GI tract, this is controversial in Indian settings where the staple diet consists of cereals containing phytic acid, which is supposed to interfere with iron absorption.

Table 14.18: Indications for use of parenteral iron therapy

Intolerance to oral form of iron.
When iron deficiency is not correctable with oral treatment.
Non-compliance on part of the patient: The patient repeatedly fails to heed instructions or is incapable of following them.
Patient is suffering from inflammatory bowel disease (e.g. ulcerative colitis) in which the symptoms may get aggravated by oral iron therapy.
The patient is unable to absorb iron orally.
Patients near term (32–36 weeks of pregnancy).

Parenteral forms of iron

The two main types of parenteral iron preparations which can be used are iron dextran (imferon), which can be used both intramuscularly and intravenously and iron sorbitol citrate, which can be used only by intravenous route. Some of the indications for parenteral iron therapy are mentioned in table 14.18.

Sometimes pregnant women with severe anemia present after 30–32 weeks of pregnancy. Though the rate of improvement in hemoglobin production by both oral and parenteral routes are similar, parental iron is preferred over oral forms during this time of pregnancy due to the certainty of administration of parenteral form of iron.

Parenteral iron can be given by either of two routes, intramuscular or intravenous. The two most commonly used iron preparations include, iron sorbitol citric acid complex (jectofer) and iron dextran (imferon), both of which are described below. Difference between the two preparations: Iron-dextran and iron sorbitol citric acid complex is shown in table 14.19. Another preparation of iron which can be considered as one of the oldest preparations and has been used since 1947 is iron sucrose.

Iron sorbitol citrate complex (Jectofer)

Jectofer is available in a vial containing about 1.5 ml of iron preparation, equivalent to about 75 mg of elemental iron (1 ml = 50 mg of elemental iron). This preparation is used by intramuscular route only.

Iron dextran injection (Imferon)

This is a dark brown, slightly viscous sterile liquid complex composed of ferric hydroxide and dextran and is used both intravenously and intramuscularly. Each one ml solution of iron dextran contains the equivalent of 50 mg of elemental iron in 0.9% sodium chloride solution in water for injection. Sodium hydroxide and/or hydrochloric acid may have been used to adjust pH. The pH of the solution varies between 5.2 and 6.5. Oral iron should be discontinued prior to administration of parenteral forms of iron. Though iron-dextran can be administered both by intramuscular and intravenous route, intravenous route should be reserved for those who do not wish to have frequent intramuscular injections as iron can be given intravenously in one shot in form of total dose infusion (TDI).

Table 14.19: Difference between iron dextran and iron-sorbitrol citrate

Iron-dextran	*Iron-sorbitol-citric acid*
High molecular weight	Low molecular weight
Can be given both intramuscularly and intravenously	Only given by intramuscular route
10% to 30% of intramuscular dosage may be locally bound. This may not be available for immediate utilization	This iron formulation is not locally bound
Not excreted	About 30% gets excreted in the urine
When administered via intramuscular route, it gets absorbed through lymphatics	This gets directly absorbed into the circulation
It does not bind to transferrin	It may bind to transferrin and may even saturate it
This formulation is slowly taken up by macrophages and made available to the erythron	Directly available

Iron sucrose

Iron sucrose is available under a variety of names like ferric hydroxide sucrose, ferric oxide, iron (III) hydroxide-sucrose complex, etc. It is the oldest intravenous iron preparation which is being used as the first line IV iron of choice in the treatment of patients with chronic kidney disease (whether or not on dialysis) who have iron deficiency anemia. Iron sucrose is a complex of polymolecular iron-ferric hydroxide in sucrose. This preparation of iron is available in the US under the brand name venofer. It contains 20 mg of elemental iron per ml of solution. Following intravenous injection, iron is cleared from the plasma with an initial half-life of 30 minutes, following which the half-life increases to 6 hours. The recommended dose of venofer by the manufacturer is 5 ml (100 mg of elemental iron) no more frequently than three times weekly. Iron sucrose has been administered without any adverse effects in those patients who had manifested sensitivity reactions to iron dextran.

Side effects associated with parenteral iron (table 14.20)

The main drawback of intramuscular iron is the pain and staining of the skin at the site of injection, development of

Table 14.20: Complications associated with use of parenteral iron

System affected	*Symptoms produced*
Cardiovascular	Chest pain, tightness in the chest, hypotension, tachycardia, flushing, arrhythmias, etc.
Dermatologic	Urticaria, purpura, rash, cyanosis
Gastrointestinal	Abdominal pain, nausea, vomiting, diarrhea, etc.
Musculoskeletal/ soft tissue	Arthralgia, arthritis, myalgia, cellulitis, Brownish discoloration/ staining of underlying tissues and skin
Respiratory	Dyspnea, bronchospasm, wheezing, respiration arrest
Hematologic/ lymphatic	Leukocytosis, lymphadenopathy etc.
Neurologic	Convulsions, seizures, syncope, headache, weakness, paresthesia, dizziness, disorientation, numbness, unconsciousness

fever, chills, myalgia, arthralgia, injection abscess, etc. The most serious side effect associated with the use of intravenous iron is the risk of anaphylactic reactions, which can occur in about 0.7% of patients taking IV iron dextran. These reactions usually occur within the first few minutes of administration of the test dose. The earlier a reaction appears after start of infusion, the more severe it will be. These allergic reactions are generally considered to be type I hypersensitivity type [IgG immunoglobulin related]. Allergic reactions can be particularly more common in individuals with previous history of multiple drug allergies. Therefore, before administering parenteral iron, it is important to elicit history regarding allergies to any drugs in the past. Also, utmost caution is needed for total dose iron therapy via intravenous route to prevent the occurrence of severe anaphylactic reaction, which may even prove fatal at times.

It has been argued that a single iron infusion (TDI) is less likely to elicit an immune response in comparison to multiple injections given over a period of several weeks. If any adverse effect is noted, injection must be terminated at once and appropriate counter measures must be taken. A syringe containing a solution of epinephrine should be immediately available for treatment of anaphylaxis, in case this potentially fatal condition occurs.

Both intramuscular and intravenous injections can result in systemic reactions which may be either immediate or delayed. Immediate side effects include hypotension, headache, malaise, urticaria, nausea and anaphylactoid reactions whereas delayed reactions include lymphadenopathy, myalgia, arthralgia, fever, etc.

Methods of administration of intravenous iron

Intravenous form of iron can be administered in form of a single dose therapy or in form of multiple doses. TDI (total dose infusion) can be associated with adverse effects like immediate vascular collapse, tachycardia, dyspnea, cyanosis, vomiting, pyrexia, anaphylactic reactions, etc. Therefore the clinician must observe utmost caution before administration of total dose of iron through intravenous route. Also, total dose of iron therapy by intravenous route should only be given in a hospital setting where facilities are available to manage severe anaphylactic reactions.

Calculation of TDI

The total iron requirement reflects the amount of iron needed to restore hemoglobin concentration to normal or near normal levels plus an additional allowance to provide adequate replenishment of iron stores in most individuals with moderately or severely reduced levels of hemoglobin. It should be remembered that iron deficiency anemia will not appear until essentially all iron stores have been depleted. Thus, therapy should aim not only at the replenishment of hemoglobin iron but iron stores as well. Total dose for iron infusion is calculated through any of the following formulae:

Total Dose (ml) = [patient's wt (kg) × 2.3 (14 – patient's observed hemoglobin (gm/dl)] + 500 to 1000 mg

or

Total dose (mg) = [15 – patient's Hb (gm/dl)] × body weight (in Kg) × 3

or

Total dose of iron (mg) = whole blood hemoglobin deficit (gm/dl) × body weight (lb)

or

Dose (mL) = 0.0442 (14 – patient's observed Hb (gm/dl) × LBW + (0.26 × LBW)

LBW = Lean body weight in kg.

For women: LBW = 45.5 kg + 2.3 kg for each inch of patient's height over 5 feet. If the clinician finds it cumbersome to remember or use either of these formulae, the dose of iron for TDI can be also estimated from table 14.21.

After the total dose of iron has been calculated, the infusion must be prepared by diluting each 5 ml of iron dextran with 100 ml of normal saline. The whole dose can be given in form of a single infusion or may be divided into three parts to be administered intravenously over three consecutive days. The flow rate in the beginning must be kept at 20 drops/min for the initial five minutes. If no side effects are observed, the flow rate may be eventually increased to 40–60 drops/minute.

Table 14.21: Total parenteral iron requirement for hemoglobin restoration and iron stores replacement based on patient's observed hemoglobin levels

Body weight kg	*Dose of Dextran Iron (in mg) required, based on the patient's observed hemoglobin levels*							
	3 (g/dl)	*4 (g/dl)*	*5 (g/dl)*	*6 (g/dl)*	*7 (g/dl)*	*8 (g/dl)*	*9 (g/dl)*	*10 (g/dl)*
20	1452	1406	1460	1414	1368	1322	1276	1230
25	1690	1633	1475	1418	1460	1403	1345	1288
30	1828	1759	1690	1621	1452	1483	1414	1345
35	1966	1866	1805	1725	1644	1464	1483	1403
40	2104	2012	1920	1828	1736	1644	1452	1460
45	2242	2139	2035	1932	1828	1725	1621	1418
50	2380	2265	2140	2035	1920	1805	1690	1475
55	2518	2392	2265	2139	2012	1886	1759	1633
60	2656	2518	2380	2242	2104	1966	1828	1690
65	2794	2645	2495	2346	2196	2047	1897	1748
70	2932	2771	2610	2449	2288	2127	1966	1805

This way the intravenous infusion is given over 6–8 hours under constant observation.

14

Precautions before administration of intravenous iron

Precautions to be taken before administration of intravenous iron include the following:

- Prior to receiving the therapeutic dose, all patients should be given an intravenous test dose of 0.5 ml. The test dose should be administered slowly over the time period of at least 30 seconds (IM route) or one minute (IV route). Flushing and hypotension may occur from too rapid injections by the intravenous route.
- Severe/Fatal **a**naphylactic reactions characterized by respiratory difficulty or cardiovascular collapse have been reported with the use of iron dextran injections. Therefore, the drug should be given only when resuscitation techniques and facilities for treatment of anaphylactic and anaphylactoid shock are readily available.
- Epinephrine should be immediately available in case there is development of acute hypersensitivity reactions. Usual adult dose of epinephrine is 0.5 mL of a 1:1000 solution, administered through subcutaneous or intramuscular route.
- Though most anaphylactic reactions, following intravenous iron administration are usually evident within a few minutes, it is recommended that the patient must be observed for at least one hour before the administration of remainder of the therapeutic dose. If no adverse reactions are observed, iron can be administered until the calculated total amount of total iron has been administered.
- The clinician should regularly observe the patient to evaluate the occurrence of side effects such as difficulty in breathing, dizziness, development of rash, itchy skin etc.

Table 14.22: Technique of administration of intramuscular iron dextran injections

An intramuscular test dose of 0.5 ml should be given before the administration of the total intramuscular dose of iron.
The maximum daily dose of undiluted iron dextran should not exceed 2 mL (100 mg). This dose may be given daily until anemia is corrected.
Injection should be given into the muscle mass of the upper outer quadrant of the buttock.
Deep injection with a 2-inch or 3-inch 19 or 20 gauge needle is given.
While giving the injection, the patient must be in a lateral position with the injection site being uppermost.
A Z-track technique (displacement of the skin laterally prior to injection) is recommended to avoid tattooing of the skin.

Multiple dose therapy

Individual doses of 2 mL of iron dextran or less may be administered on a daily basis (after testing for hypersensitivity) until the required amount of iron (as calculated previously) has been reached. Intravenous injections of undiluted iron dextran are given slowly at a gradual rate, not exceeding 50 mg (1 mL) per minute.

Intramuscular iron Injections

The technique of administration of intramuscular iron injections is described in table 14.22.

Management of Anemic Patients During Intrapartum Period

Precautions to be taken during the time of labor and delivery are enumerated below:

First stage of labor

- Patient's blood grouping and cross-matching needs to be done.
- Though ideally the patient must be placed in a propped up position, the woman can be placed in any position which is comfortable to her.
- Adequate pain relief must be provided.
- Oxygen inhalation through face mask must be provided.
- Digitalisation may be required especially if the patient shows a potential to develop congestive heart failure.
- Antibiotic prophylaxis must be given as the anemic women are prone to develop infections.
- Strict asepsis needs to be maintained at the time of delivery or while performing procedures like artificial rupture of membranes.
- In case of preterm labor, β-mimetics and steroids must be administered cautiously in order to prevent pulmonary edema.

Second stage of labor

- In order to shorten the duration of second stage of labor, forceps or vacuum can be applied prophylactically.

At the time of delivery

The following precautions must be taken during the time of labor and delivery in order to reduce the amount of blood loss at the time of delivery:

- Routine administration of oxytocics (methargin, oxytocin etc) during delivery in order to reduce the blood loss.
- Late clamping of cord in baby at the time of delivery prevents anemia in infancy and should be employed as a routine practice in all babies. This simple practice helps in transferring 80 ml of blood with 50 mg of iron to the baby.
- Breast feeding for first six months after delivery reduces maternal iron loss by producing amenorrhea. Maternal iron and folic acid supplementation should be also continued in postpartum period.

Third stage

- Active management of third stage of labor.
- PPH to be managed aggressively.
- Advice regarding contraception must be given (e.g. barrier contraception).
- Postpartum sterilization may be offered to these women if the family is complete.

Complications

Anemia in pregnancy can have numerous adverse effects on the mother and the fetus. Some of these include:

MATERNAL

Adverse effects of anemia on the mother include the following:

1. High maternal mortality rate. In India 16% of maternal deaths are due to anemia.
2. Cerebral anoxia, cardiac failure.
3. Increased susceptibility to develop infection.
4. Inability to withstand even slight blood loss during pregnancy or delivery.
5. Abortions, preterm labor.

Maternal risk during antenatal period: Poor weight gain, preterm labor, PIH, placenta previa, accidental Hg, eclampsia, premature rupture of membrane (PROM), etc.

Maternal risk during intranatal period: Dysfunctional labor, intranatal hemorrhage, shock, anesthesia risk, cardiac failure, etc.

Maternal risk during postnatal period: Postnatal sepsis, subinvolution, embolism.

FETAL

Fetal adverse effects include the following:

- Preterm, low birth weight and IUGR babies.
- Fetal distress and neonatal distress requiring prolonged resuscitation and low APGAR scores at birth.
- Impaired neurological and mental development.
- Anemia can result in hypertrophy of placenta and cause increased placental: fetal ratio, which has been suggested to be a predictor for development of diabetes and cardiovascular diseases later in life.
- Reduction in fetal iron stores may extend into the first year of life. This may result in the higher tendency of infants to develop iron deficiency anemia and other associated adverse consequences on infant development related to this condition.
- Infants with anemia have higher prevalence of failure to thrive, poorer intellectual developmental milestones and higher rates of morbidities and neonatal mortalities in comparison to the infants without anemia.

Important Questions and Answers

Q.1. What should be the further management in the above mentioned case?

Ans. In this case, anemia is suspected clinically. Investigations like complete blood count (especially hematocrit and hemoglobin) with peripheral smear; blood indices especially MCV need to be carried out. The algorithm for diagnosis and treatment of patients with IDA are described in flow charts 14.2 and 14.3 respectively.

Q.2. Peripheral smear revealed presence of microcytic hypochromic type of anemia. What is the likely cause of anemia in the above mentioned case study?

Ans. Microcytic hypochromic picture on the peripheral smear examination is suggestive of iron deficiency anemia. The common causes of anemia during pregnancy are: Physiological causes, iron deficiency anemia and anemia due to hemorrhagic causes. In this case the history revealed that the patient had yet not started taking iron supplements and gave a history of menorrhagia prior to conception. These could be reasons for her to develop iron deficiency anemia.

Q.3. What are the periods of pregnancy during which the mother is at an increased for mortality?

Ans. The periods during pregnancy when the mother is at an increased risk for mortality include the following:

- 30–32 weeks of pregnancy
- During labor
- Immediately following delivery
- Purperium (pulmonary embolism/cardiac failure)

Q.4. What is hematocrit value and how is it influenced by anemia?

Ans. The hematocrit value refers to the percentage of red blood cells relative to plasma volume. In nonpregnant women hematocrit can range from 38% to 45%. However, in pregnant women due to hemodilution, normal values can be much lower, e.g. 34% in single and 30% in twin or multiple pregnancy even with normal stores of iron, folic acid and vitamin B12. The lower range of hematocrit during pregnancy is probably due to "the physiologic hemodilution of pregnancy" and does not indicate a decrease in oxygen carrying capacity or true anemia. Hematocrit levels less than 33% is considered iron deficient and should be treated.

Q.5. Should excessive iron consumption be avoided?

Ans. Besides being an essential mineral nutrient, iron in excessive dosages can also act as a toxin. The detrimental effects of iron in the body are related to the ability of iron to catalyze the formation of free radicals. Reactive oxygen species initiate lipid oxidation required for atherogenesis. Levels of body iron stores are a strong predictor of coronary risk in men and of carotid atherosclerosis in both men and women. However the exact contribution of iron stores to atherosclerosis and its complications is presently unknown because of lack of availablility of good evidence in the form of prospective randomized trials designed to test effects of reduction of iron stores.

Bibliography

1. Auerbach M, Witt D, Toler W, Fierstein M, Lerner RG, Ballard H. Clinical use of the total dose intravenous infusion of iron dextran. J Lab Clin Med. 1988;111(5):566-70.
2. Brokering, KL, Qaqish, RB. Management of Anemia of Chronic Disease in Patients With the Human Immunodeficiency Virus. Pharmacotherapy. 2003;23(11):1475-85.
3. Burns DL, Mascioli EA, Bistrian BR. Parenteral iron dextran therapy: A review. Nutrition. 1995;11(2):163-8.
4. Center for disease control. Recommendations to prevent and control iron deficiency in the United States. MMWR 1998; 47 (No. RR-3) p. 51 [online] Available from http://www.cdc.gov/ [Accessed April 2009]
5. Committee on Nutritional Status during Pregnancy and Lactation, Institute of Medicine. "Dietary intake during pregnancy". Nutrition during pregnancy: Part I: Weight gain, Part II: Nutrient supplements. Washington DC, National Academy Press 1990.
6. De Maeyer EM et al. Preventing and controlling iron deficiency anaemia through primary health care. Geneva, World Health Organization, 1989.
7. Hanson DB, Hendeles L. Guide to total dose intravenous iron dextran therapy. Am J Hosp Pharm. 1974;31(6):592-5.
8. Jacinto MS, Madan S. Iron deficiency anemia. Pharmacist. 2000;HS39-HS48.
9. Koda-Kimble MA, Applied Therapeutics for Clinical Pharmacists, 2nd ed, edited by Koda-Kimble et al, Applied Therapeutics, Inc., San Francisco 1978.
10. Kumpf VJ, Holland EG. Parenteral iron dextran therapy. DICP. 1990;24(2):162-6.
11. Kumpf VJ. Parenteral iron supplementation. Nutr Clin Pract. 1996;11(4):139-46.
12. Lange R, Diamant M, Marx JJM. Parenteral administration of iron: Possibilities and risks. Pharm Weekbl. 1997;132:103-11.
13. Low CL, Bailie GR, Eisele G. Sensitivity and specificity of transferrin saturation and serum ferritin as markers of iron status after intravenous iron dextran in hemodialysis patients. Ren Fail. 1997;19(6):781-8.
14. Reveiz L, Gyte GML, Cuervo LG. Treatments for iron-deficiency anemia in pregnancy. Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD003094. DOI: 10.1002/14651858.CD003094.pub2
15. Richter AW, Hedin HI. Dextran hypersensitivity. Immunol Today. 1982;3:132-8.
16. Rusia U, Gupta S, Agarwal N, Singh KC, Sikka M, Madan N. Efficacy of the new program of iron supplement in pregnancy in India. Indian Journal of hematology and blood transfusion. 1999;17(4):87-91.
17. Sloand JA, Shelly MA, Erenstone AL, Schiff MJ, Talley TE, Dhakal MP. Safety and efficacy of total dose iron dextran administration in patients on home renal replacement therapies. Perit Dial Int. 1998;18(5):522-7.

Chapter

15

Heart Disease during Pregnancy

Case Study

A 34-year-old primigravida patient gives a history of having valve prosthesis one year back and presently is on warfarin. She presents for the first time in the antenatal clinic at 28 weeks of gestation. Presently she is asymptomatic.

Introduction

Pregnancy is a physiological condition that places considerable burden on the heart, forcing it to work harder during the entire period of gestation. While a normal heart is quite capable of taking this extra workload right in its stride, a diseased heart may not be able to cope. Therefore, the preexisting cardiac lesions should be evaluated with respect to the risk imposed due to the stress of pregnancy. Confidential enquiry into the causes of maternal death in the UK (1997–1999) has shown maternal cardiac disease to be the cause for greatest number of maternal deaths. Thus, it is of prime importance for any obstetrician to be aware about the consequences of the presence of underlying cardiac disease in a pregnant woman.

Effect of Pregnancy on Heart Disease

- The obstetrician needs to be aware regarding the major cardiac drug classes, especially those used for treatment of hypertension and heart failure, which are contraindicated during pregnancy.
- Anticoagulation during pregnancy presents unique challenges because of the maternal and fetal side effects of warfarin, unfractionated heparin and LMWH.

Pregnancy is associated with significant hemodynamic changes that can aggravate valvular heart disease and increase the risk of thromboembolic events. These normal physiological changes pose a substantial demand on cardiac function in patients with valvular heart disease and may require the initiation or titration of cardiovascular medications to manage volume overload, hypertension, or arrhythmias. Furthermore, pregnancy is a state of relative hypercoagulability which clearly increases the risk of thromboembolic events.

Hemodynamic Changes Occurring During Pregnancy

The following hemodynamic changes occur during pregnancy (figure 15.1 and table 15.1):

- There is a 30% to 50% increase in cardiac output. The increase in cardiac output is achieved by three factors:
  - An increase in preload because of greater blood volume. Blood volume increases by 40% to 50% during normal pregnancy. The increase in plasma volume is greater than the increase in red blood cell mass, contributing to the fall in hemoglobin concentration (i.e., the "anemia of pregnancy", see chapter 14). The cause of underlying blood volume increase is related to an estrogen-mediated stimulation of the

Table 15.1: Normal hemodynamic changes during pregnancy

Hemodynamic parameter	*Change during normal pregnancy*	*Change during labor and delivery*	*Change during postpartum*
Blood volume	Increases by 40% to 50%	Increases	Decreases (auto-diuresis)
Heart rate	Increases by 10–15 beats per minute	Increases	Decreases
Cardiac output	Increases by 30% to 50% above the base line	Additional increase by 50%	Decreases
Blood pressure	Decreases by 10 mm of Hg	Increases	Decreases
Stroke volume	Increases during the first and second trimesters; decreases during the third trimester	Additional increase of 300–500 ml with each uterine contraction	Decreases
Systemic vascular resistance	Decreases	Increases	Decreases

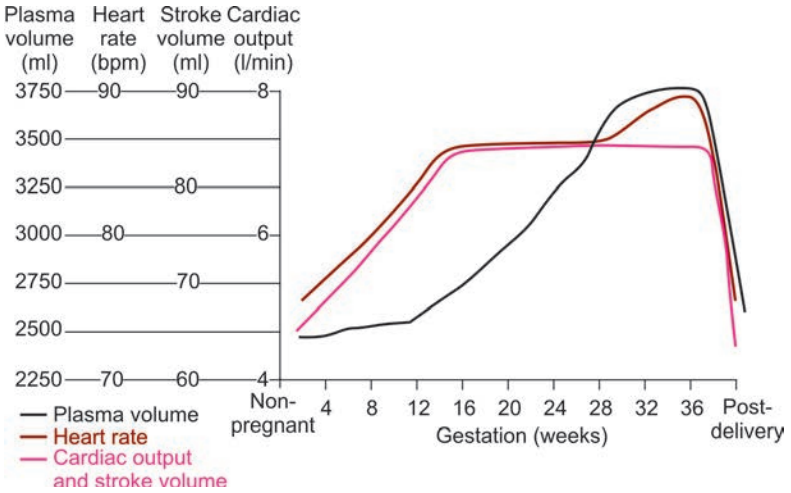


Fig. 15.1: Normal physiologic changes during pregnancy

renin-angiotensin system, which results in sodium and water retention.
  - Reduced afterload due to reduction in systemic vascular resistance; and
  - A rise in the maternal heart rate by 10 to 15 beats/min.
- Stroke volume increases during the first and second trimesters, but declines in the third trimester due to the compression of inferior vena cava by the uterus.
- Both plasma and interstitial colloid oncotic pressure decrease throughout pregnancy. There is an accompanying increase in the capillary hydrostatic pressure. An increase in capillary hydrostatic pressure or a decrease in colloid oncotic pressure is likely to cause edema.
- Blood pressure typically falls by about 10 mm Hg below baseline by the end of the second trimester because of reduction in systemic vascular resistance and the addition of new blood vessels in the uterus and placenta.

These changes begin early in the first trimester, peak during the second trimester and continue throughout the gestation and into the early postpartum period (figure 15.1). During labor, there is further increase in cardiac output, heart rate, blood pressure and systemic vascular resistance due to the stress and anxiety of labor and delivery and uterine contractions. Therefore, while preparing a woman for labor and delivery, it is important to anticipate that there will be important changes in maternal hemodynamic parameters.

These marked hemodynamic changes during pregnancy account for the development of several signs and symptoms during normal pregnancy that can mimic the signs and symptoms of heart disease. Normal pregnancy is typically associated with fatigue, dyspnea and decreased exercise capacity. Pregnant women usually have mild peripheral edema and jugular venous distention. Most pregnant women have audible physiologic systolic murmurs, created by augmented blood flow. A physiologic third heart sound (S_3), reflecting the increased blood volume, can sometimes be auscultated.

Hemodynamic Changes Occurring During Labor and Delivery

- During labor and delivery, hemodynamic fluctuations can be profound. Each uterine contraction displaces 300 to 500 mL of blood into the general circulation. Stroke volume increases, along with a resultant rise in cardiac output by an additional 50% with each contraction. Thus, it is possible for the cardiac output during labor and delivery to be 75% above baseline.
- Mean arterial pressure also rises, in part because of maternal pain and anxiety. Blood loss during delivery (300 to 400 mL for a vaginal delivery and 500 to 800 mL for a cesarean section) can contribute to hemodynamic stress.

Hemodynamic Changes Occurring During the Postpartum Period

Hemodynamic changes during the postpartum state are equally dramatic. Some of them are as follows:

- Relief of inferior vena caval compression results in an increase in venous return, which augments cardiac output and causes a brisk diuresis.
- The hemodynamic changes return to the prepregnant baseline within 2 to 4 weeks following vaginal delivery and within 4 to 6 weeks after cesarean section.

CONGENITAL OR ACQUIRED CARDIAC LESIONS

Specific Congenital or acquired cardiac lesions encountered during pregnancy are as follows:

Low-Risk Lesions

Mitral regurgitation

Chronic mitral regurgitation, most commonly encountered as a result of rheumatic heart disease is usually well tolerated during pregnancy. However, new-onset atrial fibrillations or severe hypertension can precipitate hemodynamic deterioration. Pulmonary edema and life-threatening cardiac decompensation can be produced as a result of acute mitral regurgitation (e.g., from rupture of chordae tendineae). Women with severe mitral regurgitation and signs of cardiac decompensation before pregnancy are advised to undergo mitral valve repair before conception.

Aortic regurgitation

Aortic regurgitation, similar to mitral regurgitation is generally well tolerated during pregnancy. Aortic regurgitation may be encountered in women with rheumatic heart disease, a congenitally deformed bicuspid aortic valve, infective endocarditis, or in presence of connective tissue disease. Women with bicuspid aortic valves are at increased risk for aortic dissection. Therefore, it is important to follow up such patients to assess if they develop signs and symptoms of this complication. Ideally, women with severe aortic regurgitation and signs of cardiac decompensation should undergo operative repair before conception.

Congestive heart failure resulting from mitral or aortic regurgitation can be treated with digoxin, diuretics and vasodilators (e.g. hydralazine). Angiotensin converting enzyme (ACE) inhibitors are teratogenic and therefore are contraindicated during pregnancy. Though use of β-blockers may be at times associated with fetal bradycardia and growth retardation, beta blockers are generally considered safe during pregnancy.

Moderate-Risk Lesions

Mitral stenosis

The most common valvular heart disease encountered during pregnancy is mitral stenosis. In mothers with rheumatic heart valve disease, the fetus develops almost normally. The only difference noted may be mild growth retardation. The hypervolemia and tachycardia associated with pregnancy may aggravate the pressure and volume gradient across mitral valve. Elevated pressure of left atrium as a result of mitral stenosis may cause atrial fibrillations and pulmonary edema. This can sometimes precipitate heart failure and cause rapid cardiac decompensation, primarily due to an uncontrolled ventricular rate. Even patients with only mild to moderate mitral stenosis (who have no symptoms before pregnancy) may develop atrial fibrillation and heart failure during the antepartum and peripartum periods. Patients with moderate to severe mitral stenosis often experience hemodynamic deterioration during the third trimester or during labor and delivery. Additional displacement of blood volume into the systemic circulation during contractions makes labor particularly hazardous.

Mild mitral stenosis can often be managed with careful medical therapy during pregnancy. Drugs like digoxin and beta blockers can be used to reduce heart rate and diuretics can be used to reduce the blood volume and left atrial pressure. With development of atrial fibrillations and hemodynamic deterioration, electrocardioversion can be performed safely. Anticoagulation must be initiated with the onset of atrial fibrillations in order to reduce the risk of stroke. Patients with moderate to severe mitral stenosis should be referred to a cardiologist.

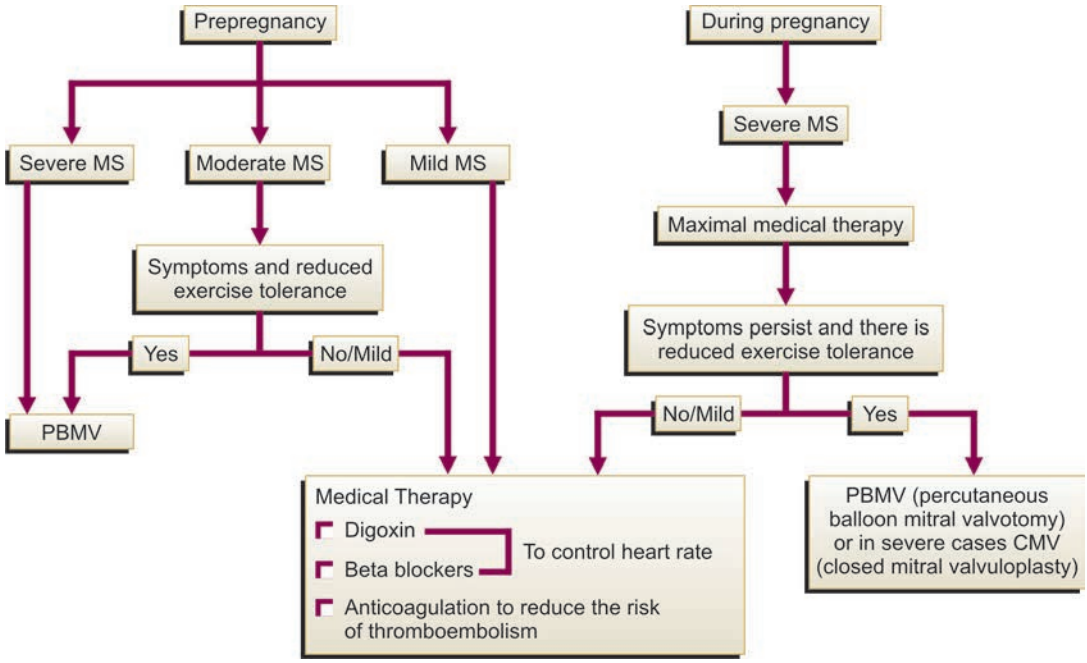
Severe mitral stenosis is associated with a high likelihood of maternal complications (including pulmonary edema and arrhythmias) or fetal complications (including premature birth, low birth weight, respiratory distress and fetal or neonatal death). As a result, these women may require corrective surgery via operative repair or replacement or percutaneous mitral balloon valvotomy before conception or during pregnancy (flow chart 15.1). Heart surgery may be necessary when medical treatment fails to control heart failure or symptoms remain intolerable to the patients despite medical therapy. While open heart surgery should not be undertaken lightly during pregnancy because of the risks to the fetus, closed mitral valvuloplasty (CMV) is a relatively safe procedure. CMV is usually done in cases of severe pulmonary congestion unresponsive to drugs, profuse hemoptysis and any episode of pulmonary edema before pregnancy (because there is a high chance of a recurrent attack during the present pregnancy). While the second trimester of pregnancy is usually the preferred time for any heart surgery, CMV can be safely performed at any stage of pregnancy if required. During pregnancy, percutaneous valvotomy is usually postponed to the second or third trimesters to avoid the chances of radiation exposure to the fetus during the first trimester.

Most patients with mitral stenosis can undergo vaginal delivery. However, patients with symptoms of congestive heart failure or moderate to severe mitral stenosis may require close hemodynamic monitoring during labor, delivery and for several hours into the postpartum period.

Aortic stenosis

The most common cause of aortic stenosis in women of childbearing age is congenital bicuspid valve. Mild to moderate aortic stenosis with preserved left ventricular function usually

Flow chart 15.1: Management of women with mitral stenosis during and prior to pregnancy



is well tolerated during pregnancy. On the other hand, severe aortic stenosis (aortic valve area less than 1.0 cm^2) may be associated with a high risk of maternal morbidity. Symptoms such as dyspnea, angina pectoris, or syncope usually become apparent late in the second trimester or early in the third trimester. Women with known severe aortic stenosis should be referred to a cardiologist. Ideally, they should undergo correction of the valvular abnormality before conception. Treatment options include surgical repair, surgical valve replacement, and percutaneous balloon valvotomy.

When severe symptomatic aortic stenosis is diagnosed during pregnancy, maximal medical therapy is preferred over any intervention. However, if a patient has refractory symptoms and hemodynamic deterioration, despite maximal medical therapy, percutaneous balloon valvotomy may be performed. Similar to the cases with mitral stenosis, hemodynamic monitoring must be performed during labor and delivery in the cases of aortic stenosis.

High-Risk Lesions

The high-risk conditions are associated with an increased maternal and fetal mortality. Pregnancy is not advisable in these cases. However, if pregnancy does occur, the risks of maternal mortality and morbidity must be assessed on an individual case basis. If the maternal risk appears to be extremely high, the option of medical termination of pregnancy may be considered in order to safeguard maternal health. If the pregnancy is continued, these patients are best managed with the help of a cardiologist and maternal-fetal medicine specialist at a tertiary care center with high-risk ICU facilities and a level three neonatal unit.

Acquired Cardiovascular Disorders During Pregnancy

Maternal placental syndromes

A group of disorders, known collectively as maternal placental syndromes, have been associated with an increased maternal risk of premature cardiovascular disease. In the CHAMPS study, the maternal placental syndrome (MPS) was defined as the presence of preeclampsia, gestational hypertension, placental abruption or placental infarction during pregnancy. There has been growing body of evidence which shows close association between cardiovascular risk factors, MPS and future development of cardiovascular disease. It is possible that an underlying abnormal vascular health that predates pregnancy manifests in the form of MPS during pregnancy or as chronic cardiovascular disease later in life. Women with MPS have been shown to be twice as likely to experience a hospital admission or revascularization procedure for coronary, cerebrovascular, or peripheral vascular disease in comparison to the women without MPS. The risk of premature cardiovascular disease is higher after a maternal placental syndrome, especially in the presence of fetal compromise.

Affected women should have their blood pressure and weight assessed about 6 months postpartum and a healthy lifestyle should be emphasized.

Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is defined as the development of idiopathic left ventricular systolic dysfunction (demonstrated by echocardiography) in the interval between the last month of pregnancy up to the first 5 postpartum months in women without preexisting cardiac dysfunction. The incidence of PPCM in the United States is estimated to be 1 in 3000 to 4000 live births. The exact cause of PPCM is unknown, although causes like viral myocarditis, autoimmune phenomena and specific genetic mutations have been proposed as possible causes of peripartum cardiomyopathy.

Medical therapy for PPCM may be initiated during pregnancy and continued uptil the postpartum period. Drugs like digoxin, beta blockers and hydralazine may be used safely during pregnancy and at the time of breastfeeding. Treatment of peripartum cardiomyopathy involves salt restriction and the use of diuretics to decrease pulmonary congestion and volume overload. In patients with systolic dysfunction, afterload is usually reduced with vasodilators. Beta blockers may improve left ventricular function in patients with cardiomyopathy. Beta blockers are considered safe during pregnancy, although there have been case reports of fetal bradycardia and growth retardation. ACE inhibitors, angiotensin receptor blockers and aldosterone antagonists are contraindicated during pregnancy. Most ACE inhibitors can be initiated during the postpartum period, even in women who breastfeed. Anticoagulation can be considered for select patients with severe left ventricular dilation and dysfunction. When conventional medical therapy becomes unsuccessful, women with PPCM may require intensive intravenous therapy, mechanical assist devices, or even cardiac transplantation. More than 50% of the women with PPCM completely recover normal heart size and function, usually within 6 months of delivery. Women with PPCM and persistent left ventricular dysfunction who attempt subsequent pregnancy face a high risk of maternal morbidity and mortality. These women should be counseled against subsequent pregnancies.

The mode of delivery for patients with peripartum cardiomyopathy is generally based on obstetric indications. After stabilization of the maternal condition, in most cases induction and vaginal delivery can be attempted in consultation with consultant obstetrician and anesthetic staff. The advantages of vaginal delivery are minimal blood loss, greater hemodynamic stability, avoidance of surgical stress and lower chances of postoperative infection and pulmonary complications. Effective pain management is a necessity to avoid further increases in cardiac output from pain and anxiety. The use of local infiltration anesthesia in combination with bilateral ilio-inguinal nerve block has been described. However, regional anesthesia has the additional advantages of reducing preload and afterload and minimizes the fluctuations in cardiac output associated with labor. Cesarean delivery is reserved for indications such as fetal distress or failure to progress.

Table 15.2: Clinical definition of peripartum cardiomyopathy

Heart failure within last month of pregnancy or five months postpartum
Absence of prior heart disease
No determinable cause
Strict echocardiographic indication of left ventricular dysfunction: Ejection fraction <45% and/or fractional shortening <30% or end diastolic dimension >2.7 cm per m^2 body surface area

The clinical diagnosis of peripartum cardiomyopathy is based on parameters enlisted in table 15.2. The diagnosis of peripartum cardiomyopathy presents a challenge because many normal women in the last month of a normal pregnancy may experience symptoms like dyspnea, fatigue and pedal edema, which may be indicative of early congestive cardiac failure. Symptoms and signs which raise the suspicion of heart failure include paroxysmal nocturnal dyspnea, chest pain, nocturnal cough, presence of new regurgitant murmurs, pulmonary crackles, elevated jugular venous pressure and hepatomegaly.

Diagnosis of peripartum cardiomyopathy rests on the echocardiographic identification of new left ventricular systolic dysfunction during a limited period around parturition, when other causes of cardiomyopathy have been excluded (table 15.2). All patients usually exhibit cardiomegaly on chest X-ray. Endomyocardial biopsy demonstrates myocarditis in more than 70% of the patients.

Coronary Artery Disease

Acute myocardial infarction (AMI) during pregnancy is rare, occurring in 1 in 35,000 pregnancies. Independent predictors of AMI during pregnancy include chronic hypertension, maternal age, diabetes and preeclampsia. Most myocardial infarctions occur during the third trimester in women older than 33 years who have had multiple prior pregnancies. Medical therapy for acute myocardial infarction must be modified in the pregnant patient. Percutaneous coronary intervention using both balloon angioplasty and stenting with the use of lead shielding to protect the fetus has been successfully performed in pregnant patients with AMI. Although

thrombolytic agents substantially increase the risk of maternal hemorrhage, their use may be permitted in situations where facilities for cardiac catheterization are not available. Low-dose aspirin and nitrates are considered safe. Beta blockers are generally safe. Short term heparin administration has not been associated with increased maternal or fetal adverse effects. ACE inhibitors and statins are contraindicated during pregnancy. Hydralazine and nitrates may be used as substitutes for ACE inhibitors. Clopidogrel and glycoprotein IIb/IIIa receptor inhibitors have been used safely in individual pregnant patients.

Arrhythmias in Pregnancy

Premature atrial or ventricular complexes, or both, are the most common arrhythmias during pregnancy. They are not associated with adverse maternal or fetal outcomes and do not require antiarrhythmic therapy. Supraventricular tachyarrhythmia (SVT) is also common. Patients with SVT should be instructed about the performance of vagal maneuvers. Additionally, beta blockers or digoxin, or both, can be used for controlling the ventricular rate. Adenosine and direct current cardioversion are both safe during pregnancy and can be used to treat SVT.

Congenital Heart Disease in Pregnancy

The commonest birth defects seen during pregnancy include patent ductus arteriosus, atrial septal defects and ventricular septal defects. Other less common causes include pulmonary valve stenosis, tetralogy of Fallot and coarctation of aorta. While the tetralogy of Fallot may carry a maternal mortality risk of 4% to 20% at the time of pregnancy, atrial septal defects can be considered as the safest of all birth defects during pregnancy.

In mothers with congenital heart disease, pregnancy is almost normal in diseases without cyanosis. However, in cyanotic mothers (e.g. tetralogy of fallot), many problems like severe growth retardation and higher abortion rates may arise. Since the maternal blood has very low oxygen content in these cases, there is a lower oxygen exchange across the placenta and the fetus gets lesser oxygen than normal. As a result, the fetus may be growth retarded, may die or may be delivered prematurely. Coarctation of the aorta (CoA) is another special condition, in which fetal loss is higher than normal as a result of lower blood flow to the placenta due to the narrowed aorta. In uncorrected CoA, the recommended management options include medical termination of the pregnancy or surgical repair of the CoA before delivery. In case, the pregnancy does occur in cases with uncorrected CoA, cesarean delivery is usually preferred in order to avoid the risk of dissection that might be brought on by the mother straining in labor. Also, the risk of congenital heart disease in such pregnancies is 2% to 4%, which is twice the incidence of heart disease in the general population. In pregnancy, the fall in systemic vascular resistance and increase in blood volume and cardiac output can cause functional deterioration in certain conditions. A minimally symptomatic woman with good ventricular function, normal oxygen saturation and no left heart obstruction would be able to tolerate pregnancy well. Women with pulmonary hypertension or dilated aortic root (pre-replacement) should be counseled against pregnancy and given appropriate contraceptive advice.

History

Women with preexisting cardiac dysfunction usually experience cardiac deterioration during the end of the second trimester. Typical signs and symptoms include fatigue, dyspnea on exertion, orthopnea, nonspecific chest pain, peripheral edema and abdominal discomfort and distention.

It is important to elicit the history of the following symptoms while taking history:

Dyspnea

Though some of amount of exertional dyspnea or breathlessness can commonly occur during normal pregnancy, severe dyspnea, especially that occurring at rest or while sleeping or that resulting in inability to perform normal activities may be suggestive of heart disease. Dyspnea can commonly result from LVF, pulmonary embolism, etc. Pulmonary embolism is associated with acute onset of dyspnea and pleuritic chest pain. While taking the history of dyspnea it is important to enquire the circumstances under which the patient experiences breathlessness. The dyspnea can be graded into four categories (table 15.3) depending on whether dyspnea occurs during exertion, while doing daily activities, or at rest. The

Table 15.3: Medical research council classification of dyspnea

Grade	*Description*
I	No dyspnea at rest; dyspnea is present only while doing strenuous exercise (e.g. walking up the hill).
II	Shortness of breath when walking with the people of same age group on ground level.
III	Limitation of walking pace (slower than others) as a result of dyspnea. The individual has to stop inbetween to catch breath.
IV	The individual needs to stops to catch for breath after walking nearly every 100 meters on level ground.
V	Severe degree of dyspnea which severely limits the individual's activities of daily living and prevents her from leaving her house.

history of orthopnea or shortness of breath while sleeping at night can be elicited by asking about the number of pillows the patient uses at night in order to prevent breathlessness. Paroxysmal nocturnal dyspnea can be diagnosed if the patient gives history of waking up at night, gasping for breath.

Peripheral Edema

Pulmonary embolism is associated with acute onset of dyspnea and pleuritic chest pain. In cases with clinical suspicion for pulmonary embolism, history about various risk factors associated with DVT also needs to be taken.

Palpitation

Palpitation may be due to ectopic beats, atrial fibrillations, supraventricular tachycardia and ventricular tachycardia, thyrotoxicosis, anxiety, etc. The obstetrician must take the history about previous episodes of palpitations; precipitating/relieving factors; duration of symptoms and presence of associated symptoms like chest pain, dyspnea, or dizziness.

Chest Pain

Acute history of chest pain radiating to shoulders/neck may be suggestive of myocardial infraction. Chest pain in association with headache, dysarthria, limb weakness, etc may be indicative of CNS causes.

Light-headedness or Fainting

Owing to the normal pregnancy related cardiovascular changes (described previously), many healthy pregnant women may show symptoms mimicking those of cardiac disease, including fatigue, dyspnea, and light-headedness, etc. Even in normal pregnancy, numerous abnormal findings suggestive of cardiac abnormalities may be observed on physical examination, electrocardiography and echocardiography. Some of these are described in table 15.4

General Physical Examination

Vital Signs

Pulse: The pulse rate is important. A rapid heart rate is almost always an indication that the patient is anxious or ill. The pulse must be recorded in both the upper limbs. Abnormalities in pulse pattern may be suggestive of underlying cardiac disease. Presence of radiofemoral delay could be suggestive of coarctation of aorta.

Blood pressure: The correct method of measuring the blood pressure has been fully described in chapter 12.

Respiratory rate: Look for any signs which suggest that the patient has difficulty breathing (dyspnea).

Finger clubbing: Clubbing of fingers may be associated with the diseases of heart or lungs.

Cyanosis: Cyanosis is bluish discoloration of the skin and mucous membranes due to presence of at least 5 gm% of deoxygenated hemoglobin in the blood. Presence of cyanosis suggests that arterial saturation is less than 85%. The place to look for peripheral cyanosis is the finger tips including underneath the nail beds. The places to look for central cyanosis are the lips and tongue.

Table 15.4: Normal findings in pregnancy suggestive of heart disease

CLINICAL EXAMINATION	
Symptoms	*Physical findings*
Fatigue, tiredness	Peripheral edema, hyperventilation
Dyspnea, orthopnea	Displaced apical impulse
Light-headedness	Prominent juglar venous pulsations
Syncope	Widely split first and second heart sounds
	Soft ejection systolic murmur
	Increased intensity of S_1; persistent splitting of S_2.
INVESTIGATIONS	
ECG	*ECHO*
Right or left axis deviation	Small pericardial effusion
ST-segment depression, T-wave changes	Functional tricuspid and mitral regurgitation
Sinus tachycardia	Mild increase in ventricular diastolic dimension
Premature atrial or ventricular ectopic beats	Preservation of ejection systolic volume

Features indicative of infective endocarditis: Features such as splinter hemorrhages (areas of hemorrhage under the fingernails or toenails), Janeway lesions (small, nontender, erythematous or hemorrhagic macular or nodular lesions, occurring most commonly on the palms and soles including the thenar and hypothenar eminences), Osler's nodes (tender, transient nodules commonly present in the pulp of fingers; at times also may be present in the sole of the feet), etc.

Hepatomegaly: Presence of hepatomegaly or ascites on abdominal examination could be due to congestive heart failure.

Peripheral edema: Presence of edema in the feet or sacral edema could occur as a result of congestive cardiac failure.

Specific Systemic Examination

EXAMINATION OF CARDIOVASCULAR SYSTEM

Palpation

In normal individuals, the cardiac apex is normally palpated in the left fifth intercostal space, one centimeter medial to the midclavicular line. The cardiac apex may be shifted downwards and outwards in cases of left ventricular enlargement.

Auscultation

Upon auscultation of the precordial area, normal heart sounds (S_1 and S_2) can be heard. Upon auscultation, it is important to note whether or not an additional sound (e.g. murmur, opening snap, click, third or fourth heard sounds, etc) are present.

Table 15.5: Characteristics of a functional murmur

It is midsystolic
It is soft, not louder than 2/6
It is ejection in character
It does not radiate
It is usually heard best over the mitral or aortic areas
It is usually asymptomatic

The cardiac areas, which are most commonly auscultated, include the following:

- *Mitral area* (at the point of cardiac apex): Corresponds to the left fifth intercostal space and is 1 cm medial to the mid clavicular line.
- *Tricuspid area:* The lower left parasternal border is the tricuspid area.
- *Pulmonary area:* The left second intercostal space.
- *The aortic area:* The right second intercostal space.
- *The second aortic area or the Erb's area:*The left third intercostal space.

Functional murmurs are frequently heard during pregnancy due to the increased cardiac output and do not require further investigation or management. The functional murmur needs to be distinguished from a pathological one. The characteristics of a functional murmur are enumerated in table 15.5. The characteristics of some commonly encountered pathological murmurs are described below in table 15.6.

A detailed examination of the cardiovascular system is beyond the scope of this book. The reader needs to refer to a standard medical text book for that.

Table 15.6: The characteristics of some common pathological murmurs

	Location	*Character*	*Shape*	*Duration*	*Radiation*
Mitral stenosis	Mitral area	Low pitched, rough and rumbling	Plateaus with presysolic accentuation	Mid diastolic and presystolic	-
Tricuspid stenosis	Tricuspid area	Low pitched, rumbling	Plateaus	Mid diastolic	-
Mitral regurgitation	Apex	High pitched	Plateaus	Holosystolic	Radiates to axilla
Tricuspid regurgitation	Tricuspid area	High pitched	Plateaus	Holosystolic	-
Ventricular septal defect	Lower left sternal border	High pitched	Plateaus	Holosystolic	Heard across the sternum
Aortic stenosis	First aortic area	High pitched, harsh or musical	Crescendo-decrescendo	Mid systolic	Radiates to carotids
Pulmonary stenosis	Pulmonary area	High pitched, harsh or musical	Crescendo-decrescendo	Mid systolic	-
Aortic regurgitation	Second aortic area	High pitched, blowing	Decrescendo	Early diastolic	Towards apex
Pulmonary regurgitation	Pulmonary area and one interspace below	High pitched, blowing	Decrescendo	Early diastolic	-

ABDOMINAL EXAMINATION

Palpation of abdomen in pregnant women with heart disease is unlikely to show any abnomality related to the heart disease per se except for organomegaly or ascites as previously described.

Management

In a woman with heart disease, the following areas must be considered at the time of pregnancy or while considering pregnancy:

- Prepregnancy management
- Antepartum management
- Peripartum management.

PREPREGNANCY MANAGEMENT

Management of women with heart disease should be preferably by a multidisciplinary team involving the obstetrician and cardiologist. The impact that her heart condition is likely to have on the pregnancy must be discussed well in advance before the patient becomes pregnant. The various issues which need to be discussed at this time are described below:

Risk assessment: A careful cardiac examination and assessment of functional capacity is required to determine the likelihood that patient would be able to tolerate the increased hemodynamic burden of pregnancy, labor and delivery and the risk of complications during gestation. The patients with heart disease who are planning pregnancy must have their risk assessed by performing the following tests:

- A thorough cardiovascular history and examination
- A 12-lead electrocardiogram
- A transthoracic echocardiogram
- An arterial oxygen saturation measurement by percutaneous oximetry
- *Risk stratification:* The New York Heart Association functional classification of heart disease is shown in table 15.7. Patients can be classified into various NHYA classes based on their underlying functional cardiac status. Patients with NYHA class III and IV are at a higher risk. Depending on the type of heart disease diagnosed (table 15.8), the

Table 15.7: New York Heart Association functional classification of heart failure

Class I	Patients with cardiac disease, but without resulting limitations of physical activity. Ordinary physical activity does not cause fatigue, palpitations, dyspnea or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity results in fatigue, palpitations, dyspnea or anginal pain.
Class IV	Patients with cardiac disease resulting in an inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency may even be present at rest. If any physical activity is undertaken, discomfort is increased.

Table 15.8: Risk stratification of patients depending upon the underlying cardiac disease

Low-risk lesions
Atrial septal defect; ventricular septal defect; patent ductus arteriosus
Small left to right lesions
Repaired lesions without residual cardiac dysfunction
Bicuspid aortic valve without stenosis
Mild-moderate pulmonic stenosis,
Valvular regurgitation with normal ventricular systolic function
Isolated mitral valve prolapse without significant regurgitation
Mitral regurgitation with normal left ventricular function and NYHA class I or II
Aortic Regurgitation with normal LV function and NYHA class I or II
Asymptomatic aortic stenosis with low mean gradient (<50 mm Hg) and normal left ventricular function (Ejection Fraction > 50%)
Intermediate-risk features
Mitral stenosis
Large left to right shunts
Uncorrected coarctation of aorta
Unrepaired cyanotic congenital heart disease
Moderate aortic stenosis
Prosthetic valves
Severe pulmonary stenosis
Moderate-to-severe systemic ventricular dysfunction
Marfan syndrome with a normal aortic root
Moderate or severe MS
High-risk lesions
Eisenmenger Syndrome
NYHA (Class III or IV symptoms)
Patients with significant pulmonary hypertension
Marfan syndrome with aortic root or major valvular involvement
Peripartum cardiomyopathy with residual left ventricular systolic dysfunction
Complex cyanotic heart disease (TOF, Ebstein's anomaly, TA, TGA, tricuspid atresia)
Severe AS with or without symptoms
Aortic or mitral valve disease, or both (stenosis or regurgitation), with moderate or severe LV dysfunction (EF < 40%)

Table 15.9: Indications for medical termination of pregnancy in patients with heart disease

Primary pulmonary hypertension (PPH)
Eisenmenger syndrome
Pulmonary venoocclusive disease
Severe lung disease with pulmonary hypertension - some cases
Cardiomyopathy with NYHA Class III or IV symptoms
Marfan syndrome with an abnormal aorta
History of peripartum cardiomyopathy
Severe uncorrected valvular stenosis

patients can be stratified into low-risk, intermediate-risk or high-risk. In women who have only milder forms of heart disease with no underlying hemodynamic problems, nothing special needs be done. However, in patients belonging to high-risk and having potential or real hemodynamic problems (signs of heart failure or low cardiac output), important decisions including the need for medical termination of pregnancy may be required. Indications for medical termination of pregnancy in patients with heart disease are enumerated in table 15.9. In these cases, other alternatives of motherhood including options like surrogacy or adoption can be considered.

- *Risk associated with the use of anticoagulant drugs:* Women who have prosthetic heart valves and are of childbearing age should be counseled about the potential issues that might arise, including the development of thrombosis. If these individuals are prescribed anticoagulant drugs, there could be risks associated with the use of these drugs during pregnancy.
- *Women undergoing ART:* Women with heart disease undergoing any procedure related to assisted reproductive techniques are often at an increased risk. The matter should be discussed by the multidisciplinary team before initiating any such treatment.
- *Cardiac surgical interventions:* Any cardiac surgical interventions in women of childbearing age should take into account the effect these may have on pregnancy. For example, due to the increased risk of thrombosis associated with the use of prosthetic mechanical valves during pregnancy, consideration should be given towards using tissue valves for valve replacement.
- *Advice regarding contraception*: In women with severe heart disease, preconception counseling (including advice regarding contraception) should be started right from adolescence. Advice regarding contraception should be given in a way so as to take into account any increased risks of thrombosis or infection associated with the various contraceptive methods and their interaction with various heart lesions. The parameter of key importance regarding contraception in these patients is its efficacy. The consequences of contraceptive failure in women with severe heart disease can prove fatal. Barrier methods are safe for all cardiac patients and clearly have the added benefit of providing protection against sexually transmitted diseases. Subdermal progestogen implants and progestogen-loaded intrauterine devices are efficacious and are safe method for most women with significant heart disease. Combined oral contraceptive pills are relatively contraindicated in women with heart disease because the estrogen component of the combined oral contraceptive confers an increased risk of thrombosis. It is therefore contraindicated in pregnant woman with heart disease who already has a high thrombotic risk. These women must also be educated regarding the importance of emergency contraception in case she does have an unprotected sexual intercourse. Sterilization by tubal ligation may be appropriate for women in whom pregnancy would be high risk.
- In anticipation of pregnancy, drugs with potential harm to the fetus should be discontinued.

ANTENATAL MANAGEMENT

Investigations

Noninvasive testing in patient with heart disease may include an electrocardiogram (ECG), chest radiograph and echocardiogram. The ECG may reveal a leftward shift of the electrical axis, especially during the third trimester, when the diaphragm is pushed upward by the uterus. Routine chest radiography should be avoided, especially in the first trimester, due to the risk of radiation exposure to the fetus. Echocardiography is an invaluable tool for the diagnosis and evaluation of suspected cardiac disease in the pregnant patient.

Antenatal Care

Prevention of risk factors: The focus of care early in pregnancy must be to avoid risk factors including infection, high blood pressure, obesity, multiple pregnancies, anemia, arrhythmia, etc. Since these risk factors are likely to exacerbate the symptoms related to heart disease, they must be identified as soon as possible and treated aggressively.

Treatment of heart failure: If heart failure develops during the antenatal period, the woman must be preferably admitted to the hospital. The drugs like digoxin and diuretics form the cornerstones of therapy. Once heart failure is brought under control, most women can be discharged from hospital.

Fetal surveillance: Strict fetal surveillance may be required during the antenatal period. When the patient is

stable, no special treatment is needed. However when there are signs of hemodynamic compromise, careful fetal monitoring is required. Intrauterine growth retardation (IUGR) and fetal asphyxia are the major concerns. Clinical and ultrasound examinations are most commonly performed. Ultrasonographic examination is very helpful, and helps in the assessment of following parameters:

- Considering termination of pregnancy in highly complex cases.
- Providing maternal reassurance that everything is fine.
- Confirmation of gestational age.
- Assessment of the amniotic fluid volume.
- To rule out fetal anomalies in cases of congenital heart disease.

Other tests that might be required in special circumstances are:

- Cardiotocography to measure fetal heart rate
- Color Doppler flow studies to measure fetal and maternal placental blood flow.
- Fetal blood sampling to detect low oxygen content.
- Women with congenital heart disease are at a relatively increased risk of having a baby affected with congenital heart disease and should be offered fetal echocardiography.

Management by a multidisciplinary team: Similar to the preconceptional period, these women with heart disease must be assessed clinically as soon as possible in the antenatal period by a multidisciplinary team comprising of a cardiologist, obstetrician, anesthetists, midwives, neonatologists, etc. Delivery should be planned to take place at a tertiary unit which would be able to provide combined obstetric, cardiological and surgical care for a women with heart disease.

Use of beta blockers: In women on beta blockers (for example for the treatment of systemic hypertension or to reduce the risk of arrhythmia) there is a small increased risk of intrauterine growth restriction. Therefore in these cases fetal growth should be monitored regularly, using ultrasound measurement of fetal abdominal circumference. Empirical therapy with beta blocker is advisable in patients with aortic coarctation, marfan syndrome and ascending aortopathy for other reasons (e.g., a bicuspid aortic valve).

Levels of mitral and aortic stenosis that are not problematic in nonpregnant women may be poorly tolerated in pregnancy. Reduction of heart rate is often the key to successful management, especially in cases of stenosis of the mitral valve. Beta blockers are useful in this context. Beta blockers rather than digoxin should be used to control the heart rate for patients with functionally significant mitral stenosis.

Bed rest: According to the guidelines by ACC/AHA (2006), the importance of simple interventions, such as bed rest, limitation of activities and avoidance of the supine position, should not be overlooked.

Increased frequency of antenatal visits: In general, prenatal visits should be scheduled every month in women with mild disease and every 2 weeks in women with moderate or severe disease, until 28 to 30 weeks and weekly thereafter until delivery.

Use of various cardiac interventions: Percutaneous catheter interventions are safe and effective in the treatment of coronary disease and mitral and pulmonary valve stenosis. In contrast, balloon dilation for aortic valve disease should only be considered for highly selected cases as it carries a higher risk and a lower success rate. Such interventions in pregnancy should only be performed by experienced operators and radiation exposure should be minimized. If cardiac surgery requiring the use of cardiopulmonary bypass does need to be performed, consideration should be given to early delivery of the fetus if it is viable. The standard technique of cardiopulmonary bypass is often associated with deep hypothermia and low perfusion pressure, which carries nearly 30% risk of fetal mortality. Therefore, in order to protect the fetus, hypothermia should be avoided as far as possible and perfusion pressures must be kept as high as possible. In pregnancy, if there is clinical evidence of acute coronary insufficiency or myocardial infarction, coronary angiography is appropriate. The radiation exposure to the fetus is not sufficient so as to contraindicate this essential diagnostic procedure.

Use of antiarrhythmic medicines during pregnancy: Premature atrial or ventricular beats are common in normal pregnancy. These usually are not treated. However in patients with preexisting arrhythmias, their frequency and hemodynamic severity may be exacerbated due to pregnancy. Pharmacologic treatment is usually reserved for patients with severe symptoms or in presence of sustained episodes, which are poorly tolerated. Sustained tachyarrhythmias, such as atrial flutter or atrial fibrillation, should be treated promptly.

If possible, all antiarrhythmic drugs should be avoided during the first trimester and those known to be teratogenic should be avoided throughout pregnancy. Based on their safety profiles, preferred drugs during pregnancy include digoxin, beta blockers (possibly excluding atenolol) and adenosine. Sometimes antiarrythmic drugs like quinidine, sotalol, lidocaine, flecainide and propafenone can also be considered. However, presently there is lack of evidence regarding the use of appropriate drugs during pregnancy. Amiodarone is generally regarded as contraindicated in pregnancy, although it has been described as successful in certain case reports. It is not teratogenic, but may cause neonatal hypothyroidism. Electrical cardioversion is considered to be relatively safe during pregnancy.

Intrapartum Care

- Management of intrapartum care should be supervised by a multidisciplinary team experienced in the care of women with heart disease as described previously.
- A clear plan for management of labor and the puerperium in women with heart disease should be established well in advance.
- The main objective of management should be to minimize any additional load on the cardiovascular system from delivery and the puerperium. This is usually best achieved with the help of the following:
  - Aiming for spontaneous onset of labor,
  - Providing effective pain relief with low-dose regional analgesia,
  - Assisting vaginal delivery with instruments such as the ventouse or forceps.
  - Limiting or even avoiding active maternal bearing down ("pushing").
- Vaginal delivery over cesarean section is the preferred mode of delivery for most women with heart disease – whether congenital or acquired. Cesarean section is considered only in the presence of specific obstetric or cardiac considerations. Some of the indications for cesarean section are described in table 15.10.
- Induction of labor may sometimes be more appropriate, especially in order to optimize the timing of delivery in relation to anticoagulation or due to the deteriorating maternal cardiac function. However, it should be recognized that induction of labor before 41 weeks of gestation, especially in nulliparous women with an unfavorable cervix, increases the likelihood of cesarean section.
- Pain control should be offered with epidural anesthesia and adequate volume preloading.
- Positioning the patient on the left lateral side helps in reducing the associated hemodynamic fluctuations.
- If any surgical intervention in undertaken (e.g. episiotomy), meticulous attention must be paid to hemostasis in order to avoid hemorrhage. Even a mirror degree of hemorrhage can cause marked cardiovascular instability in pregnant women with reduced cardiac reserve.

Intrapartum antibiotic prophylaxis: There is currently no evidence that prophylactic antibiotics are necessary to prevent endocarditis in cases of uncomplicated vaginal delivery. American Heart Association guidelines do not recommend the routine use of endocarditis prophylaxis for cesarean section delivery or for uncomplicated vaginal delivery without infection. However, in developing countries prophylactic antibiotics are usually given in all cases of operative delivery and to women at increased risk, such as those with mechanical valves or a history of previous endocarditis. Prophylactic antibiotic cover should also be given in case any intervention is likely to be associated with risk of significant or recurrent bacteremia. Also, some centers do administer endocarditis prophylaxis at the time of vaginal delivery in women with structural heart disease, as an uncomplicated delivery cannot always be anticipated. Recommended antibiotic prophylaxis for high-risk women with heart disease undergoing genitourinary or gastrointestinal procedures is described in table 15.11.

Use of various cardiovascular drugs during pregnancy: Commonly used cardiovascular drug classes and their potential adverse effects during pregnancy are shown in table 15.12.

Table 15.10: Indications for cesarean section

Marfan syndrome with dilated aortic root
Aortic aneurysm
Women with a mechanical Bjork-Shiley mitral valve who have opted for warfarin anticoagulation should also be considered for elective section to reduce the time off warfarin.
Taking warfarin within 2 weeks of labor

Table 15.11: Recommended antibiotic prophylaxis or high-risk women with heart disease undergoing genitourinary or gastrointestinal procedures

Category	*Drug and dosage*
High-risk patient	Ampicillin, 2 g IM or IV, plus gentamicin sulfate, 1.5 mg/kg IV 30 min before procedure; and ampicillin, 1 g IV, or amoxicillin, 1 g PO 6 hr after the procedure.
High-risk patient who has penicillin allergy	Vancomycin HCl, 1 g IV over 2 hr, plus gentamicin sulfate, 1.5 mg/kg IV 30 min before the procedure.

Management of the Third Stage of Labor

At the time of management of the third stage of labor in women with heart disease, bolus doses of oxytocin can cause severe hypotension and should therefore be avoided. Low-dose oxytocin infusions are safer and may be equally effective. Ergometrine is best avoided in most cases as it can cause acute hypertension. Misoprostol may be safer but it can cause problems such as hyperthermia. Presently, the evidence regarding the use of misoprostol in patients with heart disease is largely limited. It should be used only if the benefits outweigh any potential risks. At the time of cesarean section, uterine compression sutures may be effective in controlling postpartum hemorrhage due to uterine atonicity.

Postpartum Care

- Since the hemodynamic parameters may not return to baseline for many days after delivery, patients at intermediate

Table 15.12: Cardiovascular drugs used during pregnancy

Drug	*Use*	*Potential side effects*	*Safety during pregnancy*	*Safety during breastfeeding*
Adenosine	Arrhythmia	None reported	Yes	No data available
Beta blockers	Hypertension, arrhythmias, MI, ischemia, HCM, hyperthyroidism, mitral stenosis, Marfan syndrome, cardiomyopathy	Low birth weight, hypoglycemia, respiratory depression, prolonged labor	Yes	Yes
Digoxin	Arrhythmia, CHF	Low birth weight, prematurity	Yes	Yes
Diuretics	Hypertension, CHF	Reduced uteroplacental perfusion	Unclear	Yes
Lidocaine	Arrhythmia, anesthesia	Neonatal CNS depression	Yes	Yes
Low-molecular-weight heparin	Mechanical valve hypercoagulable state, DVT, AF, Eisenmenger's syndrome	Hemorrhage, unclear effects on maternal bone mineral density	Limited data	Limited data
Nitrates	Hypertension	Fetal distress with maternal hypotension	Yes	No data
Procainamide	Arrhythmia	None reported	Yes	Yes
Unfractionated heparin	Mechanical valve hypercoagulable state, DVT, AF, Eisenmenger's syndrome	Maternal osteoporosis, hemorrhage, thrombocytopenia, thrombosis	Yes	Yes
Warfarin	Mechanical valve hypercoagulable state, DVT, AF, Eisenmenger's syndrome	Warfarin embryopathy, fetal CNS abnormalities, hemorrhage	Yes, after 12 weeks of gestation	Yes

Source: Elkayam U: Pregnancy and cardiovascular disease. In Zipes DP, Libby P, Bonow RO, Braunwald E (eds): Braunwald's Heart Disease. A Textbook of Cardiovascular Medicine, 7th ed. Philadelphia, Elsevier Saunders, 2005, p 1965.

or high risk may require monitoring for at least 72 hours postpartum.

- Patients with Eisenmenger syndrome are at risk of death for up to 7 days postpartum and therefore require close observation for a longer period of time, postpartum. Unstable cardiac conditions such as pulmonary hypertension or cardiomyopathy and conditions like Eisenmenger syndrome, which are at a high risk of death in the postpartum period, may require surveillance for up to two weeks. The cases at high risk should be assessed by a multidisciplinary team, as a minimum, at 6 weeks after delivery. In cases where there are continuing concerns, another assessment can take place at 6 months. Following these assessments, the woman should return to her periodic cardiac outpatient care.
- If any pregnant or postpartum woman has unexpected and persistent dyspnea or is noted to be unusually tachypneic or tachycardic and the possibility of pulmonary embolism has been excluded, she may have peripartum cardiomyopathy. She should be investigated further by echocardiography.
- Angiotensin converting enzyme (ACE) inhibitors are safe to use in breastfeeding mothers.
- Due to an increased risk of postpartum hemorrhage in women with heart disease who are on anticoagulation therapy, the introduction or reintroduction of warfarin should be delayed until at least 2 days postpartum. Meticulous monitoring of anticoagulation is essential.

Pregnancy in the Presence of Prosthetic Heart Valve

Several conditions like the use of mechanical valves, certain prothrombotic conditions (antiphospholipid antibody syndrome, atrial fibrillation, etc), prior episode of venous thromboembolism, acute deep vein thrombosis or thromboembolism during pregnancy, require the initiation or maintenance of anticoagulation during pregnancy. The use of prosthetic heart valves in patients at the time of pregnancy is likely to be associated with an increased risk of thrombosis. One of the most important concerns in pregnant patients with heart disease is the state of hypercoagulability that exists throughout pregnancy, which is likely to put women at higher than usual risk of thromboembolism, especially in women with prosthetic heart valves. As a result, there is a need to use anticoagulant drugs through out the pregnancy. The three most common agents considered for use during pregnancy are: Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) and warfarin. However, at present, no anticoagulation strategy has been currently found to be equally safe for both the mother and fetus.

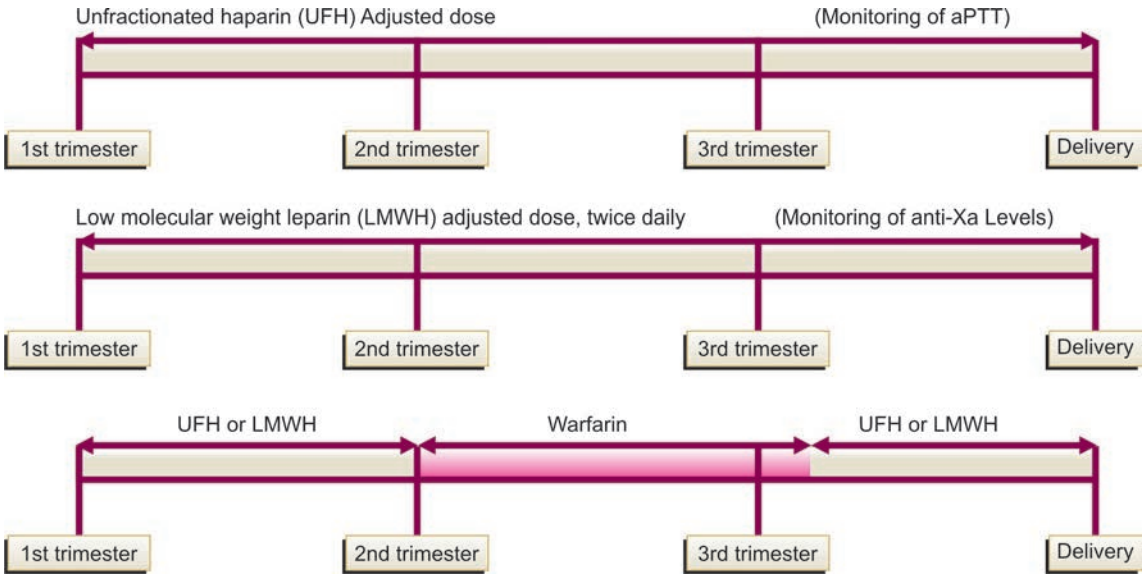


Fig. 15.2: Regimens for administration of anticoagulation therapy during pregnancy

15

Oral therapy with warfarin is effective, but has the potential of causing congenital embryonic abnormalities because of its potential to cross the placenta. However, some studies show that a dosage of 5 mg of warfarin per day may not be teratogenic. Also regular use of warfarin throughout the pregnancy is associated with the risk of fetal intracranial bleeding, particularly during vaginal delivery, unless warfarin is stopped before labor. The incidence of warfarin embryopathy (abnormalities of fetal bone and cartilage formation) has been estimated to be between 4% to 10%; the risk is highest when warfarin is administered during 6–12 weeks of gestation. When administered during the second and third trimesters, warfarin has been found to be associated with fetal central nervous system abnormalities. However, the use of warfarin has been found to be safe during breastfeeding.

On the other hand, heparin is not associated with any teratogenic defects as it does not cross the placenta. However, it may cause side effects like maternal osteoporosis, hemorrhage, thrombocytopenia or thrombosis (HITT syndrome) and a high incidence of thromboembolic events with older generation mechanical valves. Also, its efficacy is lower in comparison to warfarin for preventing thrombosis in patients with prosthetic valves. If heparin is administered during pregnancy, it should be discontinued at least 12 hours before induction, or reversed with protamine if spontaneous labor develops. It can usually be resumed 6 to 12 hours postpartum. UFH may be administered parenterally or subcutaneously throughout pregnancy; when used subcutaneously for the anticoagulation of mechanical heart valves, the recommended starting dose is 17,500 to 20,000 U twice daily. The appropriate dose adjustment of UFH is based on an activated partial thromboplastin time (aPTT) of 2.0 to 3.0 times the control level. High doses of UFH may be required during pregnancy to achieve the target aPTT because of the hypercoagulable state associated with pregnancy. Lower doses of UFH may be appropriate for anticoagulation in certain cases, such as the prevention of venous thromboembolism during pregnancy. Parenteral infusions should be stopped 4 hours before cesarean section. Action of UFH can be reversed with protamine sulfate.

Low-molecular-weight heparin (LMWH) produces a more predictable anticoagulant response than UFH and is less likely to cause side effects like HITT. The authors of the "ACC/AHA 2006 practice guidelines for the management of patients with valvular heart disease" acknowledged the absence of sufficient evidence base in order to make definitive recommendations regarding the use of optimal antithrombotic therapy in pregnant patients. However, they have recommended the use of either of the following regarding the use of anticoagulation therapy during pregnancy (figure 15.2):

1. *Adjusted-dose heparin during the entire pregnancy:* This could be either with low molecular weight heparin (LMWH) throughout pregnancy with monitoring of anti-Xa levels or dose-adjusted subcutaneous UFH throughout pregnancy with monitoring of the aPTT.
2. *A combination of adjusted-dose heparin and warfarin:* Under this regimen, adjusted-dose heparin is continued until the 13th week of gestation, followed by warfarin from the 14th week to the middle of the third trimester. After this, the adjusted-dose heparin is started. Low-molecular-weight heparin in adjusted doses is easier to administer

Table 15.13: Predictors of maternal risk for cardiac complications

Criteria	*Example*	*Points*
Prior cardiac events	Heart failure, transient ischemic attack, stroke before current pregnancy	1
Prior arrhythmia	Symptomatic sustained tachyarrhythmia or bradyarrhythmia requiring treatment	1
NYHA III or IV or cyanosis		1
Valvular and outflow tract obstruction	Aortic valve area < 1.5 cm^2, mitral valve area < 2 cm^2, or left ventricular outflow tract peak gradient > 30 mm Hg	1
Myocardial dysfunction	LVEF < 40%, restrictive cardiomyopathy, or hypertrophic cardiomyopathy	1

Abbreviations: LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
Source: Siu SC, Sermer M, Colman JM, et al: Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation 2001;104:515-521.

and has been suggested as an alternative to adjusted-dose unfractionated heparin. In women with prosthetic valves at high risk of thromboembolic complications, adding low-dose aspirin should also be considered. Although high-dose aspirin may promote premature duct closure, low-dose aspirin is considered as a safe option during pregnancy. Heparin therapy can be restarted 4 to 6 hours after delivery in absence of any contraindications. Warfarin therapy may be resumed the night after delivery if no bleeding complications occur. If labor begins while the woman is receiving warfarin, anticoagulation should be reversed and cesarean delivery be performed.

Complications

MATERNAL COMPLICATIONS

A validated cardiac risk score which helps in predicting a woman's chance of having adverse cardiac complications during pregnancy is enlisted in table 15.13. Each risk factor has been given a value of 1 point. The probability of mother to experience adverse cardiac event is 5%, 27% and 75%, respectively for the points of 0, 1 and higher than 1.

Cardiac disease during pregnancy can cause considerable maternal morbidity. Pregnant women with heart disease are at an increased risk for cardiac complications such as heart failure, arrhythmias, and stroke. The diseases which are associated with the highest risk to the mother during pregnancy are enumerated in table 15.14. However few women with heart disease actually die during pregnancy. The high risk exceptions, which are associated with high mortality rate include women with Eisenmenger syndrome, pulmonary vascular obstructive disease, or Marfan's syndrome with aortopathy. Pregnant women with congenital heart lesions are at an increased risk for heart failure, arrhythmia, stroke, neonatal complications and even death in some conditions.

Eisenmenger syndrome can cause severe pulmonary hypertension as a consequence of a long standing left-to-right shunt lesion like ASD, VSD or PDA. In these cases, the risk of maternal mortality can be as high as 30% to 50%. Among the congenital heart diseases, tetralogy of Fallot carries a 4% to 20% risk of mortality in the mother. Atrial septal defects are perhaps the safest of all birth defects. Rheumatic heart valve disease is another risk, with patients having mitral stenosis associated with a 1% chance of developing pulmonary edema during pregnancy. Connective tissue disorders like Ehlers Danlos syndrome (a disorder of the connective tissue of the body resulting in loose skin and lax joints) can cause a higher risk of bleeding from major blood vessels that might rupture during pregnancy.

Table 15.14: Heart diseases associated with an increased risk for cardiac complications

Eisenmenger syndrome
Primary pulmonary hypertension
Marfan's syndrome with aortopathy
Cor pulmonale
Congenital heart diseases (tetralogy of Fallot)
Rheumatic heart valve disease (mitral stenosis)
Connective tissue disorders (e.g., Ehlers Danlos syndrome)

Table 15.15: Predictors for adverse neonatal outcomes during pregnancy

NYHA III or IV or cyanosis during the baseline prenatal visit.
Maternal left ventricular dysfunction
Anticoagulation during pregnancy
Maternal smoking
Multiple gestation

FETAL COMPLICATIONS

In most mothers with cardiac disease, the fetus develops almost normally. However some cardiac conditions may be associated with adverse neonatal outcomes during pregnancy (table 15.15). For example, patients with rheumatic heart

valve disease may suffer mild growth retardation, with babies born being lighter by around 200 grams.

In cyanotic mothers, many problems like severe growth retardation and higher abortion rates may arise. In these conditions, the maternal blood has very low oxygen content, due to which there is a lower oxygen exchange across the placenta. As a result, the fetus gets lesser supply of oxygen than normal, which can cause fetal death or premature delivery. Another condition which is associated with high rates of fetal loss due to reduced blood flow to the placenta as a result of narrowing of aorta includes coarctation of aorta.

Important Questions and Answers

Q.1. What are the chances that a fetus of the mother with congenital heart disease will also develop congenital heart disease?

Ans. The risk of congenital heart disease in pregnant women with congenital heart disease is about 2% to 4%, which is about twice the incidence of heart disease in the general population. This risk also varies with different conditions. For instance, it is 3% in parents with tetralogy of Fallot, but almost 18% in those with aortic stenosis. These defects are usually concordant i.e., the defect in the child is usually the same one as that of the mother.

Q.2. Are all valve lesions problematic, or are there specific conditions where you may have to focus on in the pregnant woman?

Ans. The risk stratification based on their order of severity during pregnancy is described in table 15.8. Many valve lesions in pregnant women are well tolerated, e.g. mild or moderate degrees of mitral or aortic regurgitation, particularly with normal left ventricular function and no evidence of heart failure. In contrast to regurgitant lesions, severely stenotic lesions are very poorly tolerated and must be treated prior to conception.

Q.3. In the above mentioned case study what should be the next line of management?

Ans. This is a very tricky and controversial situation. Presence of prosthetic valves is associated with a significant risk of maternal thrombosis or thromboembolism. As previously mentioned, the three most commonly used anticoagulant drugs during pregnancy include warfarin or heparin (either unfractionated or low molecular weight). Assuming that the woman and her partner wish to proceed with the pregnancy, they should first be educated about the hazards of warfarin or heparin anticoagulation, alone or in sequence, throughout pregnancy and in the peripartum period. Whatever strategy is chosen, they should be told that neither of the strategies are perfect and may be associated with some amount of maternal or fetal risk. The parents should be counseled that while warfarin crosses the placenta, heparin does not. However, warfarin has greater efficacy than heparin in preventing an episode of thromboembolism.

One approach for obtaining effective anticoagulation is to consider using low molecular weight heparin, on a dose-adjusted basis, throughout the pregnancy. The second option would be to use heparin (either unfractionated or low molecular weight) during the first trimester instead of warafarin. This strategy appears to be useful because the risk of warfarin related embryopathy seems to be highest with exposure between week 6 and week 12. Warfarin should again be started in the second trimester and continued until approximately 36 week of pregnancy. After that time, it would be appropriate to substitute heparin for warfarin leading up to labor and delivery, with resumption of warfarin after delivery.

Q.4. When is open heart surgery indicated in cases of heart disease?

Ans. The most reasonable approach would be to consider pre-pregnancy intervention in a pregnant patient with severe valvular heart disease for whom the obstetrician anticipates trouble because of the associated volume load. Open heart surgery during pregnancy is associated with considerable risks to the fetus. Therefore, this procedure can be justified only if the cardiac lesion would prove to be harmful to the mother if left untreated. Such conditions would include life threatening pulmonary edema which cannot be managed by medical treatment. Open heart surgery is rarely indicated for congenital heart disease in pregnancy.

Bibliography

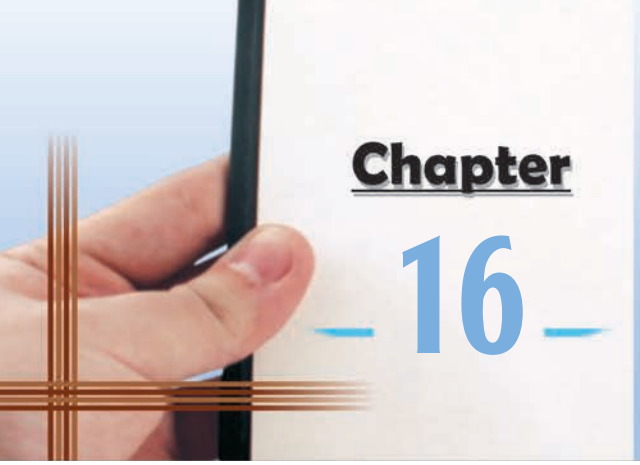
1. [No authors listed] ACC/AHA 2006 guidelines for management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association. Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease). J Am Coll Cardiol. 2006;48:e1-e148.
2. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. JACC. 2006;48(3).
3. Bates SM, Greer IA, Hirsh J, Ginsberg JC. Use of antithrombotic agents during pregnancy: The seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest. 2004;126: 627S-44S.
4. De Swiet M. Cardiac disease. In: Lewis G, Drife J, eds. Why mothers die 1997–1999. The Confidential enquiries into

maternal deaths in the United Kingdom. London: Royal College of Obstetricians and Gynaecologists. 2001;153-64.
5. Dwyer BK, Taylor L, Fuller A, Brummel C, Lyell DJ. Percutaneous transluminal angioplasty and stent placement during pregnancy. Obstet Gynecol. 2005;106:1162-64.
6. Early and intermediate term outcomes of pregnancy with congenital aortic stenosis. Am J Cardiol. 2003;91:1386-89.
7. Elkayam U, Akhter MW, Singh H, Khan S, Bitar F, Hameed A, Shotan A. Pregnancy associated cardiomyopathy: Clinical characteristics and a comparison between early and late presentation. Circulation. 2005;111:2050-55.
8. Elkayam U, Tummala PP, Rao K, Akhter MW, Karaalp IS, Wani OR, Hameed A, Gviazda I, Shotan A. Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. N Engl J Med. 2001;344:1567-71.
9. Elkayam U. Pregnancy and cardiovascular disease. In Zipes DP, Libby P, Bonow RO, Braunwald E (eds): Braunwald's Heart Disease. A Textbook of Cardiovascular Medicine, 7th ed. Philadelphia, Elsevier Saunders, 2005, p 1965.
10. Fletcher C. Standardised questionnaire on respiratory symptoms: A statement prepared and approved by the MRC Committee on the Aetiology of chronic bronchitis (MRC breathlessness score). Br Med J. 1960;2:1665.
11. James AH, Jamison MG, Biswas MS, Brancazio LR, Swamy GK, Myers ER. Acute myocardial infarction in pregnancy: A United States population-based study. Circulation. 2006;113: 1564-71.
12. Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. N Engl J Med. 2001; 344:1567-71.
13. Ray, P., Murphy, GJ, Shutt LE. Recognition and management of maternal cardiac disease in pregnancy. British Journal of Anesthesia. 2004;93(3):428-39.
14. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): A population-based retrospective cohort study. Lancet. 2005;366:1797-1803.
15. Silversides CK, Colman JM, Sermer M, Farine D, Siu SC. Early and intermediate term outcomes of pregnancy with congenital aortic stenosis. Am J Cardiol. 2003;91:1386-89.
16. Silversides CK, Colman JM, Sermer M, Siu SC. Cardiac risk in pregnant women with rheumatic mitral stenosis. Am J Cardiol. 2003;91:1382-85.
17. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation. 2001;104:515-21.
18. Siu SC, Sermer M, Harrison DA, Grigoriadis E, Liu G, Sorensen S, Smallhorn JF, Farine D, Amankwah KS, Spears JC, Colman JM. Risk and predictors for pregnancy related complications in women with heart disease. Circulation. 1997;96:2789-94.

Section 4

Normal and Abnormal Menstruation

- Normal Gynecological Examination
- Abnormal Uterine Bleeding due to Endometrial Cancer
- Menorrhagia due to Leiomyomas
- Dysfunctional Uterine Bleeding



Chapter

16

Normal Gynecological Examination

Case Study

A 55-year-old G4P4 lady visits the clinic for routine gynecological check-up. She attained menopause five years ago. There is no significant family history or past treatment history. She underwent myomectomy for symptomatic uterine fibroids ten years ago. On examination, her BP was 120/80 mm of Hg and pulse rate was 84 beats per minute. There were no signs and symptoms of anemia and no lymphadenopathy. The patient does not have any problem and has just presented for routine gynecological check-up.

Introduction

There are many aspects to women's health which are related to gynecological care. Some such gynecological problems commonly encountered in clinical practice include abnormal menstrual bleeding, abdominal mass, gynecological cancers, pelvic pain, infertility, etc. Some such common gynecological problems would be discussed in details in the following chapters. For being able to diagnose the abnormal gynecological complaints, it is important for the clinician to be able to perform a normal gynecological examination. Since taking an adequate history and performing a complete pelvic examination is of utmost importance for detection of underlying pathology, this would be discussed in details in this chapter.

History

The history must be taken in a nonjudgmental, sensitive and through manner. Detailed history and clinical vaginal examination forms an important aspect of a normal gynecological check-up. Importance must be given towards maintenance of patient-physician relationship. It is important for the gynecologist to maintain good communication with the patient in order to elicit proper history and to be accurately able to recognize her problems. The manner of speaking, the words used, the tone of speaking and the body language are important aspects of the patient-physician interaction. Kindness and courtesy must be maintained at all times. These aspects are especially important in case of male gynecologists because the gynecological history entails asking some private and confidential questions from the female patients. Also, the women may be reluctant while telling the history regarding her menstrual cycles to the male gynecologist. It is important for a male gynecologist to take the history and perform the vaginal examination in presence of a third party or a chaperone (a female nurse or the patient's female relative or friend). The clinician must adopt both an empathetic and inquisitive attitude towards the patient. The patient's privacy must be respected at all costs. The gynecologist must refrain from asking personal questions until appropriate patient confidence has been established. The gynecologist needs to listen more and talk less while taking the patient's history. The clinician must avoid interrupting, commanding and lecturing while taking history. If any serious condition (e.g. malignancy) is suspected, the diagnosis must not be disclosed to the patient until it has been confirmed by performing investigations. Bad news must be preferably told to the patient when she is being accompanied by some one (relative, friend or spouse). The seriousness and urgency of the situation must be explained to the patient without causing undue alarm and fright to the patient. The clinician must never give false reassurance to the patient. Honest advice and opinion must always be provided.

History of Presenting Complaints

Asking the age of the patient is especially important. Risk factors related to a particular pathology in question (e.g., post menopausal bleeding) need to be asked. Some common gynecological problems with which the patient may present are described below:

Abnormal menstrual bleeding (AUB)

For detailed history and examination in cases presenting with AUB, please refer to chapter 17.

Abdominal pain

Pain in the abdomen is one of the most common clinical complaints in medical practice. Besides gastrointestinal pathology, underlying gynecological pathology is also a common

cause of pain per abdomen. Gynecological problems like pelvic tuberculosis, PID and endometriosis may be commonly associated with chronic pain. Acute lower abdominal pain may occur in association with gynecological abnormalities like ectopic pregnancy, torsion or rupture of an ovarian cyst and chocolate cyst.

The following points need to be asked while taking history of pain.

Exact site of pain: Pain of ovarian or tubal origin is usually felt in the lower abdomen, above the inguinal ligament. Pain of uterine origin is diffusely present in the hypogastric region.

Radiation of pain: Pain of uterine origin is often referred to the inner aspect of the thighs, but does not usually extend beyond the knees. Pain due to appendicitis may initially start in the right iliac region and later radiate to the umbilicus.

Nature of pain: The nature of the pain, whether burning, gnawing, throbbing, aching or excruciating in nature, needs to be determined.

Intensity of pain: The degree of severity of pain, whether mild, moderate or severe needs to be determined. Pain of severe intensity may interfere with sleep and work.

Aggravating and relieving factors for pain: The history of various relieving and aggravating factors for pain must be taken.

Relationship of other factors with pain: Relationship of pain to other factors such as menstruation (dysmenorrhea), coital activity (dyspareunia), micturition (dysuria), defecation (dyschezia), posture and movement needs to be determined. Dymenorrhea or pain associated with menstruation can be of two types: Spasmodic and congestive dysmenorrhea. Spasmodic dysmenorrhea usually has no cause and is seen on day one or two of menstruation. On the other hand, pain due to congestive dysmenorrhea is usually due to some underlying pathology (endometriosis, PID, etc). This pain may be premenstrual, menstrual or post menstrual in origin. In case of dysmenorrhea due to PID, the pain improves with menstruation, whereas in case of endometriosis, the pain worsens after menstruation due to ectopic menstruation. Dysmenorrhea during the menstrual periods could be due to fibroids, or adenomyosis. Dysmenorrhea during the three phases of menstrual cycle (premenstrual, menstrual and post menstrual) is typical of endometriosis.

Abdominal lump

History and examination for lump in the abdomen has been described in details in chapter 24.

Infertility/amenorrhea

For taking detailed history regarding infertility and amenorrhea refer to chapter numbers 26 and 27 respectively.

Hirsutism

Hirsutism refers to increased or excessive growth of hair in women. This is usually related to increased androgen production in the body.

Vaginal discharge

For detailed information regarding various causes of vaginal discharge, please see chapter 20.

Past Medical History

Past history of medical illnesses such as hypertension, hepatitis, diabetes mellitus, cancer, heart disease, pulmonary disease and thyroid disease needs to be taken. Patient's previous medical and surgical problems may have a bearing on her present complaints. For example, a history of longstanding diabetes could be responsible for development of genital candidiasis and associated pruritis. A patient with previous medical history of severe anemia or cardiovascular heart disease may require special anesthetic preparation (e.g. correction of anemia, or treatment of cardiovascular pathology) before undergoing a major gynecological surgery (e.g. hysterectomy). Triad of diabetes, hypertension and obesity is associated with an increased risk of endometrial carcinoma. A history of sexually transmitted disease (especially infection with Chlamydia) may have a direct bearing on future infertility. Previous history of pelvic inflammatory disease (PID) or puerperal sepsis could be responsible for producing gynecological complaints like menstrual disturbances, lower abdominal pain, congestive dysmenorrhea and infertility. Presence of endocrinological disorders (e.g. thyroid dysfunction) could be responsible for producing menstrual irregularities.

History of undergoing previous abdominal surgery like cesarean section, removal of appendix, excision of ovarian cyst, myomectomy etc, may result in the development of pelvic adhesions. These may not only make any subsequent surgery difficult, but also may be the cause of common gynecological problems like pelvic and abdominal pain, infertility, menstrual disturbances and dyspareunia.

Family History

Certain gynecological cancers (e.g. cancer ovary, uterus and breast) have a genetic predisposition. A woman may be at a high risk of development of such cancers in the future if there is a positive family history of such cancers in her first degree relatives (especially mother and sister). Menstrual patterns, including age of menarche, frequency and regularity of cycle, associated dysmenorrhea and age of attaining menopause tend to be similar amongst the family members. The common gynecological problems like premature menopause, menorrhagia and premenstrual tension have been observed to run within families. Other medical disorders, like thyroid

dysfunction, allergic diathesis and coagulation disorders, which may be responsible for development of gynecological complaints are often familial in nature.

Marital and Sexual History

Details of the woman's marital life including her age at the time of marriage, how long she has been married and sexual history needs to be asked. Details of the woman's sexual history are particularly important. Some such details include her age at the time of first sexual intercourse; her current sexual activities (vaginal, oral, anal and manual); frequency of her sexual intercourses; is she currently seeking a pregnancy; is she presently using any method of contraception, if yes, the type of contraception used, is she or her partner experiencing any sexual dysfunction (frigidity in the woman or impotence or premature ejaculation in the male or problems with libido, arousal, lubrication or orgasm in both males and females), current frequency of her sexual activities, past sexual activities, number of sexual partners (currently and in the past), sexual preferences (heterosexual, homosexual or both), pain at the time of sexual intercourse (dyspareunia), etc.

Obstetric History

Details of every pregnancy conceived irrespective of their ultimate outcome needs to be recorded. Number of previous live births, stillbirths, deaths, miscarriages (both spontaneous and induced), history of recurrent miscarriages if any, medical termination of pregnancies and number of children living at present need to be noted. The ages of the youngest and eldest children also need to be enquired. The mode of delivery of each baby (normal vaginal delivery or cesarean section) and details of any obstetric complications encountered, e.g. puerperal or postabortal sepsis, postpartum hemorrhage (PPH), obstetrical interventions (use of forceps, vacuum, etc) and other obstetric or gynecological complications (soft tissue injuries such as cervical tears, an incompetent cervical os, genital fistulae, complete perineal tear, genital prolapse, stress urinary incontinence) and chronic backache also needs to be enquired from the patient. Severe degree of PPH and obstetric shock may lead to pituitary necrosis and Sheehan syndrome or postpartum hypopituitarism.This could be cause of amenorrhea or hot flushes in a young woman who had recently suffered from massive postpartum hemorrhage at the time of delivery. It is a good idea to ask the names of the patients' children at the time of taking history. It helps in reducing patients' anxiety and increasing the confidence in her health care provider.

History of Previous Surgery

The patient should be asked about any surgery she has undergone in the past. The reason for undergoing surgery, particularly of abdominal or pelvic origin, type of incision (laparoscopy or laparotomy) and any history of post-operative complications needs to be enquired.

Past medication history

In the medication history, the patient should be asked about the various medicines she has been consuming. The details of various medicines including their dosage, route of administration, frequency and duration of use needs to be asked. The patient must be specifically asked about the various medicines she has been taking including prescription drugs, OTC drugs, herbal drugs and any therapy related to alternative medicine. History of allergy to any medication also needs to be asked.

Previous gynecological history

History of prior gynecologic problems including abnormalities in Pap smear, bleeding problems, sexually transmitted diseases etc also needs to be taken.

Menstrual History

The menstrual history needs to be taken in details. The following details need to be recorded: Age of menarche, date of last menstrual period, cycle length, whether regular or irregular, number of days the bleeding takes place, amount of bleeding (in terms of pads soaked), and presence of any associated symptoms, such as cramps, bloating or headaches. Detailed menstrual history which needs to be asked in cases of AUB has been described in chapter 17.

Normal Menstrual Cycle

The events of the normal menstrual cycle are shown in figure 16.1. The first day of a typical menstrual cycle (day l) corresponds to the first day of menses. The menstrual phase usually lasts for 5 days and involves the disintegration and sloughing of the functionalis layer of the endometrium. Interplay of various prostaglandins (e.g. prostaglandin F2-alpha and prostaglandin E2) is involved in regulation of menstrual cycle. Prostaglandin F2-alpha causes myometrial contractions and vasoconstriction, where as prostaglandin E2 causes vasodilatation and muscle relaxation. A typical menstrual cycle comprises of 28 days. Ovulation occurs in the middle of the menstrual cycle, i.e. day 14 of a typical cycle. The first 14 days of the cycle, before the menstruation occurs form the proliferative phase, while the next 14 days of the cycle form the secretory phase. During the follicular phase of normal ovarian cycle (equivalent to the proliferative phase of endometrial cycle), there is an increase in the blood levels of the hormone estrogen. During this phase, the maturation of the dominant follicle takes place. At the midpoint of the cycle, ovulation occurs. Following the process of ovulation, the ruptured ovarian follicle gets converted into corpus

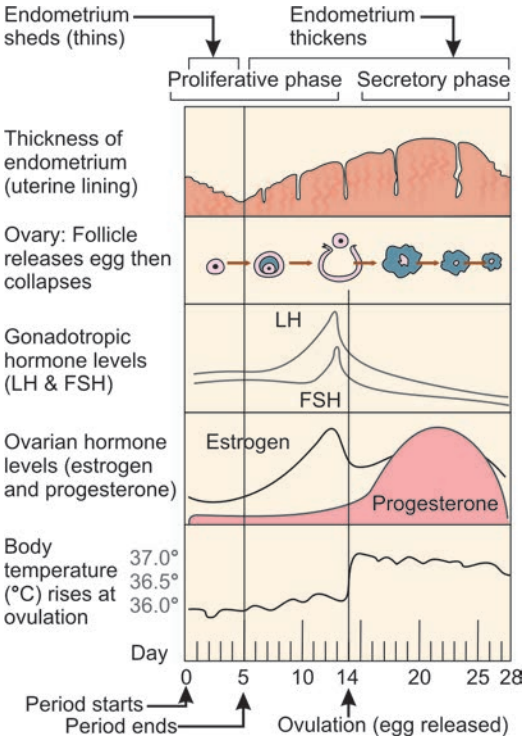


Fig. 16.1: Normal menstrual cycle

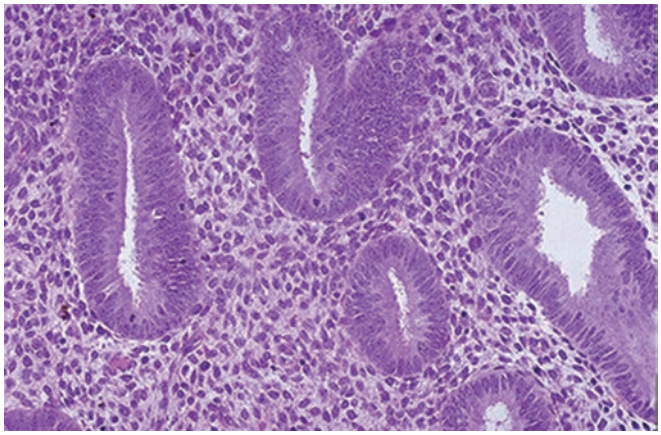


Fig. 16.2: Proliferative endometrium

luteum (CL); the main hormone produced by CL being progesterone. During the luteal phase of the ovarian cycle (corresponding to the secretory phase of endometrial cycle) as the CL matures, the main hormone produced is progesterone. The endometrium during this phase gets transformed for implantation of conceptus in anticipation of the pregnancy. If pregnancy occurs, the rising levels of human chorionic gonadotropin (hCG) stimulates and rescues the endometrium. In case the pregnancy does not occur, the CL undergoes regression. As a result, the levels of estrogen and progesterone rapidly decline causing withdrawal of the functional support of the endometrium. This results in menstrual bleeding, marking the end of one endometrial cycle and the beginning of the other.

Role of various hormones in regulation of menstrual cycles

Initial follicular development is independent of hormonal influence. However soon FSH takes control and stimulates a cohort of follicles encouraging them to develop into preantral stage. FSH causes aromatization of the androgens present in the theca cells into estrogen in the granulosa cells. Out of the various follicles, only one single follicle is destined to develop into a dominant follicle, which undergoes ovulation. Estrogen exerts a negative feedback effect on FSH as a result of which growth of all the follicles except dominant follicle is inhibited. Estradiol levels derived from the dominant follicle increase rapidly and exert a negative feedback effect on FHS release. While causing a decline in FHS levels, the mid-follicular rise in estradiol levels exert a positive feedback influence on LH secretion. The presence of LH in the follicle prior to ovulation is important for optimal follicular development which ultimately results in formation of a healthy oocyte. A surge of LH takes place just prior to ovulation. LH levels rise steadily during the late follicular phase. LH initiates luteinization and progesterone production in the granulosa layer. A preovulatory rise in progesterone facilitates the positive feedback action of estrogen and may be required to induce the midcycle FSH peak. Ovulation occurs about 10–12 hours after the LH peak and 24–36 hours after the peak estradiol levels have been attained. The onset of LH surge is the most reliable indicator of impending ovulation.

The proliferative (follicular) phase

The proliferative (follicular) phase extends from day 5 to day 14 of the typical cycle. In this phase, the endometrial proliferation occurs under estrogen stimulation. The estrogen is produced by the developing ovarian follicles under the influence of follicle stimulating hormone (FSH). This causes marked cellular proliferation of the endometrium and an increase in the length and tortuosity of the spiral arteries. Endometrial glands develop and contain some glycogen. This phase ends as ovulation occurs.

The following changes take place during the proliferative phase (figure 16.2):

- The functional and the basal layers of endometrium become well defined. The proliferation mainly occurs in the functional layer. The basal layer measures 1 mm in thickness, while the functional layer reaches a maximum thickness of about 3.5–5 mm by 14th day.

- The glands become elongated and slightly sinuous and the columnar epithelium lining them becomes taller. In the beginning, the glands are narrow and tubular, lined by low columnar epithelial cells. Mitosis become prominent and the areas of pseudostratification are observed.
- There is an increase in ciliated and microvillous cells in the endometrial glands.
- Endometrial stroma becomes edematous with wide separation of the individual cells. The stroma gets infiltrated with numerous cells including macrophages, leukocytes, etc.
- In the initial phase, the spiral vessels are uncoiled and unbranched. However, soon the growth of the straight vessels occurs so that they start becoming more coiled and spiraled.

Ovulation

The events preceding ovulation are as follows: Estrogen production peaks (must be greater than 200 pg/ml for more than 24 hours) and is responsible for triggering the FSH and luteinizing hormone (LH) surge. Rupture of the ovarian follicle follows, resulting in ovulation.

The secretory (luteal) phase

This phase is marked by production of progesterone and less potent estrogens by the corpus luteum. It extends from day 15 to day 28 of the typical cycle. The functionalis layer of the endometrium increases in thickness and the stroma becomes edematous. The glands become tortuous with dilated lumens and stored glycogen. If pregnancy occurs, the placenta produces human chorionic gonadotropin (hCG) to replace progesterone and the endometrium (and the accompanying pregnancy) are maintained.

If pregnancy does not occur, the estrogen and progesterone levels cause negative feedback at the hypothalamus, resulting in the fall in the levels of the hormones FSH and LH. The spiral arteries become coiled and have decreased blood flow. At the end of this period, they alternately contract and relax, causing disintegration of the functionalis layer and eventually menses.

Proliferative phase

The Proliferative phase of the endometrium starts when the regeneration of the menstruating endometrium (which had been sloughed off) begins. The endometrial features of the secretory phase include the following (figure 16.3):

- The most characteristic feature of this phase is development of subnuclear vacoulation in the glandular epithelial cells. In this, the glycogen filled vacuoles develop between the nuclei and the basement membrane (by the day 17–18). This is the first evidence that ovulation has taken place.
- The endometrium measures about 8–10 mm in the secretory phase. The secretory phase reaches its peak activity by the 22nd day of the cycle after which no growth occurs.
- The glands become crenated and tortuous to assume a characteristic corkscrew shaped appearance. The corkscrew pattern of the glands becomes sawtoothed in the later part of the secretory phase.
- The stroma of the functional layer becomes edematous further.
- The functional layer of the endometrium can be divided into two layers:
  - Superficial or compact layer
  - Deep spongy layer.
- The spiral vessels become dense and deeply coiled.

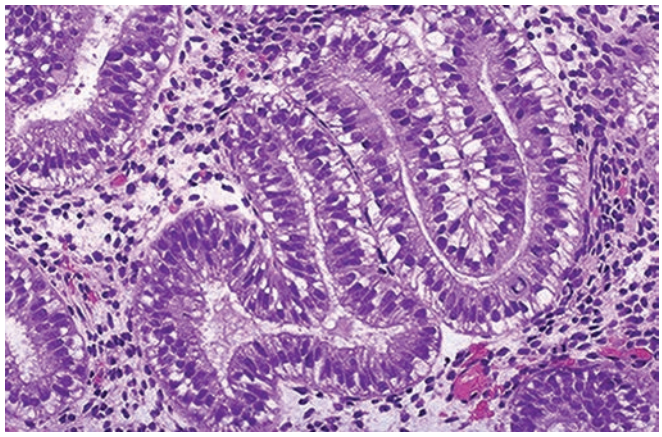


Fig. 16.3: Secretory phase endometrium

General Physical Examination

General physical examination involves the observation of the patient's general appearance, orientation in time, place and person, nutritional status and patient's demeanor (calm, anxious, or aggressive). The following features need to be observed at the time of general physical examination:

Vital Signs

Patient's vitals signs such as temperature, blood pressure, pulse, respiratory rate, height and weight needs to be taken.

Height and Weight

Height of the patient (in meters) and her weight (in pounds) can be used for calculation of BMI. The classification of the

Table 16.1: Classification of weight according to BMI

Weight for height status	*Body mass index*
Very low	<16.5
Low	16.5–19.8
Normal	19.8–25.9
High	26.0–29.9
Very high	> 30.0

woman as underweight, normal weight and obese has been described in table 16.1. Calculation of BMI is especially important in women who appear underweight or overweight. Underweight women may commonly suffer from amenorrhea and other menstrual irregularities, whereas overweight women are at an increased risk for endometrial cancer.

Anemia, Dehydration

Excessive blood loss may result in the development of anemia.

Signs Suggestive of Hyperandrogenemia

Signs suggestive of hyperandrogenemia such as hirsuitism (presence of facial hair), deepening of voice, etc may be related to the presence of androgen secreting tumors or chronic anovulatory states (polycystic ovarian disease).

Blood Pressure

Blood pressure that is persistently ≥ 140 mm of Hg (systolic) or ≥ 90 mm of Hg (diastolic) is considered as elevated. Patients with hypertension are at an increased risk for the development of endometrial cancer.

Neck Examination

Local examination of the neck may reveal enlargement of thyroid gland or lymph nodes of the neck. Neck examination should also involve palpation of cervical and supraclavicular lymph nodes.

Lymphadenopathy

Lymphadenopathy could be a sign of advanced metastatic disease associated with malignancy. The neck, axilla and groins must also be palpated for the presence of enlarged lymph nodes.

Thyroid Examination

It is important to examine the thyroid gland because menstrual abnormalities may be commonly associated with thyroid dysfunction. While hypothyroidism is commonly associated with oligomenorrhea, hyperthyroidism may be responsible for producing menorrhagia. Various signs and symptoms associated with hypothyroidism and hyperthyroidism are described in details in chapter 19.

Breasts Examination

Examination of the breasts should be carried out in three positions: With patient's hands on her hips (to accentuate the pectoral muscles), with her arms raised and then in supine position. Both the breasts must be inspected for symmetry, skin or nipple retraction, presence of any obvious growth or mass and skin changes such as dimpling, retraction, crusting or peau d'orange appearance. Both the breasts must be then palpated bilaterally for the presence of lumps, masses and tenderness The nipples are assessed for presence of discharge. Axillary and supraclavicular regions are palpated for presence of any lymphadenopathy. The following points need to be particularly observed on examination of breast:

- Breast examination may reveal changes indicative of early pregnancy. This is especially important in cases, where pregnancy is not suspected, for example in young unmarried girls.
- Staging of breast development: This could be important in women who have yet not attained sexual maturity.
- In all women and especially those above the age of 30 years, breasts must be routinely palpated to exclude tumor formation.
- Bilateral milk discharge from the nipples may indicate galactorrhea due to hyperprolactinemia. Ruling out the presence of galactorrhea is especially important in cases that are infertile and suffer from oligomenorrhea or amenorrhea.
- Unilateral bloody nipple discharge could be associated with an intraductal papilloma.

Examination of Back and Spine

Back must be assessed for symmetry, tenderness or masses. Flanks must be assessed for pain on percussion as it could be indicative of renal disease.

Specific Systemic Examination

ABDOMINAL EXAMINATION

Inspection

The patient must be advised to breathe normally and relax. The examiner must stand on the right side of the patient. The following points need to be noted on inspection of the abdomen:

- *Abdominal shape*: The clinician must note for abdominal shape, whether symmetrical or asymmetrical.

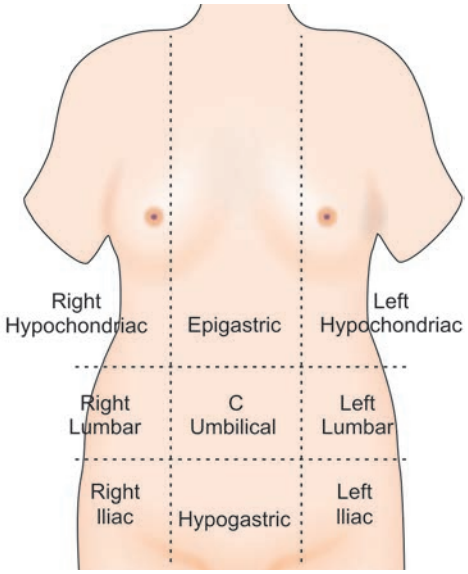


Fig. 16.4: Abdominal quadrants

- *Umbilical eversion or inversion*: In normal women, umbilicus is usually inverted (sunken) even if abdomen is distended due to obesity. Umbilical eversion can occur as a result of increased intra-abdominal pressure in conditions such as pregnancy, ascites, intra-abdominal tumors, etc.
- *Abdominal enlargement*: The specific region of abdominal distension (ascites, intraabdominal lump) needs to be noted. The different abdominal quadrants are shown in figure 16.4.
- *Organomegaly*: Very large spleen or liver arising from left or right hypochondriac regions respectively can be identified on abdominal inspection. Gross enlargement of the liver may produce a bulge in the right upper quadrant; whereas gross enlargement of the spleen may be seen as a bulge in the left upper quadrant.
- *Presence of dilated veins and varicosities*: Presence of prominent veins over the abdomen are abnormal and may be due to inferior cava obstruction or portal hypertension.
- *The mobility of abdominal wall with breathing*: If the abdominal mass moves up and down while breathing, it is likely to be intraabdominal in origin. In case of a pelvic mass, the movements of the lower abdominal wall may be restricted.
- *Presence of striae or scar marks over the abdomen*: Abdominal striae (stripes over the abdomen) may be often present in parous women. Presence of striae could be indicative of previous pregnancies in the past or recent weight loss. Scars over the abdomen may indicate previous surgical operations and deserve further enquiry.
- *Signs of intraperitoneal and retroperitoneal hemorrhage*: The following signs are indicative of intraperitoneal and retroperitoneal hemorrhage:
  - Grey-Turner's sign: This is the sign which is associated with discoloration (bruising) at the flanks.
  - Cullen's sign: This is the sign which is associated with periumbilical bruising.

Palpation

Normal abdomen should be soft and nontender, with no masses. It is important that the clinician warms his/her hands before palpating the patient's abdomen. The patient should be instructed to flex her hips and knees, which helps in relaxing the abdominal musculature, thereby making palpation easier. If the patient does not relax sufficiently, the clinician may find it difficult to elicit relevant findings during the abdominal examination. Adequate relaxation can be achieved by making the patient comfortable and gaining her confidence. Asking the patient to take slow deep breaths can also help. The clinician must place his/her palm flat over the patient's abdomen. Palpation must be done gently, while applying pressure by flexing the fingers in unison at the metacarpal-phalangeal joints. The following points must be noted while palpating the abdomen:

- *Tone of abdominal muscles: T*one of the abdominal muscles can be assessed upon palpation. When muscle tone is increased, there may be resistance to depression of the abdominal wall by the palpating hand. This hypertonia is commonly accompanied with the presence of tenderness. Reduced tone of the abdominal muscles, on the other hand, could be associated with divarication of rectus muscles.
- *Abdominal tenderness:* There must be no tenderness or rebound tenderness present on abdominal palpation. Rebound tenderness refers to pain upon removal of pressure and may be indicative of localized peritonitis or appendicitis. Tenderness must be recorded on a scale of 1 to 4, where one corresponds to mild and four to most severe type of pain.
- *Organomegaly:* In the absence of any pathology, most abdominal organs are not palpable in normal people. Palpation of all the abdominal quadrants for presence of any mass, firmness, irregularity or distension must be performed. The clinician should preferably adopt a systemic approach while palpating the abdomen. The clinician must start from the right upper quadrant and systemically palpate all the quadrants while moving down in a clockwise direction. Though a grossly enlarged organ (especially spleen and liver) can be visualized on inspection of the abdomen, organomegaly can be better appreciated

on palpation. The normal edge of liver is sharp, smooth, soft and flexible. The liver can descend for upto 3 cm on deep inspiration. In some normal subjects, its edge can be palpable just below the right costal margin without being enlarged. The normal spleen in a healthy subject is not palpable.

- *Abdominal mass:* If an abdominal mass is felt on abdominal palpation, the following need to be determined:
  - *Location of the mass and its shape, size and texture*: Location of the mass in relation to the various abdominal quadrants needs to be determined. Shape of the mass (round, oval, irregular, etc) and its size (in cms) also needs to be determined. The surface texture of the mass, whether smooth, nodular, regular and irregular, needs to be determined.
  - *Margins of the mass:* The clinician must try to locate the margins of the mass. In case of the mass arising from the uterus, it may not be possible to localize the lower margin of the mass. Margins of a malignant tumor may be irregular and may not be well defined.
  - *Consistency of the mass:* Consistency of the mass whether hard, firm, rubbery, soft, fluctuant, indentable, or pulsating needs to be determined. Masses like leiomyomas usually have firm consistency unless they have undergone degeneration. On the other hand, ovarian masses may have cystic consistency. In case of a malignant ovarian tumor, there may be variegated consistency. Furthermore, a malignant mass may be associated with indistinct margins, fixed or restricted mobility and presence of ascites. The pregnant uterus is soft in consistency and hardens with contractions. A full bladder may present as a tense and tender mass in the hypogastric region.
  - *Mobility of the mass:* The mobility of the mass, whether free or fixed to adjacent tissues and its movement in relation to respiration needs to be determined. While a benign tumor is freely mobile, the malignant tumor may be fixed or has a restricted mobility.
  - *Unilateral or bilateral mass:* Tumorous masses arising from both the ovaries are more likely to be malignant in comparison to the unilateral masses arising from a single ovary.
  - *Tenderness on palpation:* Benign masses like fibroids and benign ovarian cysts are usually non tender on palpation. Tenderness upon palpation may be associated with conditions such as ectopic pregnancy, PID, twisted ovarian cysts and red degeneration of fibroids. In conditions like acute peritonitis, there may be guarding, rigidity and rebound tenderness of the lower abdomen.
  - *Differentiating between the intraabdominal masses from those arising from abdominal wall*: Masses arising from the abdominal wall can be distinguished from those inside the abdomen by asking the patient to tighten her abdominal wall muscles. The patient can tighten her abdominal wall muscles by lifting her head off the pillow and looking at her toes. When the patient tightens her abdominal wall muscles, the masses arising from the abdominal wall will remain palpable, while the intra-abdominal masses would no longer be palpable.

Percussion

For percussion, the fingers of the clinician's left hand are spread slightly. He/she then places the palmar surface of the middle phalanx of the middle finger flat over the area, he/she wishes to percuss. The distal two phalanges of the middle finger of the clinician's right hand must be then flexed and its tip used to strike perpendicularly the middle phalanx of the middle finger of the left hand (already placed in an area wished to be percussed) (figure 16.5). The striking finger must be withdrawn as soon as the stroke is delivered. Delivery of the stroke is through flexion of the wrist and the finger at the metacarpo-phalangeal joint and not through any actions in the elbow or shoulder.

The percussion sound note is tympanitic when the site is over an area of airfilled bowel, whereas it is dull in presence of fluid. Shifting dullness on percussion can be used to determine whether the abdominal distension is due to the presence of fluid (ascites) or an intraabdominal tumor.

Percussion of the abdomen is valuable in the diagnosis of tumor and in distinguishing it from ascites and in deciding

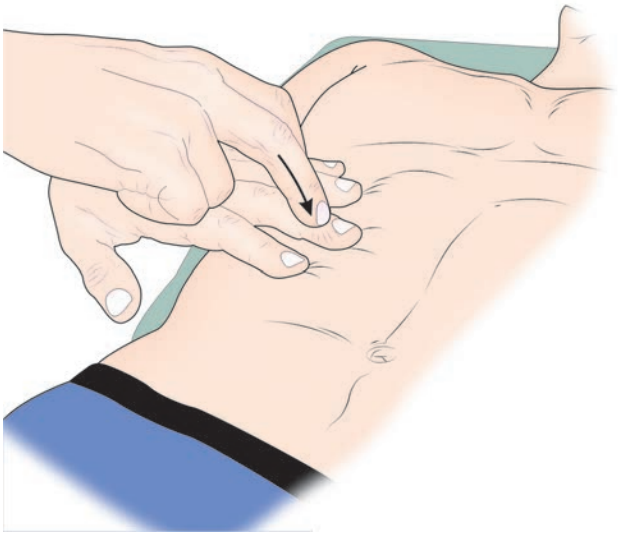
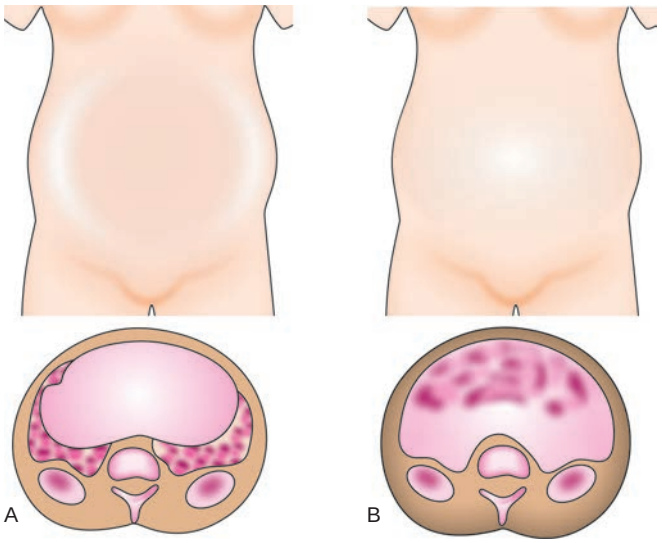


Fig. 16.5: Technique of percussion



Dullness is indicated by shaded areas, whereas resonance is shown in white.

Fig. 16.6: Shifting dullness. (A) Shows presence of an ovarian or uterine tumor, whereas (B) Shows ascites

whether it is intraperitoneal or retroperitoneal. Most intraperitoneal tumors arising from the pelvic organs are dull to percussion, whereas a retroperitoneal tumor usually has one or more loops of bowel adherent to it in front, which may give a tympanitic note on percussion. Percussion also helps in differentiating between a large ovarian cyst and ascites. In case of an ovarian cyst, the tumor is dull on percussion, where as both the flanks are tympanitic due to the presence of intestines. In case of ascites, on the other hand, the abdomen is tympanitic in the midline due to the presence of intestines, whereas both the flanks are dull on percussion (figure 16.6). The technique of percussion also helps in the detection of the following:

Liver dullness: Measurement of liver dullness.

Presence of ascites: Ascites is commonly associated with malignant tumors. However all malignant tumors may not be associated with ascites, because only epithelial ovarian malignancies produce ascites. Some benign conditions which may also be associated with ascites include tubercular peritonitis and Pseudo-meig's syndrome. Presence of ascites is basically detected by two tests: Fluid thrill and shifting dullness. Dullness in the flanks upon percussion and shifting dullness indicates the presence of free fluid in the peritoneal cavity.

Shifting dullness

Presence of dullness in both flanks when the patient is supine and dullness only in the dependent flank when the patient is on her side indicates the presence of ascites. The ability to demonstrate shifting dullness increases with the volume of ascitic fluid. Shifting dullness may be absent if the volume of ascitic fluid is only small. This test comprises of the following steps:

- The patient is laid supine and the clinician starts percussing from the midline of the abdomen towards one of the flanks. The level at which the percussion note changes from tympanitic to dull is noted and then the patient instructed to turn to the side opposite to the one where the percussion is being done. In normal individuals (without presence of any intra-abdominal mass), gas-filled bowels float on top of the ascitic fluid when the patient is in supine position, whereas fluid gravitates in the flanks. This is responsible for producing tympanitic note in the midline of abdomen and a dull note in the flanks.
- The patient is then turned to her side and allowed time so that the fluid gravitates to the side of dependent flank. Now the clinician performs the percussion once again. The dependent flank where the fluid had gravitated would sound dull to percussion, while the nondependent flank would be tympanitic.
- The patient is then turned to the other side and the above mentioned step is again repeated.

Fluid thrill

Another test for ascites is the demonstration of fluid thrill. The test comprises of the following steps (figure 16.7):

- The patient is laid supine and the clinician places one hand flat against his flank on one side.
- An assistant (e.g., a nurse) or the patient herself is asked to place the ulnar aspect of her hand firmly in the midline of the abdomen.

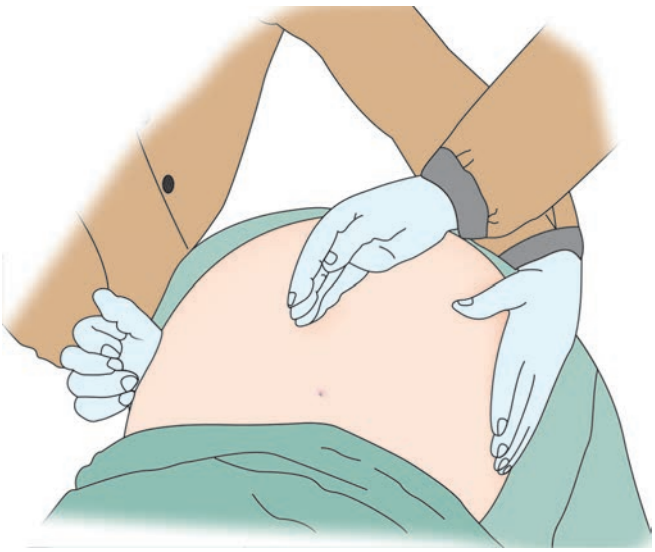


Fig. 16.7: Fluid thrill

- Without crossing arms, the gynecologist taps the opposite flank of the abdomen with his/her other hand. In case the ascitic fluid is present, the impulse generated by the tap will be transmitted to the clinician's other hand on the flank. The hand on the abdomen helps in preventing the transmission of the impulse over the abdominal wall. Fluid thrill is demonstrable only if a large volume of ascitic fluid is present. Absence of shifting dullness or fluid thrill or both does not rule out the presence of a small volume ascites.

Auscultation

Auscultation does not form an important part of abdominal examination. The purpose of auscultation of the abdomen is mainly to listen for bowel sounds produced by peristaltic activities and vascular sounds. Presence of bowel sound in the abdomen of the patient who had undergone surgery is indicative of recovering bowel activity in the postoperative period.

CARDIOVASCULAR SYSTEM EXAMINATION

Routine examination of cardiovascular system involves palpation of cardiac impulse and auscultation of the heart at the apex for presence of any sounds, murmurs, clicks, etc. Detailed examination of the cardiovascular system is required in cases of past history of cardiovascular disease or complaints suggestive of a possible cardiovascular pathology while taking history.

EXAMINATION OF THE PULMONARY SYSTEM

Examination of the pulmonary system may be required to detect the presence of wheezes, rales, ronchi and bronchial breath sounds.

PELVIC EXAMINATION

Pelvic examination forms an important aspect of the gynecological check-up of a woman. The anatomy of female external and internal genitalia is shown in figures 16.8A and B respectively.

If the patient is virginal, the opening of the hymen may be wide enough to allow only one finger or narrow speculum examination. As far as possible a per vaginal examination must be avoided in virginal women. The prerequisites before performing a pelvic examination are described below:

- The patient must be asked to empty her bladder before lying down on the table for the examination.
- Gloves and instruments, if not disposable, should be sterilized by autoclaving before reuse.

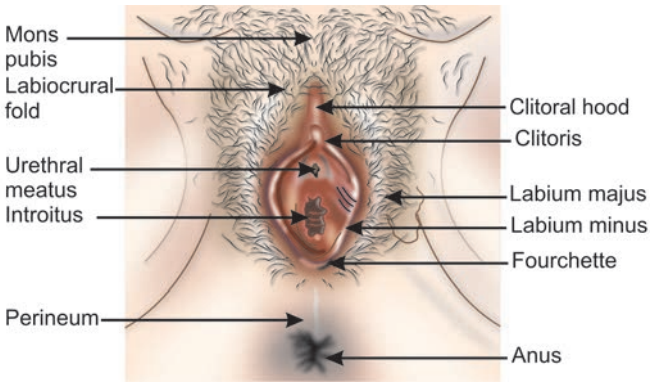


Fig. 16.8A: Normal anatomy of female external genitalia

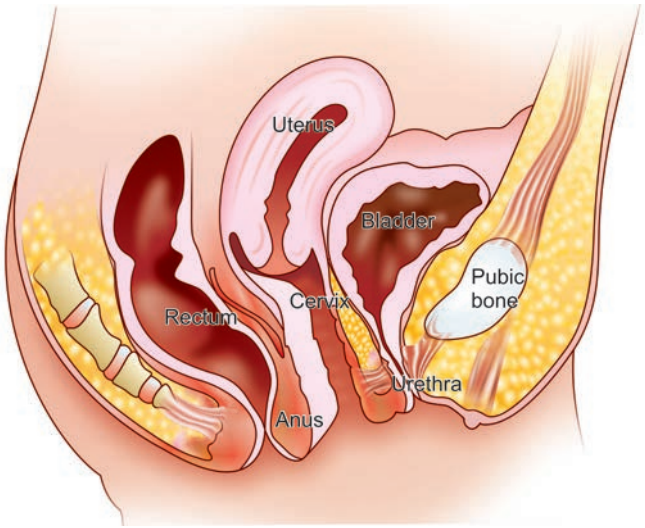


Fig. 16.8B: Normal anatomy of female internal genitalia

- Since this is an intimate examination, it requires patient's full cooperation. The patient must be described the procedure of pelvic examination and her informed consent be taken before proceeding with the examination.
- The clinician must wear nonsterile gloves on both hands before starting with the examination.
- Both male and female examiners should be chaperoned by a female assistant.

Positioning the Patient for Pelvic Examination

Full dorsal position

The full dorsal position with the knees flexed is the most commonly employed position used for gynecological examination in clinical practice. This position allows adequate per speculum and vaginal examination. This position also enables the clinician to inspect the vagina and cervix for taking vaginal swabs and cervical smears. However, this examination

does not allow adequate exposure of the lateral vaginal walls. The examiner stands to the right of the patient. The patient can be made to relax by partly covering her knees and thighs with a sheet.

Lithotomy position

This position involves the use of stirrups to hold the flexed lower limbs and involves the movement of the patient to the edge of table. This position may be uncomfortable and awkward for the patient.

Though this position is not commonly used for clinical examination, it is often used at the time of vaginal surgeries and for examination of the patient under anesthesia.

The Steps of the Pelvic Examination

Pelvic examination comprises of the following: Examination of the external genitalia, a per speculum examination, bimanual vaginal examination and a per rectal examination (if required). These would be described in details below:

Examination of the external genitalia

The gynecologist examines the external genitalia for the presence of any obvious lesions or signs of inflammation. Examination of external genitalia reveals areas of discoloration, ulceration and redness. Ulcerative areas could be indicative of herpetic infection, vulvar carcinoma, syphilis, etc. Vulvar mass at 5'O clock or 7'O clock position may suggest a bartholin gland cyst.

Per speculum examination

Speculum examination of the vagina and cervix involves inspection of external genitalia, vagina and cervix. Per speculum examination may reveal normal vaginal wall rugosities or smoothness of vaginal epithelium, which could be suggestive of atrophic vaginitis. Presence of masses, vesicles or any other lesions can also be assessed on per speculum examination. This examination should ideally precede the bimanual examination. This is primarily because the vaginal discharge can be seen and removed for examination before it gets contaminated with the lubricant used for vaginal examination; Moreover, the cellular debris from the cervix and uterus remains undisturbed and can be obtained for cytological studies at the time of per speculum examination. Also, many superficial vaginal lesions may start bleeding following the vaginal examination and may not allow an optimal per speculum examination. The types of speculum which can be used are described below:

Examination using Sim's speculum: Cervical examination can also be performed using a Sim's vaginal speculum

Fig. 16.9: Sim's speculum

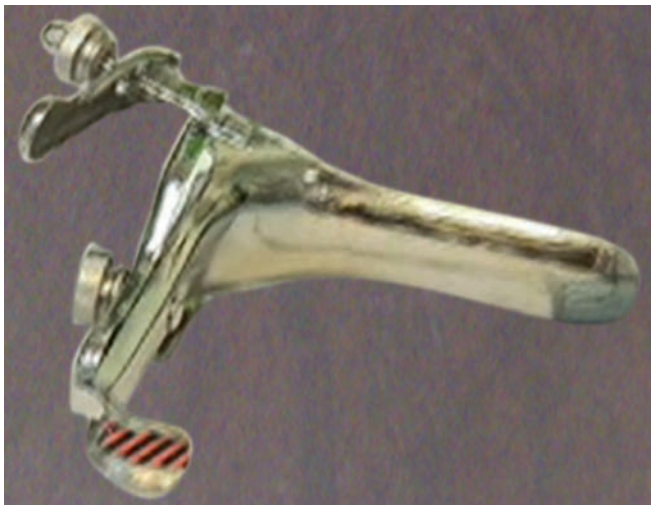


Fig. 16.10A: Cusko's speculum

(figure 16.9) and an anterior vaginal wall retractor. This speculum allows the assessment of vaginal walls and evaluation of presence of uterine prolapse such as cystocele, or rectocele. However cervical inspection using Sim's speculum is associated with two main disadvantages: The gynecologist needs to bring the patient to the edge of the table. Also help of an assistant may be required while conducting a per speculum examination using a Sim's speculum.

Examination using Cusko speculum: A self-retaining, bivalve speculum such as Cusko's speculum (figure 16.10A) serves as an ideal equipment for vaginal examination. This speculum allows appropriate vaginal exposure so as to ensure adequate vaginal inspection (figure 16.10B). Presence of cervical lesions (ectropion, polyps, cervical erosions, etc) can be visualized. Cervical inspection using this speculum also permits the gynecologist to take pap's smear at the time of per speculum examination.

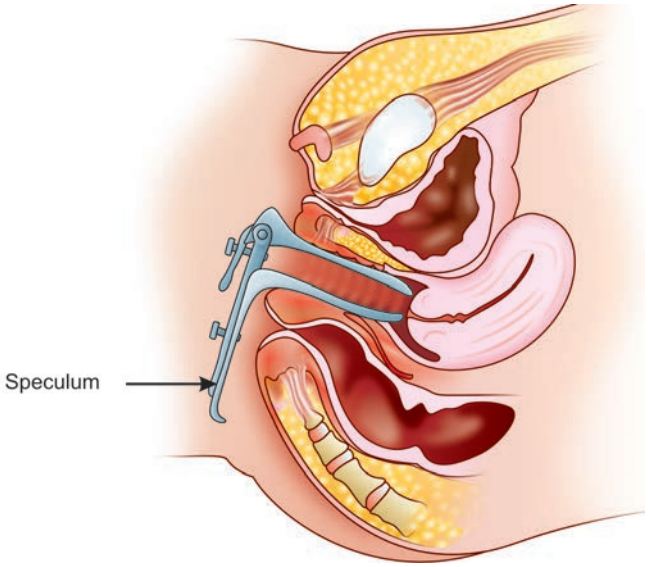


Fig. 16.10B: Per speculum examination using a Cusko's speculum

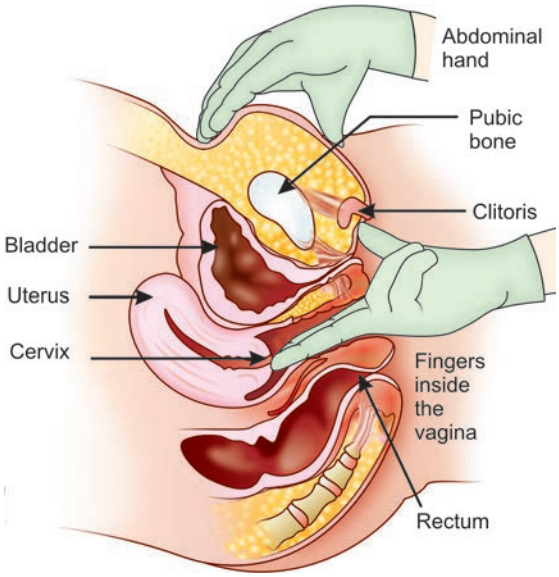


Fig. 16.11: Bimanual vaginal examination

Procedure of insertion of Cusko's speculum:

- The gynecologist must firstly warm and lubricate the speculum by holding it under running tap water.
- The vaginal introitus must be exposed by spreading the labia from below using the index and middle fingers of the left hand.
- The Cusko's bivalve speculum must then be inserted at an angle of 45°, pointing slightly downward. Contact with any anterior structures must be avoided.
- Once past the introitus, the speculum must be rotated to a horizontal position and insertion continued until its handle is almost flush with the perineum.
- The blades of the speculum are opened up for a distance of approximately 2 to 3 cm using the thumb lever in such a way that the cervix "falls" in between the blades.
- The speculum can be secured in its position by using the thumb nut in case of a metal speculum. The speculum must not be moved while it is in a locked position.
- The cervical and vaginal walls must be observed for the presence of lesions or discharge. Specimens for culture and cytology must also be obtained.
- While removing the speculum, the speculum must be withdrawn slightly to clear the cervix. As the cervix gets cleared off, the speculum must be loosened and its blades allowed to fall together. The speculum must then be rotated to an angle of 45 degrees and continued to be withdrawn.

Bimanual vaginal examination

Following the per speculum examination, a bimanual vaginal examination must be performed. First one and then two fingers are inserted into the vaginal introitus following which a bimanual vaginal examination is done (figure 16.11). Bimanual vaginal examination is usually more informative than per speculum examination and can be performed in most women.

Fig. 16.12A: Use of a water-based, soluble, non-greasy lubricant before starting bimanual examination

Procedure:

- A water-based, soluble, non greasy lubricant must preferably be used (figure 16.12A). A water soluble jelly is the best and if that is not available, cetrimide solution must be used.
- The labia are separated with the thumb and index finger of left hand.
- Following this, the two fingers of right hand, first one finger and then the second finger are inserted into the

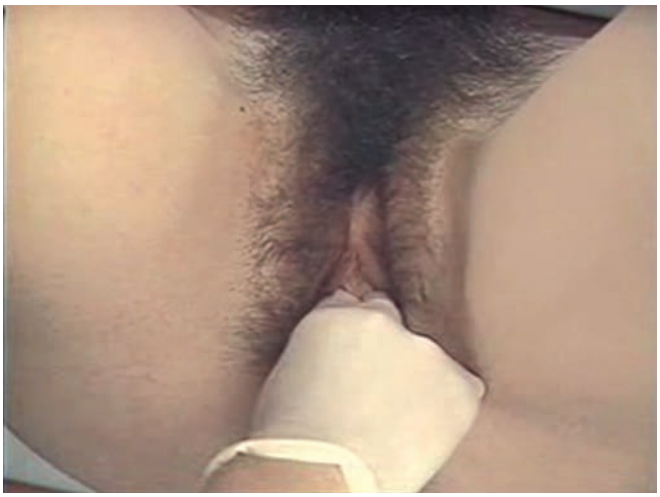


Fig. 16.12B: Two finger vaginal examination

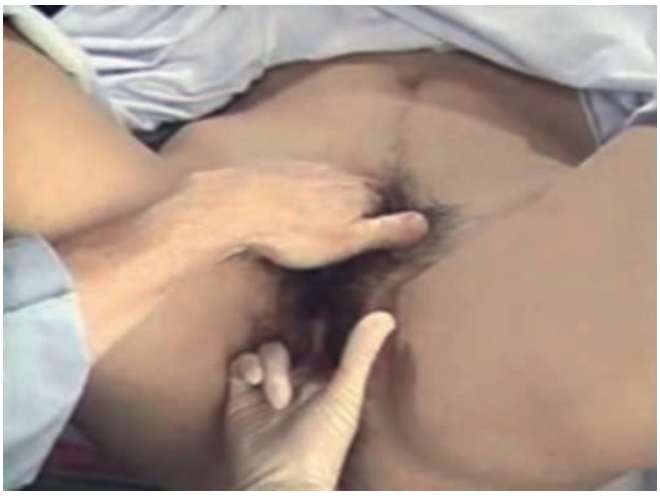


Fig. 16.12C: Bimanual vaginal examination

vagina only when the patient relaxes the muscles around the vagina and when it is clear that a two-finger examination would be possible without causing any pain (figure 16.12B).

- Cervical shape, size, position, mobility, consistency and tenderness caused by pressure or movement needs to be assessed. The position and direction of the cervix are the guides to the position of the body of the uterus. If the cervix is pointing in the downwards and backwards direction, the anterior lip of the cervix would be encountered first on the vaginal examination. This indicates the anteverted position of the uterus. On the other hand, if the cervix is pointing in the upwards and forward direction, the posterior lip of cervix would be encountered first on the vaginal examination. This indicates the retroverted position of the uterus.

A nonpregnant healthy cervix is usually firm in consistency. The cervix tends to soften during pregnancy. Under normal circumstances the movement of cervix in any direction must not be painful. However, pain upon moving the cervix (also known as cervical motion tenderness) is a common symptom of pelvic inflammatory disease (salpingo-oophoritis) and ectopic pregnancy.

- In clinical scenario, the vaginal examination is immediately followed by a bimanual examination (figure 16.12C) without removing fingers from the vaginal introitus. While the fingers of the examiner's right hand are still inside the vaginal introitus the palm of his/her left hand is placed over the abdomen. The success of bimanual examination primarily depends on the ability of the examiner to use the abdominal hand more often than the vaginal fingers.
- To feel the uterus, the vaginal fingers should move the cervix as far backwards as possible to rotate the fundus downwards and forwards. The abdominal hand is then placed just below the umbilicus and gradually moved lower until the fundus is caught and pressed against the fingers in the anterior fornix.
- The following points are noted on bimanual examination: Size of the uterus; its position, (anteverted or retroverted); mobility, (restricted mobility or fixed uterus). If there is a mass felt, its relation to the uterus is noted, like whether the mass is felt separate to the uterus or is continuous with it. When the mass is felt separate from the uterus, the origin of the mass is most likely from the adnexa or broad ligament. However, if the mass is continuous with the uterus, it probably arises from the uterus, like a fibroid.

Size of the uterus: Bulky uterus corresponds to six-weeks pregnant size and is slightly larger than the normal. When the uterus appears to be filling all the fornices, it corresponds to 12 weeks size. The in-between size could be between 8–10 weeks.

Both the adnexa must then be palpated between the vaginal fingers in the lateral vaginal fornices and the abdominal hand to look for presence of any mass or abnormality.

The rectal exam

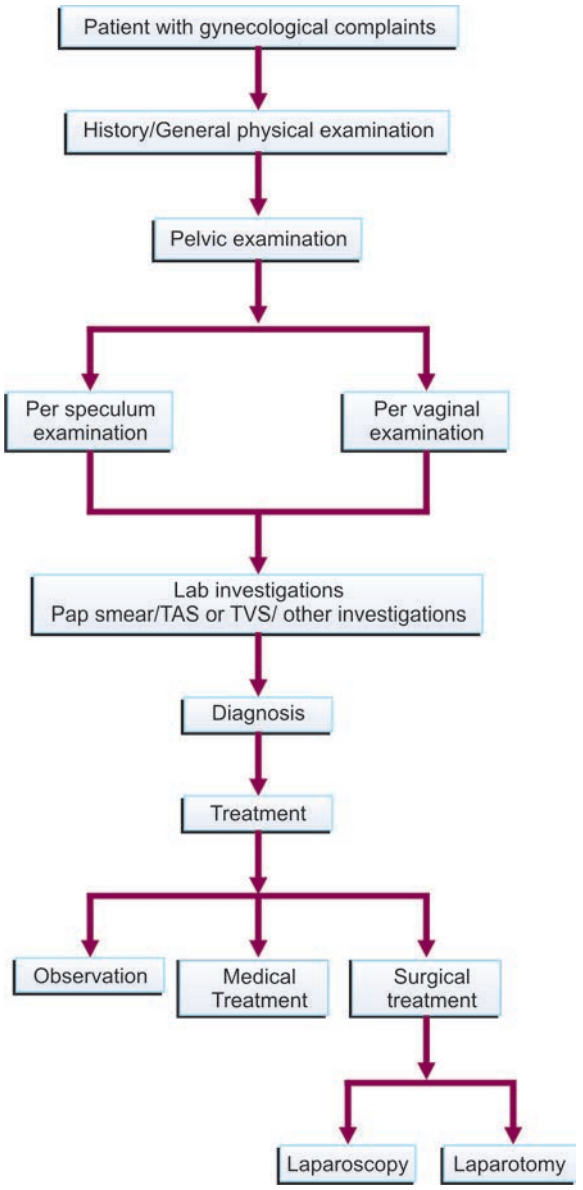
Combined rectal and vaginal examination is done when required. Similar to the bimanual exam, the examiner inserts a lubricated, gloved finger into the rectum to feel for tenderness and masses. Per rectum examination will reveal masses in the posterior pelvis. Presence of nodularity in the Pouch of Douglas and tenderness of uterosacral ligaments are signs of endometriosis. Some practitioners include rectal examination as part of the routine exam, while others do this procedure only in specific cases.

Management

Management of a patient presenting with gynecological complaints is summarized in flow chart 16.1. The aims of management are the following:

- Making and confirming the patient's diagnosis.
- Assessing the severity or stage of the disease.
- Rendering treatment based on the stage of the disease.
- Following up the patient's response to treatment.

Flow chart 16.1: Management of the patient presenting with gynecological complaints



Investigations

Ultrasound Examination

Introduction

It has been over 35 years since ultrasound was first used on pregnant women. Nowadays, besides obstetric indications, ultrasound is commonly being used for gynecological patients. Ever since its introduction in the late 1950's, ultrasonography has presently become a very useful diagnostic tool in both obstetrics and gynecology. Ultrasound examination has presently been considered to be a safe, noninvasive, accurate and cost-effective investigation for evaluation of gynecological pathology. Ultrasound waves which are very high frequency sound waves ranging between frequencies of 2.5 to 7.0 megahertz are generally used for this purpose.

Principle of Ultrasound

This is a procedure which uses high frequency sound waves to view internal organs. Ultrasound imaging uses the principles of sonar developed for ships at sea, or radar detection for speedy cars. The ultrasound probe has piezoelectric crystals in it, which convert the electric current into sound waves. These sound waves pass through the mother's abdomen as the clinician moves the transabdominal transducers over the mother's abdomen after application of water soluble gel, which acts as a coupling agent. As these sound waves pass through the internal structures and hit various body's structures, they get reflected back which can be used to identify distance between body parts and their size and shape (figure 16.13). When the sound waves hit a high density structure like bone, they are reflected back in form of high velocity waves, giving a white appearance on the screen. However, when these sound waves hit a less dense structure, reflected waves are of a lower velocity. These waves give a black appearance on the screen. These reflected waves are picked up by the piezoelectric crystals inside the transducer and get converted into electric signals which are then displayed on the screen. Repetitive arrays of ultrasound beams from the transducer scan the pelvic structures in thin slices and are reflected back onto the same transducer. The information obtained from different reflections is recomposed back into a picture on the monitor screen.

Uses of ultrasound examination in gynecological diseases

Ever since ultrasonography has been discovered it has been playing an immense role as a diagnostic tool in medical sciences. Field of obstetrics and gynecology is no exception to it. Ultrasound, both transabdominal and transvaginal are widely used in the clinical practice. TVS alone and also

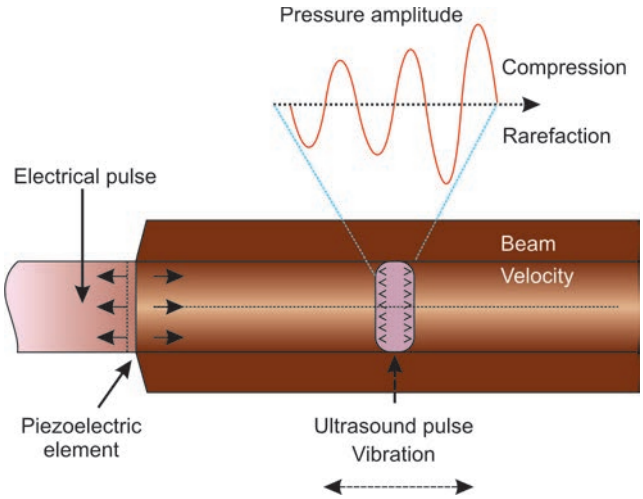


Fig. 16.13: Principle of ultrasound

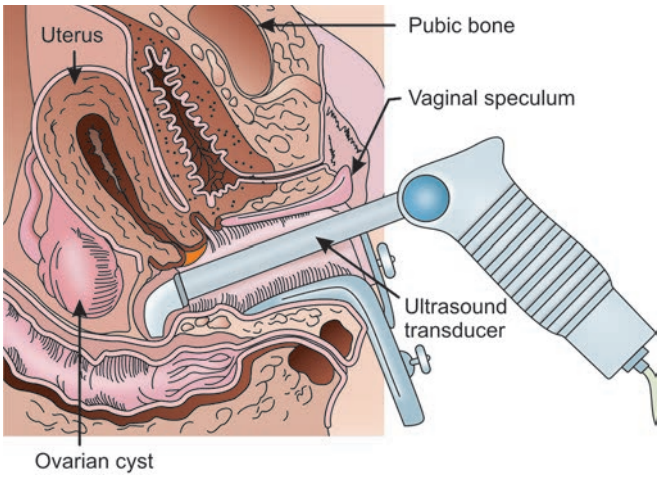


Fig. 16.14A: Technique of transvaginal ultrasonography

Fig. 16.14B: Transvaginal ultrasound probe

when supplemented with TAS could detect many clinically missed cases of pelvic masses or suspected pelvic pathology on provisional diagnosis made clinically. TVS acts as an effective complementary diagnostic aid in evaluation of many gynecologic conditions such as leiomyomas, abnormal uterine bleeding, leiomyomas, endometriosis, ovarian cysts, malignancies, ectopic pregnancy and tubo-ovarian masses. The effectiveness and accuracy of TVS is high and it increases further when TVS is supplemented with TAS. Hence TVS should be used as a diagnostic tool for any pelvic mass or suspected pelvic pathology prior to laparoscopy or laparotomy. Its diagnostic capabilities may reduce the need for other invasive procedures and aid in the clinical decision making. This being a noninvasive and an OPD procedure has resulted in the high amount of patient compliance. Also the cost incurred in lab investigations and hospital stay for laparoscopy or laparotomy can be avoided and individual organs and fine structures seen better transvaginally. However the regional survey offered by the transabdominal full bladder approach remains necessary to provide anatomic orientation, particularly when the patient has not been studied previously. In some patients TAS is required especially when the mass has extended beyond the true pelvis or has dimensions greater than 10 cm. However, there is no doubt about the fact that ultrasonography, especially TVS seems to be an important armamentarium and adjunct to the clinical acumen in day-to-day gynecological practice specially in the tertiary center.

Types of ultrasound

Ultrasound for the purpose of diagnosis of gynecological pathology is primarily done by two ways: Transvaginal and transabdominal ultrasound. Recently Doppler ultrasound is also increasingly being used.

Transvaginal ultrasound (figure 16.14A)

While doing a TVS examination, a specially designed transducer (figure 16.14B), covered with a well lubricated condom is placed inside the vagina, after having the women empty her bladder. The transducer is then moved around the vagina and pressed up on either sides of the cervix, to allow visualization inside the uterus and pelvis. Transvaginal ultrasound is most useful in the first trimester and is of great help in fat women and in those with retroverted uterus, in whom transabdominal ultrasound may not be able to visualize pelvic details clearly.

Tranvaginal examination provides images with much better resolution as compared to transabdominal examination.

Advantages of TVS

The use of a vaginal probe at the time of ultrasound examination offers the following advantages:

- Due to close proximity of the transducer to the pelvic organs, the examiner gets a detailed visualization of the structures as small as 1 mm. The closer proximity of the transducer does not result in an increased exposure or risk.
- One can use palpation to detect tenderness or presence of adhesions.

- TVS is an excellent modality for assessment of endometrial thickness and echogenicity and characterization of the ovarian tissues.
- High frequency beam used with TVS gives a far superior resolution and a better field image.
- There is much less beam scattering, as the beam does not have to travel through the abdominal wall. Therefore this method gives optimal information even in the obese patients.
- TVS avoids interference from the interposed bowel loops as in the case of abdominal scanning.
- TVS is a totally noninvasive, nontraumatic and nontoxic procedure. At the present time, there is no information regarding the influence of transvaginal ultrasound on the embryo, fetus, neonate or on child's development. Till date there have been no reports of any damage due to transvaginally guided procedures, or after scanning the patients.
- Since the transvaginal procedure does not require full bladder, it can be performed immediately especially during emergencies.
- It spares the patient the inconvenience of the full bladder. Therefore, it affords good patient acceptance without the discomfort of a full bladder.
- The physician can incorporate the procedure into the overall examination while the patient is still in the lithotomy position at the time of the bimanual examination.

Disadvantages of TVS

Some of the following disadvantages can be associated with the use of TVS:

- There is a limited field of view due to limited depth of sound penetration, caused by a higher frequency transducer. Therefore findings larger than 7 cm to 10 cm or those outside the true pelvis are difficult to scan with the vaginal probe.
- Considerable experience is required both to obtain a satisfactory image and to interpret them.
- Uterine length, which is a routine measurement by TAS, is difficult to be measured by TVS.
- TVS cannot be done in cases of vaginal stenosis or intact hymen.
- There is an inability to image the highly placed ovaries.
- Large probe caliber renders the examination difficult for some elderly post-menopausal women. In elderly patients the vagina has less elasticity, and this limits the maneuverability of the probe.

Transabdominal sonography (figure 16.15A)

Unlike the TVS examination which is performed after having the patient empty her bladder, TAS gives a clearer visualization of pelvic details when the patient's bladder is full. Therefore, the patient should be advised to drink plenty of fluids before examination so as to have a full bladder. This allows the uterus to be lifted out of the pelvis during examination for obtaining better image. After application of a lubricant over the patient's abdomen, the transducer (figure 16.15B) is then placed in contact with the patient's abdomen and moved around over the patient's abdomen in order to visualize the uterine cavity, endometrium and adnexa.

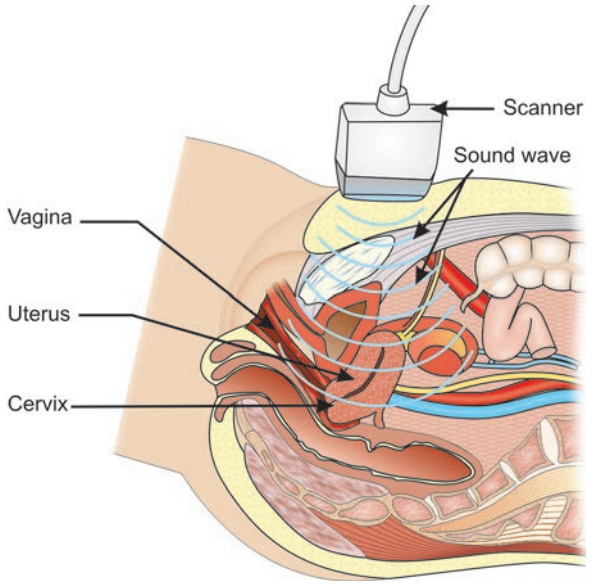


Fig. 16.15A: Technique of doing transabdominal ultrasonography

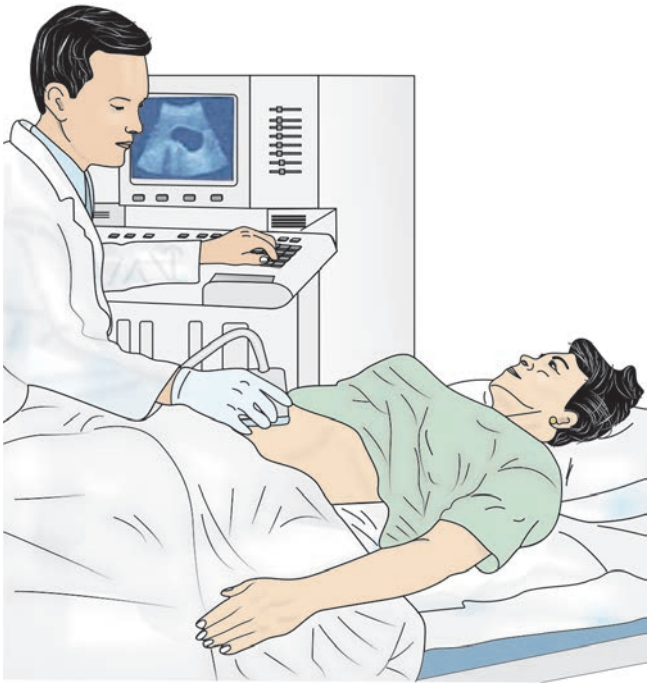


Fig. 16.15B: Transabdominal ultrasound probe

The normal endometrium as visualized by TVS (figures 16.16A to E)

During menses (day 1–4): In the menstrual phase, the endometrium appears as a thin, broken, central interface, measuring approximately 2–3 mm in thickness. Blood and tissue in the endometrial cavity produces a central anechoic area. During the first day or so of menstruation, the endometrial complex consists of a thick hyperechoic density surrounding the anechoic menstrual debris with the presence of posterior enhancement. With the progression of menstruation, the hypoechoic central echo representing blood, tissue and thickened hyperecoic endometrium will disappear.

The early proliferative phase endometrium (day 5–9): In the proliferative phase, there is presence of a well defined "three line sign". The "three line sign" is formed by the central hyerechoic reflection representing the endometrial cavity and the additional hyperchoic reflections representing the thin developing layer of the endometrium. The outer

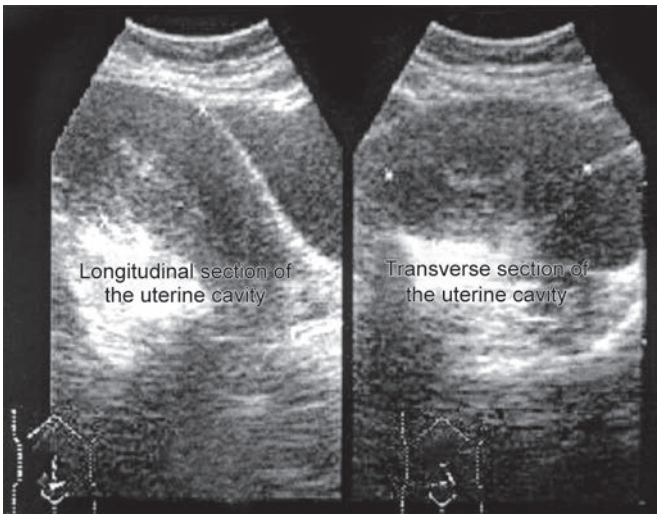


Fig. 16.16C: Normal uterus as visualized on transabdominal scan

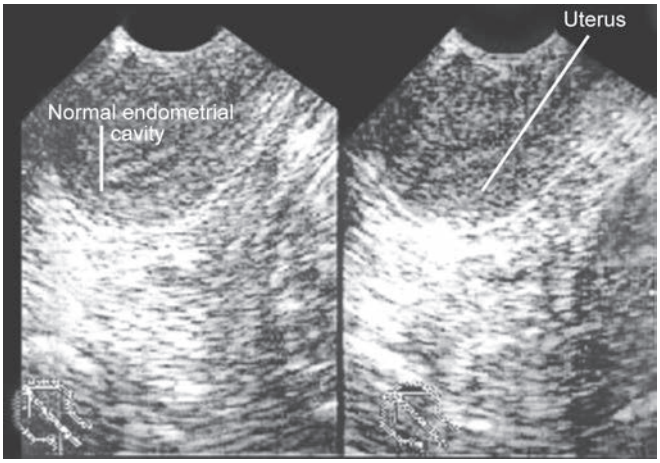


Fig. 16.16A: Normal TVS scan of the uterus

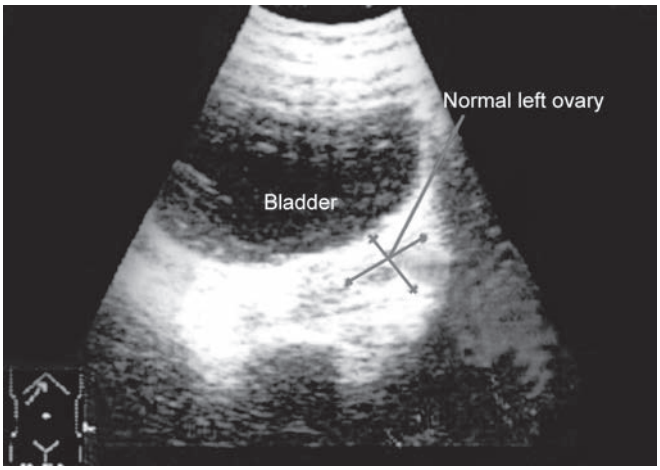


Fig. 16.16D: Normal ovary as visualized on the transabdominal scan

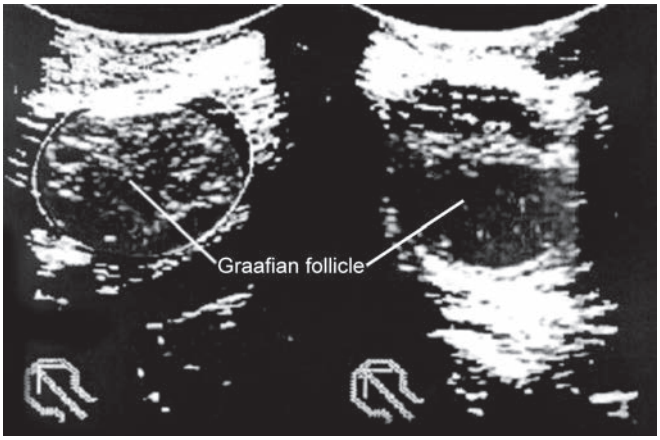


Fig. 16.16B: Normal TVS scan of the ovary

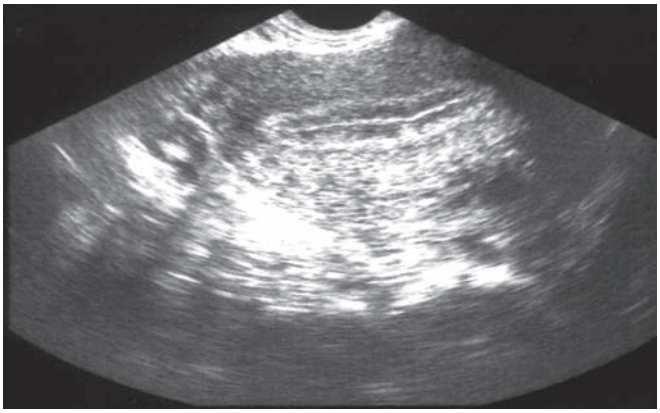


Fig. 16.16E: Normal three-line view of the uterine endometrium as visualized on transvaginal sonography

lines represent the interface between endometrium and myometrium. There is a hypoechogenic functional layer. The general hypoechogenic character of the functional layer of the proliferative endometrium is related to the simple configuration of the glands and blood vessels. There is minimal or absent posterior acoustic enhancement.

Late proliferative phase (day 10–14): Periovulatory endometrium has a thickness between 6–8 mm and is moderately echogenic. There is a continued thickening of the endometrial echo complex during this phase. The halo is still present, the three line sign is also present, but the outer lines may begin to thicken. The total endometrial thickness may increase up to 10 mm or greater.

During the luteal phase: In the immediate pre and postovulatory period (two days postovulation), an additional inner hyperechogenicity of variable thickness, which corresponds to a relatively high fluid content of these inner functional layers, could be seen with TVS. A small amount of fluid (1–2 ml) can be seen in some individuals within the lumen of the endometrium resulting in the halo sign. Since linear measurement of endometrial thickness really represents two layers of endometrium i.e. the anterior and posterior wall, some researchers have suggested that such measurements must be divided by two. The total double layer thickness in the luteal phase ranges from 4 to 12 mm with an average of 7.5 mm. The luteal phase endometrium tends to be hyperechoic and maximum in thickness. There is presence of posterior acoustic enhancement and three line sign is also absent.

CT Examination

CT examination is usually not performed during pregnancy due to the risk of radiations. It may be however useful in gynecological cases diagnosed with abdominal or pelvic masses. CT examination may also help in delineating the enlarged lymph nodes and other retroperitoneal pathologies. CT examination is usually indicated in presence of malignancy.

MRI Examination

Though MRI examination does not expose the patient to ionizing radiations, its high cost prevents its routine use in obstetric and gynecology practice. MRI examination helps in identification of soft tissue planes and diagnosis of adenomyosis, müllerian defects such as vaginal agenesis and uterine didelphys, ureteral stones and urethral obstruction.

Hysterosalpingography (HSG)

Hysterosalpingography is a radiological procedure which involves injection of a radioopaque material into the uterine cavity through the cervical canal, followed by fluroscopy with image intensification in order to investigate the shape of the uterine cavity and the shape and patency of the fallopian tubes. HSG helps in detection of intrauterine abnormalities such as submucous fibroids, intrauterine adhesions and in checking the patency of the fallopian tubes (tubal obstruction, hydrosalpinx, pyosalpinx, etc). The detailed procedure of hysterosalpingography has been described in chapter 26.

Pap Smear (Papanicolaou Test)

Pap smear has been described in detail in chapter 21.

Rx Treatment/Gynecological Management

Gynecological diagnosis is made after careful analysis of the positive findings related to the history and clinical examination. Based on the results of various investigations, the clinician should form the list of likely differential diagnosis in his/her mind. The correct diagnosis can be confirmed on the basis of findings of the various investigations. After ascertaining the diagnosis, the next step is to establish the severity of the disease. In case of malignancy, the cancer staging must be done. Treatment is decided based on the disease diagnosis and its severity. This is especially important in case of the malignancy where treatment would change depending on the stage of malignancy. The duty of the gynecologist does not end once the treatment has been dispensed; the duty of the clinician is also to assess the patient's response to the treatment by calling her for the follow up visits. Before the patient leaves the clinic, the future plans regarding management must be discussed with the patient. Patient information brochures and handouts must be provided to the patient. The patient should also be advised about the next follow up visit. The treatment options for various gynecological complaints such as abnormal bleeding patterns, pelvic organ prolapse, pelvic pain, infertility, etc. would be discussed in details in the successive chapters of this book.

Important Questions and Answers

Q.1. What would be the next line of management in the above mentioned case study?

Ans. Since the patient does not give any history of any gynecological problem and the clinical examination is essentially within normal limits, there is no requirement for any gynecological intervention. However, a routine pap smear and mammography are indicated in this patient because the patient is more than 40 years of age. The detailed description about pap smear examination has been given in chapter 21. The routine mammography has been recommended by the United States Preventive Services Task at an interval of every 1–2 years for

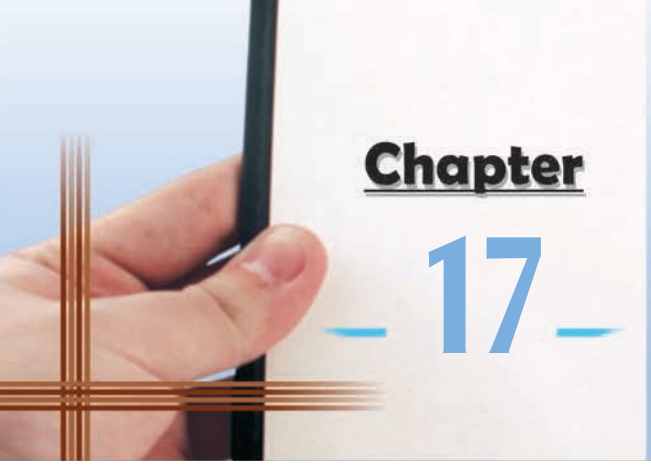
women aged 40 and older up to the age of 50 years. On the other hand, according to the NHS Breast Screening Program, free breast screening is done every three years for all women in the UK aged 50 until the age of 70 years. The recommendations for annual Pap smear examination are described in chapter 21.

Q.2. In case the vagina on per speculum examination revealed thin friable vaginal mucosa with loss of rugosities, what would be the next line of management in this case?

Ans. The above mentioned symptoms are indicative of atrophic vaginitis, which may be commonly encountered in menopausal women. The symptoms of atrophic vaginitis can be prevented by using hormone replacement therapy. The best option in such patients is to use topical estrogens, for example estrogen cream (e.g. evalon) to be applied over the vaginal mucosa for a few months until the symptoms subside.

Bibliography

1. Bates B. A guide to physical examination and history taking (6th edition), Philadelphia: J.B. Lippincott Company.
2. Bhangu AA. Please don't touch me there: The ethics of intimate examinations: Consent is crucial—but don't go too far, for students' and patients' sakes. BMJ. 2003;326:1326.
3. Department for Education and Skills (2005). Common core of skills and knowledge for the children's workforce, London: HM Government. Department of Health (2003) Confidentiality: NHS code of practice, London: DH.
4. Department of Health. Best practice guidance for doctors and other health professionals on the provision of advice and treatment to young people under 16 on contraception, sexual and reproductive health, London: DH. 2004.
5. General Medical Council. Good medical practice, London: GMC. Available from: www.gmc-uk.org. 2001.
6. Hope E, Frith P, Craze J, Mussai F, Chadha A and Noble D. Developing guidelines for medical students about the examination of patients under 18 years old. BMJ. 2005;331:1384-86.
7. Hughes B (2003). How can I make a woman comfortable during a pelvic exam? Medscape Nurses, New York: Medscape. Available from: www.medscape.com/viewarticle/461420 [Accessed July 2009].
8. Nestel D and Kneebone R. Please don't touch me there: The ethics of intimate examinations: Integrated approach to teaching and learning clinical skills. BMJ. 2003;326:1327.
9. Oakeshott P and Hay P. Best practice in primary care. BMJ. 2006;333:173-74
10. Selby M. Please don't touch me there: The ethics of intimate examinations: Informed consent failed to protect me. BMJ. 2003;326:1326.
11. Singer PA. Intimate examinations and other ethical challenges in medical education. BMJ. 2003;326:62-63.



Chapter

17

Abnormal Uterine Bleeding due to Endometrial Cancer

Case Study

A 55-year-old nulliparous woman, married since last 20 years, presented to the gynecological emergency with a severe episode of bleeding following a period of amenorrhea since past 7 months. The patient does not give any positive family history of cancer. She gives a history of undergoing treatment in the past which she was supposed to take on the first five days of the cycle. According to the patient, this was for treatment of her infertility. She also had been prescribed treatment for her excessive facial hair and advised to reduce her weight. However, she took no heed of the advice. She was unable to conceive despite of taking treatment. At the time of general physical examination her BMI was 27 (obese range) and blood pressure was 150/90 mm of Hg.

Introduction

It can been seen that the above mentioned case study has been formulated to simulate the situation of a patient presenting with abnormal uterine bleeding (AUB). Abnormal uterine bleeding can be defined as any deviation in the normal frequency, duration or amount of menstrual blood loss in a woman belonging to the reproductive age group. It also includes any bleeding from the uterus other than the normal menstrual blood loss. The parameters for normal menstrual blood loss are shown in table 17.1.

Abnormal uterine bleeding in young girls, who have not yet attained menarche is usually due to sexual abuse and cancer. It is important to rule out pregnancy and its related complications in women of childbearing age. AUB can also occur after menopause. In these cases, unpredictable bleeding may occur 12 months or more after the cessation of periods. Of all the postmenopausal women presenting with abnormal uterine bleeding, 5% to 10% percent may have endometrial carcinoma. Other potential causes of bleeding include cervical cancer, cervicitis, atrophic vaginitis, endometrial atrophy, submucous fibroids, endometrial hyperplasia and endometrial polyps. The most important thing that a clinician must remember is that AUB could be a sign of a serious underlying health problem such as endometrial malignancy.

Some terms used to describe AUB are listed in table 17.2. Out of these, menorrhagia resulting due to fibroids is described in chapter 20. Dysfunctional uterine bleeding (DUB) can be defined as a type of AUB in absence of any pelvic organ disease or a systemic disorder. DUB forms nearly 60% cases of AUB. DUB would be discussed in details in chapter 19.

As previously mentioned, the prime responsibility of the gynecologist is to rule out the presence of endometrial malignancy in case of AUB, especially in women of

Table 17.1: Parameters for normal and abnormal menstrual blood loss

	Normal	*Abnormal*
Duration	4–6 days	Less than 2 or more than 7 days
Volume	30 ml	Less than 30 ml or >80 ml
Interval	24–35 days	Less than 21 days or more than 35 days

Table 17.2: Terms used for describing AUB

Term	*Definition*
Menorrhagia	Prolonged or excessive menstrual blood loss (>80 ml) at regular intervals
Polymenorrhea	Regular bleeding at intervals of less than 21 days
Oligomenorrhea	Infrequent menstruation at intervals greater than every 35 days
Amenorrhea	No uterine bleeding for at least 6 months
Intermenstrual bleeding (spotting)	Episodes of uterine bleeding of varying amounts occurring between the regular menstrual periods
Menometrorrhagia	Combination of both menorrhagia and metrorrhagia, associated with prolonged or excessive bleeding (> 80 ml) at irregular intervals.
Metrorrhagia	Irregular, frequent uterine bleeding of varying amounts, but not excessive, at irregular intervals.
Hypomenorrhea	Scanty menstruation

perimenopausal and menopausal age groups. Most cases of endometrial cancer are histologically of adenomatous type. The endometrial cancers can be of different grades (grade I, II and III) based on the degree of cellular differentiation, anaplasia and glandular architecture, with higher grade of tumor associated with a worse prognosis. There appear to be two distinct pathogenetic types of endometrial cancer. The first type is seen in younger perimenopausal women. This cancer occurs in the background of estrogen stimulation and endometrial hyperplasia. These tumors are well-differentiated and are associated with a better prognosis in comparison to the other type. On the other hand, the other pathogenetic variety occurs in postmenopausal women with atrophic endometrium. These cancers are often poorly differentiated and associated with a worse prognosis.

History

Detailed history for assessing the nature of blood loss needs to be taken from the patient. Some of these questions are described below.

Nature of Bleeding

The clinician needs to ask questions to determine the pattern of bleeding: Amount of bleeding; the time of bleeding (the days in the menstrual cycle during which the bleeding occurs); intermenstrual intervals (between the episodes of bleeding) and cycle regularity (whether the bleeding pattern is regular or irregular).

Amount of bleeding

Initially the clinician needs to establish whether the woman is having heavy, light or moderate amount of blood loss.

Estimating the quantity of blood loss is a very subjective issue when considering vaginal bleeding. Accurate assessment of the menstrual blood loss may not be possible and best estimates of menstrual blood loss are the only source clinicians have to consider commonly. Some questions which the obstetrician can ask in order to assess the amount of blood loss are as follows:

- Total number or pads or tampons used by the patient during the heaviest days of her bleeding. This can give a rough estimation of the amount of bleeding, though the number of pads used for the same amount of bleeding may vary from woman to woman depending on their hygienic preferences.
- How frequently does she require changing her pads during the day?
- Does she has to use double protection? (e.g. simultaneous use of a tampon and pad or use of double pad. For the purpose of calculating the amount of blood loss, it can be assumed that an average tampon holds 5 ml and the average pad holds 5–15 ml of blood).
- Does she have to get up in the night to change her protection?
- Is there any history of passage of blood clots?
  Normally, the blood lost from the vessels in the endometrial lining forms small clots and this helps in reducing the blood flow. Under normal circumstances, these blood clots are broken down by fibrinolysins, present in the endometrial cavity and the menstrual blood loss is in form of a fluid. However in case of very heavy bleeding, the blood is extruded too quickly for it to clot within the uterus. In this situation, the blood clots in the vagina and the menstrual flow includes blood clots.
- Does she stain her bedding or clothes despite wearing tampons and pads?
- Does she ever experience "flooding" or sudden rushing out of a large quantity of blood?
- Does she have to stay at home or take time off work during the episode of bleeding?
- How long do her periods last?
- Is the amount of bleeding so much as to interfere with the patient's life style?
- Is there constant pain in the lower abdomen during menstrual periods?
- Are the menstrual periods irregular?
- Does she, experience tiredness, fatigue or shortness of breath (symptoms of anemia).
- The type of sanitary protection being used by the patient is also important since the patient may be required to less frequently change the newer absorbent pads in comparison to the home made cloth based sanitary protection.

Duration of bleeding

Bleeding occurring for more than seven days at a stretch can be considered as prolonged.

Pattern of bleeding

Sudden change in the bleeding pattern, for example, the excessive bleeding at regular intervals which suddenly becomes irregular must be regarded with caution. In these cases, investigations must be undertaken to discover the exact pathology.

Smell

Presence of a foul smelling vaginal discharge points towards the presence of infection or a necrotic malignant growth. Malignant growths often undergo necrosis in the areas of reduced blood supply.

Relation of bleeding to sexual intercourse

Bleeding following sexual intercourse is usually related to the lesions of cervix or vagina. Simple vaginitis (e.g., candidal infection, bacterial vaginosis) may cause intermenstrual bleeding, while gonorrhea and chlamydia may present with heavier bleeding attributed primarily to the copious discharge mixed with the blood. If a woman presents with the history of postcoital bleeding, cervical cancer must be specifically ruled out.

Other temporal associations of the bleeding episode whether postpartum, or post-pill, also needs to be asked.

Features indicative of presence of endometrial malignancy

The pointers in the history of bleeding, indicative of underlying malignancy in case of AUB include the following:

- Sudden change in the bleeding pattern
- Irregular bleeding
- Intermenstrual bleeding
- Postcoital bleeding
- Dyspareunia, pelvic pain
- Lower extremity edema, which could be secondary to metastasis.

17

Patient's Age

Patient's age can provide important pointer towards the diagnosis of underlying pathology.

Women belonging to postmenopausal age group

The risk of developing endometrial cancer increases with age. The endometrial cancer peaks in the age group of 55–70 years. However, this cancer can even occur before menopause and nearly 20% to 25% cases of endometrial cancer occur in perimenopausal women. The overall incidence of this cancer is 10.2 cases per 100,000 in women aged 19 to 39 years. On the other hand, in women aged 40 to 49 years, the incidence of endometrial carcinoma is 36.5 cases per 100,000. Thus, the American College of Obstetricians and Gynecologists recommends endometrial evaluation in women aged 35 years and older who have abnormal uterine bleeding.

Though endometrial cancer can be asymptomatic in nearly 10% cases, the most common clinical symptom associated with endometrial cancer is abnormal or irregular uterine bleeding. Therefore, in case a postmenopausal woman presents with abnormal uterine bleeding, she should receive an immediate workup for endometrial cancer. Presence of endometrial hyperplasia/malignancy must be ruled out in all postmenopausal women presenting with bleeding, especially those having risk factors for endometrial malignancy (table 17.3).

Table 17.3: Risk factors for development of endometrial cancer

Patients older than 35 years of age
Overweight or obesity
Unopposed exposure of endometrial cavity to estrogens (both endogenous and exogenous)
More than 35 days between two consecutive periods
History of diabetes or hypertension
History of intake of medications such as tamoxifen
Nulliparous women or those with low parity
Early menarche or late menopause
Non-ovulatory cycles as seen in cases of anovulatory DUB or polycystic ovarian syndrome

Women of reproductive age group

The most common cause of abnormal bleeding patterns in women belonging to the reproductive age group is pregnancy related complications. Since pregnancy related bleeding must be considered as the first differential diagnosis in the women of child bearing age who present with abnormal uterine bleeding, it is important to take history of the period of amenorrhea preceding the episode of blood loss or having a positive pregnancy test during that period. Potential causes of pregnancy related bleeding include spontaneous miscarriage, ectopic pregnancy, placenta previa, abruptio placentae, trophoblastic disease, etc. Uterine leiomyomas are a common cause for menorrhagia in the women belonging to reproductive age group. Uterine leiomyomas have been discussed in details in chapter 18.

Young patients

The most common etiology in a young patient having irregular menses since menarche is anovulation.

Other questions which need to be asked while taking history in such patients include the following:

- Sexual activity/history of vaginal infection.
- *History of chronic anovulation:* (e.g., that associated with PCOS) is associated with unopposed estrogen stimulation. Presence of hirsutism or excessive growth of facial hair, obesity and acne point towards polycystic ovarian syndrome. Polycystic ovary syndrome is associated with unopposed estrogen stimulation, elevated androgen levels, and insulin resistance and is a common cause of anovulation. Women with feminizing ovarian tumors are associated with unopposed estrogen production, which acts as a risk factor for endometrial cancer.
- *History of galactorrhea or secretion of milk from breasts:* Any patient complaining of a milky discharge from either breast (while not pregnant, postpartum or breastfeeding)

needs a prolactin level to rule out the presense of a pituitary tumor. Galactorrhea could be related to underlying hyperprolactinemia, which can cause oligoovulation or eventual amenorrhea.

- *History of any eating disorder, stress, etc:* It is important to elicit the history of any eating disorders/stress etc. Hypothalamic suppression secondary to eating disorders, stress or excessive exercise may induce anovulation, which sometimes manifests as irregular and heavy menstrual bleeding or amenorrhea.
- *History of pain in the abdomen:* Pain in the abdomen could be indicative of underlying malignancy.
- *History of foul smelling discharge per vaginum*: This could be related to the presence of sexually transmitted diseases or carcinoma cervix. Age is an important consideration in these cases because women in reproductive age groups are more likely to suffer from sexually transmitted diseases while diagnosis of cervical cancer is more likely in older women.
- *Presence of pressure symptoms*: This could be related to the presence of a large pelvic mass (uterine or adnexal mass) pressing upon the bladder or rectum resulting in pressure symptoms like increased urinary frequency and/or rectal symptoms such as constipation, tenesmus etc.
- *Plans regarding future fertility and contraception:* It is important to take the patient's history regarding her plans for future fertility and child bearing in order to decide appropriate patient management, e.g. decision for hysterectomy must be avoided as far as possible in a young women desiring future fertility.
- *Symptoms suggestive of pregnancy:* Symptoms suggestive of pregnancy, e.g. morning sickness, breast changes, etc also need to be enquired from the patient.
- *Previous Pap smears:* History of undergoing pap smears in the past needs to be elicited. Previous normal pap smears help in ruling out cervical malignancy.
- Sexual activity/history of vaginal infection.
- *History of genital trauma:* Genital trauma may result in bleeding from the vagina or rectum. It is especially important to rule out sexual abuse in young girls, presenting with bleeding who have yet not attained menarche.

Past Treatment/Drug History

- *History of drug intake*: Intake of drugs such as anticoagulants (e.g., warfarin); hormones (e.g., unopposed estrogens, tamoxifen, etc); selective serotonin reuptake inhibitors; antipsychotics; corticosteroids, etc may typically cause bleeding. Thus the patient should be asked if she had been prescribed any of the above mentioned medicines in the past. Since herbal substances, such as ginseng, ginkgo and soy supplements, may also cause menstrual irregularities, history of intake of such products must also be taken.
- *History of contraceptive use (intrauterine device or hormones)*: Commonly, an intrauterine device (IUD) causes increased uterine cramping and menstrual flow.
- *Use of unopposed estrogens without combination with progesterone (in form of oral contraceptive pills or HRT):* Use of unopposed estrogens (without combination of progesterone) may predispose the woman to develop endometrial hyperplasia or cancer in future. Chronic proliferation of the endometrium may cause adenomatous hyperplasia, which may result in the development of atypical adenomatous hyperplasia, eventually leading to the development of endometrial carcinoma.
- History of intake of drugs such as tamoxifen, usually administered for treatment of breast cancer.

Menstrual History

The history of menstrual cycles before the occurrence of episode of abnormal bleeding, including features such as duration of bleeding, the cycle length, whether cycles were regular or irregular, whether there was pain during cycles, etc needs to be enquired. The age of menarche and that at which menopause was attained also needs to be asked. Endometrial cancer is also more common in women who have had early menarche and late menopause. These factors are likely to result in a prolonged or unopposed exposure of the endometrium to estrogen, which may result in an increased risk of development of endometrial cancer.

Obstetric History

Eliciting the patient's obstetric history is particularly important because certain pathological conditions (e.g. endometrial malignancy and uterine leiomyomas) are more likely to develop in nulliparous women. Since nulliparity acts as a risk factor for the development of both endometrial carcinoma and uterine leiomyomas, the two are frequently observed to coexist together. On the other hand, conditions like cervical malignancy are more likely to develop in mulltiparous women.

Past Medical History

- *Past history of chronic illness:* The patient should be asked about the past history of any chronic medical illness like diabetes mellitus, hypertension, CAD, etc. History of any medical illness in the past including the history of diabetes, hypertension and obesity needs to be asked. This is especially important because the triad of obesity,

hypertension and diabetes is associated with an increased risk of endometrial cancer.
- *Symptoms of thyroid dysfunction*: The alteration of the hypothalamic-pituitary axis may result in either amenorrhea (hyperthyroidism) or menorrhagia (hypothyroidism).
- *Hepatic/renal failure:* History suggestive of systemic illnesses, including hepatic/renal failure needs to be asked. The disorders of these organs are likely to result in bleeding abnormalities.
- *History of excessive bruising or known bleeding/ coagulation disorders:* History of excessive bruising with mild trauma or frequent bleeding from various orifices (epistaxis, hematuria, pronged menstrual blood loss, etc) could be related to the presence of an inherited bleeding disorder (e.g. Von Willebrand disease, hemophilia, etc). This history becomes especially important in a young girl who does not stop bleeding during her first menses.

Family History

Personal or family history of endometrial, ovarian or breast cancer is another predisposing factor for development of endometrial cancer.

General Physical Examination

Body Mass Index (BMI)

Obese women (with increased BMI) are more likely to be suffering from endometrial malignancies. Obesity increases the levels of free estrogen in the body by decreasing the levels of serum hormone binding proteins. Moreover, aromatization of the androgen, epiandrostenedione to estrone occurs in peripheral fat.

Blood Pressure

Increased blood pressure could be related with increased risk for endometrial cancer.

Pallor

Pallor could be related to anemia caused by excessive blood loss.

Endocrinopathy

The clinician must look for following signs in order to rule out presence of an endocrinopathy:
- Signs of hyperthyroidism and hypothyroidism,
- *Galactorrhea:* This could be related to increased prolaction production.
- *Blood sugar:* Type 2 diabetes could be associated with an increased risk for endometrial cancer.

Cervical Cultures

Cervical cultures may be indicated if the patient is at risk for infection or if symptoms of infection are present.

Specific Systemic Examination

ABDOMINAL EXAMINATION

Abdominal examination to detect the presence of hepatic and splenic enlargement or presence of any abdominal mass has been described in chapter 16.

PELVIC EXAMINATION

The process of conducting a bimanual examination has been described in chapter 16 and may reveal enlargement due to uterine fibroids, adenomyosis or endometrial carcinoma. An enlarged uniformly shaped uterus in a postmenopausal patient with bleeding suggests endometrial cancer until proven otherwise.

Clinical findings most commonly encountered in cases of endometrial cancer are a normal examination of vagina, uterus and cervix, although advanced disease may be associated with an enlarged uterus or pelvic mass. Cervical and vaginal metastasis can cause cervical stenosis, pyometra or a mucosanguineous vaginal discharge. Regional metastasis may present in form of a bladder or rectal mass.

The clinician must look for vulvar or vaginal lesions, signs of trauma and cervical polyps or dysplasia. A bimanual examination in the postmenarcheal woman may reveal tenderness associated with infection, an adnexal mass consistent with an ovarian neoplasm or cyst or uterine enlargement consistent with fibroids, pregnancy or a tumor. The specific indicators which point towards the cause of bleeding on pelvic examination include the following:
- The actual site of bleeding can be assessed through a per speculum examination.
- Presence of vaginal/cervical discharge indicates the presence of infection.
- Careful inspection of the lower genital tract must be done to detect the presence of lacerations, vulvar or vaginal pathology and cervical lesions or polyps.

Differential Diagnosis

The specific diagnostic approach in the case of AUB should be based on patient's age i.e. whether the patient belongs to the premenopausal, perimenopausal or postmenopausal age groups (table 17.4). In premenopausal women belonging

Table 17.4: Differential diagnosis of AUB

Postmenopausal women

Cervical cancer, cervicitis

Atrophic vaginitis, endometrial atrophy

Submucous fibroids, endometrial hyperplasia and endometrial polyps

Hormone replacement therapy

Premenopausal women

Complications of pregnancy: Intrauterine pregnancy, ectopic pregnancy, spontaneous abortion, gestational trophoblastic disease, placenta previa

Infection, trauma: Cervicitis, PID, endometritis, laceration, abrasion, foreign body, IUCD

Benign pelvic pathology: Cervical polyp, endometrial polyp, leiomyoma, adenomyosis, etc

Malignancy, neoplasm: Cervical, endometrial, or ovarian malignancy

Premalignant lesions: Cervical lesions, endometrial hyperplasia

Trauma: Foreign bodies, abrasions, lacerations, sexual abuse or assault

Medications/iatrogenic: Intrauterine device, hormones (oral contraceptives, estrogen, progesterone), anovulatory cycles, hypothyroidism, hyperprolactinemia, Cushing's disease, polycystic ovarian syndrome, adrenal dysfunction/tumor, stress (emotional factors, excessive exercise).

Systemic diseases: Hepatic disease, renal disease, coagulopathy, thrombocytopenia, von Willebrand's disease, leukemia

to the reproductive age group, having normal findings on physical examination, the most likely diagnosis is dysfunctional uterine bleeding (DUB) secondary to anovulation. The diagnosis of DUB is established after excluding out other common causes of bleeding in this age group such as pregnancy, fibroids, iatrogenic causes, systemic conditions, etc. In these cases, the diagnostic investigation is targeted at identifying the etiology of anovulation. This would be described in details in chapter 19.

Abnormal uterine pathology, particularly endometrial carcinoma, is common in postmenopausal or perimenopausal women presenting with abnormal uterine bleeding. Therefore, in the women belonging to perimenopausal and menopausal age groups, endometrial biopsy and other investigations for detecting endometrial hyperplasia or carcinoma must be considered early during the course of investigations.

Women receiving hormone replacement therapy may often present with abnormal bleeding. Most sources recommend evaluation of abnormal bleeding if it lasts more than six to nine months after initiation of hormone replacement therapy.

Management

Management of AUB in women belonging to reproductive age groups and in perimenopausal age groups has been described in flow charts 17.1 and 17.2 respectively.

Investigations

Aim of diagnosis in cases of AUB is to assess the nature & severity of bleeding. In case of severe acute bleeding, the aim of management is stabilize the patient by maintaining the ABC (airway, breathing and circulation). In cases of severe bleeding, the emergency control of bleeding can be done through administration of conjugated estrogens. Once the bleeding has been controlled, steps must be taken to identify the underlying organic causes.

The following investigations need to be undertaken:

Blood Investigations

Complete blood count

Estimation of the patient's hemoglobin levels with blood counts would help in determining the patient's degree of anemia. Chronic blood loss related to AUB may often result in the development of anemia.

Urine human chorionic gonadotropin (beta hCG) levels

Pregnancy remains the most common cause of abnormal uterine bleeding in patients of reproductive age group. Bleeding could be related to pregnancy complications including threatened abortion, incomplete abortion or ectopic pregnancy. Therefore, pregnancy should be the first diagnosis to be excluded before instituting further testing or medications.

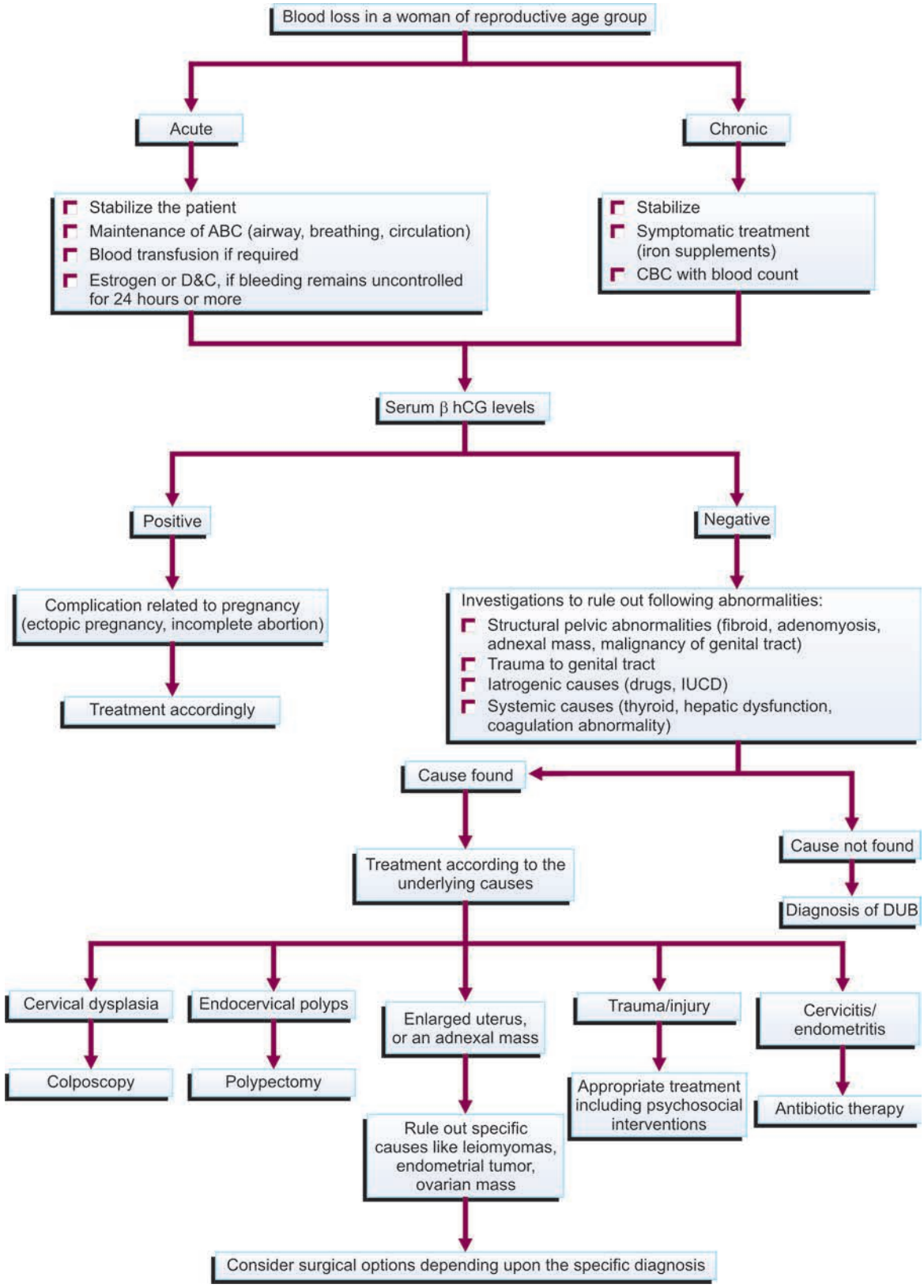
Study of coagulation factors

Tests involving study of coagulation factors include prothrombin time, partial thromboplastin time, bleeding time, platelet count, assessment of Von Willebrand factor, etc. These tests are not routinely ordered because they are expensive and the bleeding disorders are rarely encountered. However, these studies may be required in case any bleeding disorders (e.g. Von Willebrand disease, ITP, hemophilia, etc) are suspected from history or if the platelet count is reduced.

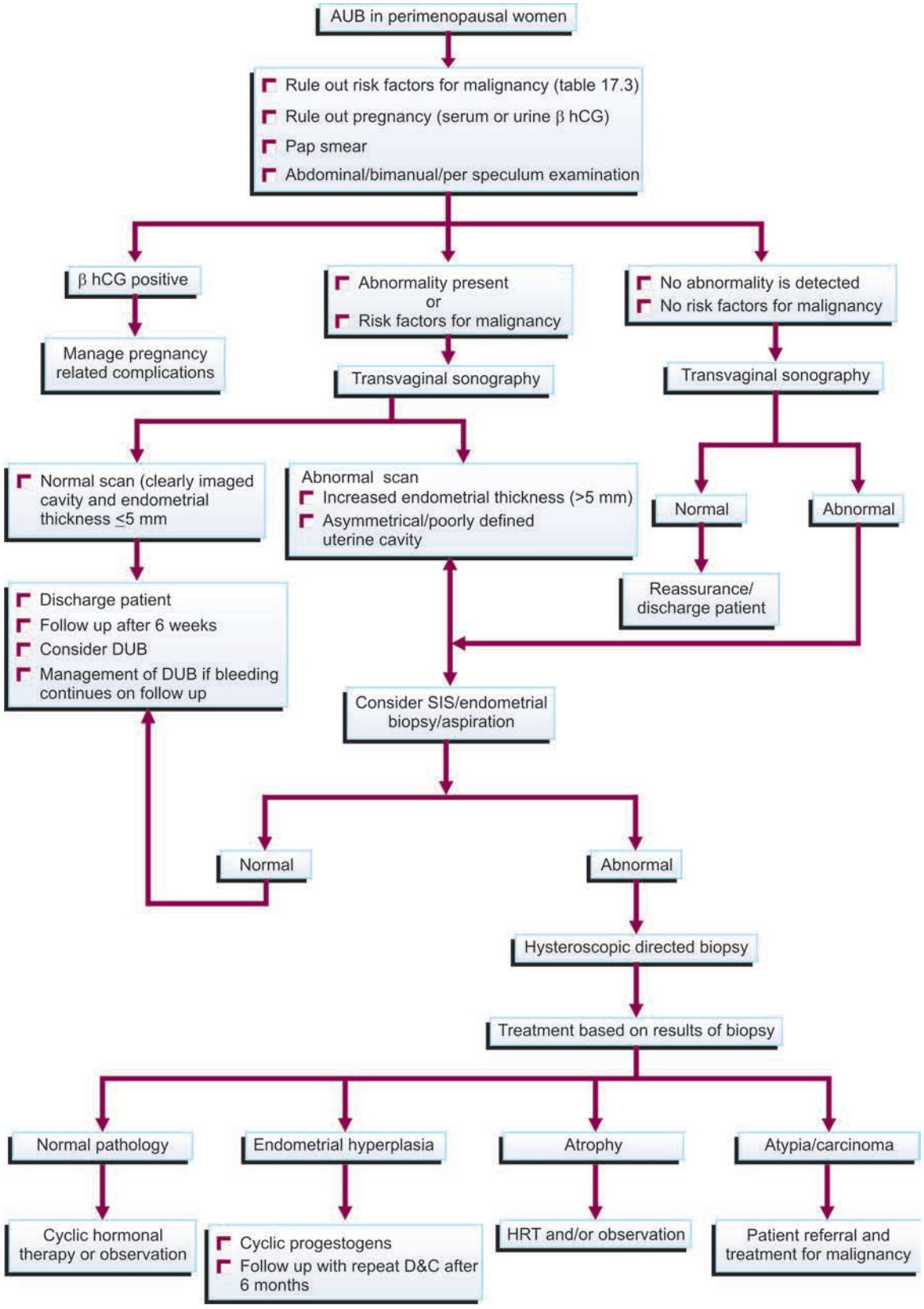
Thyroid function tests

Though thyroid dysfunction can result in menorrhagia, thyroid function should not be routinely carried out on women with heavy menstrual bleeding. While menorrhagia may result due to hyperthyroidism, oligomenorrhea is more likely

Flow chart 17.1: Management of AUB (women of reproductive age group)



Flow chart 17.2: Management of AUB in perimenopausal women



to result due to hypothyroidism. Thyroid testing should only be carried out when the patient shows signs and symptoms, suggestive of thyroid disease.

Liver function and/or renal function tests

Dysfunction of either organ can alter coagulation factors and/or the metabolism of hormones resulting in abnormal bleeding patterns. Liver function tests are ordered when liver disease is suspected, such as in persons with alcoholism or hepatitis. Liver function tests involve study of liver enzymes like SGOT, SGPT, alkaline phosphatase etc; whereas tests like BUN and creatinine levels assess renal functioning.

Hormone assays

Measurement of LH, FSH and androgen levels help in diagnosing patients with suspected PCOS.

Since in the above mentioned case study, the women belongs to the perimenopausal age group, the investigations must be especially directed to rule out malignancy. Cervical cytology (Pap smear) is helpful in diagnosis of cervical malignancy, whereas endometrial studies are required to rule out endometrial malignancies. Various endometrial studies, which help in detecting underlying endometrial malignancy include tests like endometrial biopsy, endometrial aspiration, dilatation and curettage, fractional curettage, etc. These would be described in details, later in the chapter.

Imaging Studies

Ultrasound examination

Pelvic ultrasound is the best noninvasive imaging investigation to assess uterine shape, size and contour; endometrial thickness and adnexal areas. Imaging studies help in detection of small, focal, irregular or eccentrically located endometrial lesions. Imaging should be undertaken if any of the conditions, described in table 17.5 are suspected. Ultrasound examination can be performed through two routes: Transabdominal and transvaginal. Both transabdominal and transvaginal ultrasound examination help in inspecting the uterus, endometrium, and/or adnexa.

Table 17.5: Indications for imaging in case of AUB

The uterus is palpable abdominally
Vaginal examination reveals a pelvic mass of uncertain origin
Pharmaceutical treatment fails
Bleeding in perimenopausal or postmenopausal women
AUB in a women over the age of 40 years, having a weight >90 kg
AUB in women having any of the risk factors for development of endometrial cancer including infertility, nulliparity, family history of colon or endometrial cancer and exposure to unopposed estrogens

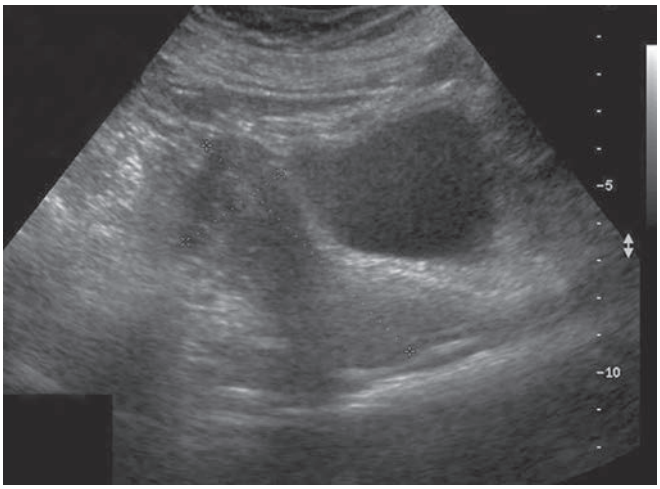


Fig. 17.1: Transabdominal ultrasound showing an enlarged uterine cavity, measuring 77 x 31 mm, with multiple cystic spaces within. Biopsy confirmed the presence of endometrial cancer

Transabdominal Ultrasound

Transabdominal sonography (TAS) helps in excluding pelvic masses, and various pregnancy related complications. It helps in delineating the presence of an enlarged uterine cavity and/or presence of cystic/solid spaces within the uterine cavity (figure 17.1). Transvaginal sonography (TVS) is more informative than TAS.

Transvaginal Ultrasound

Transvaginal ultrasound is especially indicated in the women at high risk for endometrial cancer. If transvaginal ultrasound is not available then an endometrial sample should be taken. Measurement of the endometrial thickness is not a replacement for biopsy. If the endometrial stripe on ultrasound examination is greater than 4 mm, endometrial sampling should be performed, although sonohysterography may sometimes delineate a submucous fibroid or an endometrial polyp.

Measurement of endometrial thickness on transvaginal ultrasound has become a routine investigation in patients with abnormal uterine bleeding, especially those belonging to the perimenopausal age groups. If the endometrial thickness on TVS is ≥4 mm, an endometrial sample should be taken to exclude endometrial hyperplasia. Presently there is a great controversy regarding whether a cut-off point of 5 or 4 mm endometrial thickness should be employed for diagnosing an abnormal endometrial thickness. At some centers, the cut-off limit of 5 mm is being considered as suspicious in the postmenopausal patients presenting with AUB, whereas at other centers the limit of 4 mm is being used. Increased endometrial thickness on transvaginal ultrasound examination is an indication for further follow-up by SIS or hysteroscopic guided

endometrial biopsy. Histopathological examination is especially important in these cases to rule out endometrial hyperplasia, atypia and carcinoma.

Normal ultrasound examination of the uterus

On ultrasound imaging the normal myometrium should have a homogeneous echodensity. The bladder should be anechoic. Uterine measurements of 5 cm width, 4 cm anterior posterior plane thickness and 8 cm length is taken as the general upper limits of a normal uterus.

The normal endometrium as visualized by TVS is described in chapter 16. As described previously, the endometrial thickness and appearance changes during the various phases of the menstrual cycle.

Saline Sonography (SIS)

Saline sonography serves as an alternative to hysteroscopy. This technique employs the use of sterile saline solution as a negative contrast medium in conjunction with traditional transvaginal ultrasound (figure 17.2). Thus, besides imaging the uterine cavity, this technique also helps in evaluating the patency of the fallopian tubes. The advantage of SIS over hysteroscopy is that this technique also helps in scanning the ovaries, pelvis and peritoneal cavity, while imaging the uterine cavity. While abdominal or transvaginal sonography can identify myomas and thickened endometrium, these imaging techniques are unable to differentiate between the various potential etiologies of thickened endometrium, e.g. polyps, submucous myomas and homogenously thickened endometrium, etc. Sonohysterography, helps in differentiating between these intracavitary lesions and focal or diffuse endometrial abnormalities and helps in determining whether an abnormality is endometrial or subendometrial in origin (figures 17.3A and B). When the endometrium cannot be accurately measured on TVS or when there is a nonspecific thickened central endometrial complex, sonohysterography can provide additional information. SIS is able to clearly delineate the masses or defects inside the uterine cavity. SIS helps in differentiating between focal lesions (polyps and submucosal myomas) and global endometrial thickening. SIS can be used as a second line diagnostic procedure in women with AUB when findings from transvaginal ultrasound are nonconclusive.

SIS is associated with minor side effects like pelvic discomfort (cramping or menstrual like pain). Complications like severe pain and infection can occur but are relatively rare complications. SIS has been observed to have high sensitivity rate of 94.9% and specificity rate of 89.3%. Thus, this would

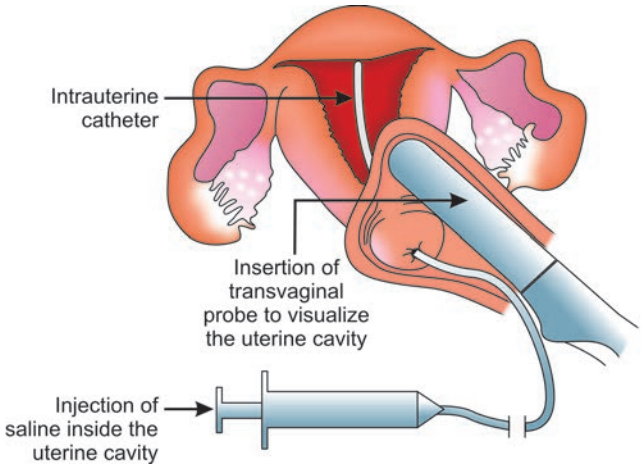


Fig. 17.2: Procedure of doing SIS

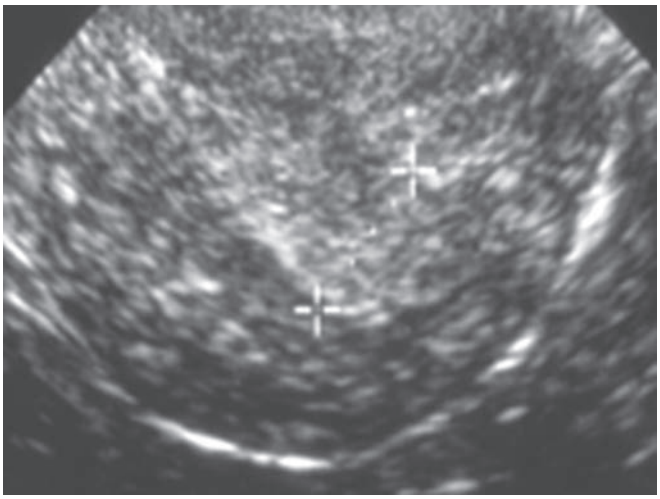


Fig. 17.3A: Presence of thickened endometrium on TVS in a patient with AUB

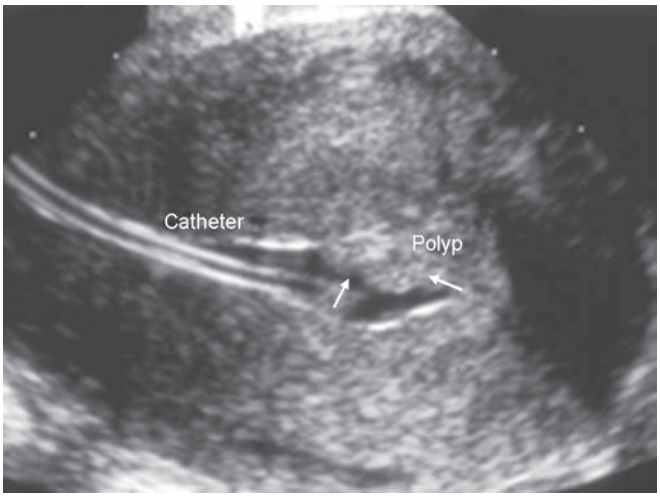


Fig. 17.3B: In the same patient whose TVS has been shown above, saline infusion sonography revealed presence of an endometrial polyp

help in avoiding hysteroscopy in nearly 40% cases. There is a theoretical possibility of propulsion of cancer cells from the uterine cavity into the peritoneal cavity. This can be prevented by using low pressure infusion in women at risk for cancer.

Procedure

The procedure of SIS involves the following steps:

- The patient is asked to empty her bladder.
- A speculum, is used to expose the cervix, which is cleansed with a betadine swab.
- A catheter is then inserted inside the uterine cavity. Various catheters may be used, including: 5-F urinary catheter, with or without an occlusive balloon; pediatric feeding tubes; insemination catheters, etc.
- It is important to flush the catheter with sterile saline solution before inserting it inside the uterine cavity in order to prevent the introduction of echogenic air bubbles.
- Advancement of the catheter inside the uterine cavity can be assisted by grasping the end of the catheter 2 to 3 cm from the tip with a ring forceps and gently feeding it through the cervical os so as to position the tip beyond the endocervical canal.
- After the correct placement of the catheter, the speculum is carefully removed while the catheter is left in place. Following the correct placement of the catheter, sterile saline solution is instilled inside the uterine cavity. Only about 2–5 ml of sterile solution is required to produce an adequate distension.
- While the sterile saline solution is being instilled inside the uterine cavity, a covered transvaginal probe is inserted into the vagina and continuous scanning in the sagittal and coronal or transverse planes is performed.

There is no contraindication to SIS in nonpregnant, noninfected women who are bleeding.

Endometrial Studies

In case the endometrial thickness is > 4 mm on transvaginal ultrasound examination, endometrial studies should be done in order to exclude endometrial hyperplasia.

Endometrial Biopsy

Endometrial biopsy (EB) is the most commonly used diagnostic test for AUB, which helps in providing the histopathological examination of the endometrium. It helps in providing an adequate sample for diagnosis of endometrial problems in nearly 90% to 100% of cases. However, it may fail to detect the presence of small masses including polyps and leiomyomas. The indications for endometrial biopsy are listed in the table 17.6 below. Perimenopausal and menopausal women with bleeding following a period of amenorrhea must also have an EB because these women are at a high risk for development of endometrial carcinoma, polyps or hyperplasia in future. Other patients who are at an increased risk of development of endometrial malignancy include patients with triad of hypertension, diabetes and obesity and those with chronic anovulation (e.g., PCOS), atypical glandular cells (AGUS) on Pap smear, new-onset menorrhagia, etc. Endometrial curettage can be performed as an outpatient investigation and does not require general anesthesia as is required for D&C. Thus this procedure has superseded dilatation and curettage and has presently become the present gold standard for obtaining endometrial tissue and for detecting endometrial diseases.

Table 17.6: Indications for endometrial biopsy

Endometrial thickness on TVS is >4 mm (in postmenopausal women)
Persistent intermenstrual bleeding
AUB in a woman >35 years of age
AUB in postmenopausal women
Treatment failure or ineffective treatment
Patients having high risk factors for the development of endometrial cancer
There is a pelvic mass and the uterus is larger than 10 weeks gestation in size
There is a pelvic mass and no facility for urgent ultrasound scan is available

Histological findings on EB

Identifying the underlying endometrial histopathology is important for the gynecologist in order to initiate correct treatment for AUB. Simple proliferative endometrium is normal and does not require treatment.

Endometrial hyperplasia

Chronic proliferation of the endometrium results in the development of hyperplasia (first simple hyperplasia, followed by atypical hyperplasia), leading to the development of endometrial carcinoma in future. Endometrial hyperplasia usually results from unopposed estrogen production, regardless of the etiology. If a woman takes unopposed estrogen (without progesterone), her relative risk of developing endometrial cancer is 2.3 compared to that of nonusers and increases to 9.5 if unopposed estrogens are taken for 10 years or longer.

Endometrial hyperplasia can be classified as simple or complex (with or without cytological atypia). Lesions of simple endometrial hyperplasia without atypia represents only exaggerated forms of persistent proliferative endometrium which regress spontaneously after curettage or following treatment with progestins. These lesions are associated with little risk for progression to adenocarcinoma. On

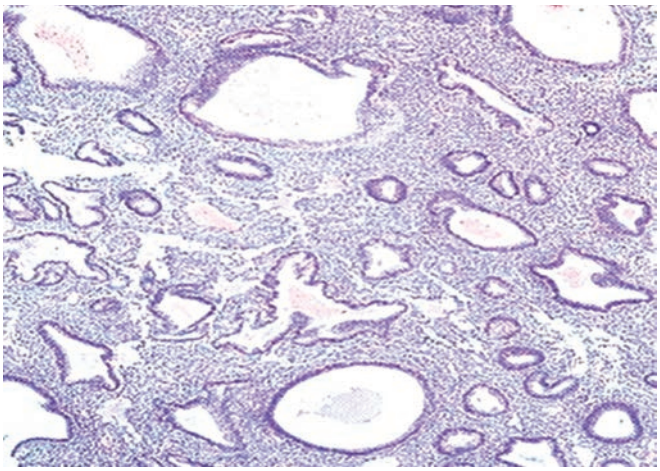


Fig. 17.4A: Histopathological appearance of simple endometrial hyperplasia

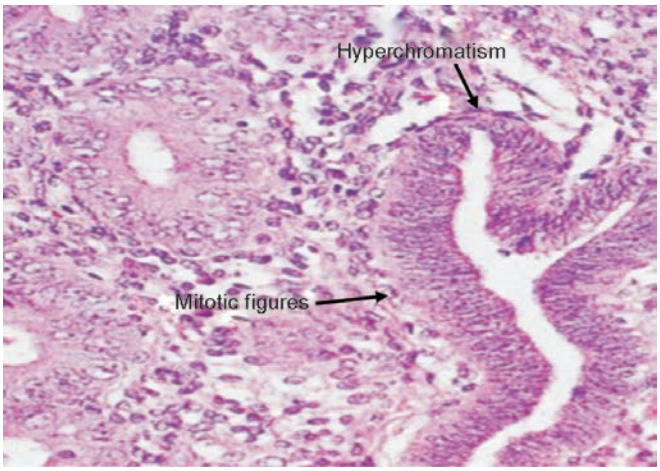


Fig. 17.4C: Histopathological appearance of complex endometrial hyperplasia with atypia

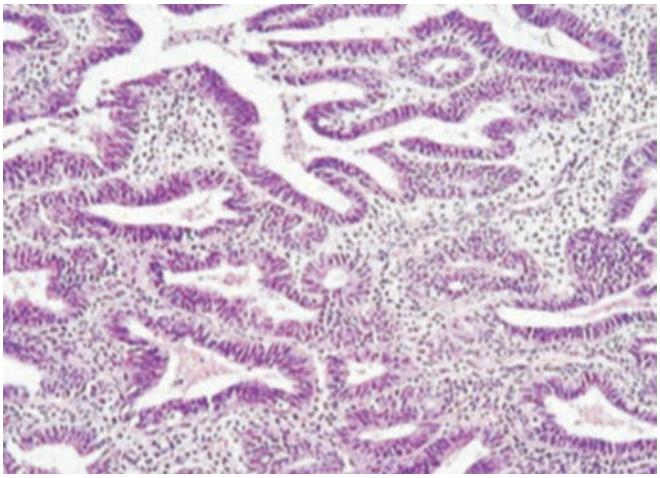


Fig. 17.4B: Histopathological appearance of complex endometrial hyperplasia without atypia

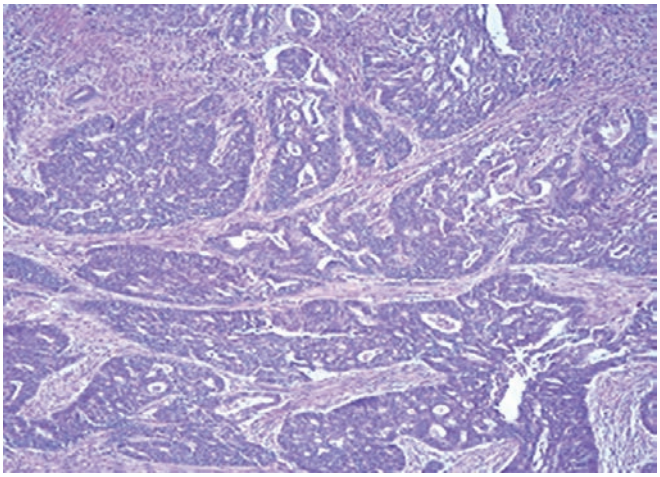


Fig. 17.4D: Histopathological appearance of frank endometrial cancer

the other hand, the endometrial hyperplasia with cytological atypia has high chance for progression into adenocarcinoma, if left untreated. Such lesions usually do not show spontaneous regression, are resistant to repeated curettage or prolonged high-dose progestational therapy. These lesions must be regarded as precancerous lesions. Atypical lesions are distinguished from invasive cancer by the absence of stromal invasion. The histological appearances of different types of endometrial hyperplasias is described below:

Simple endometrial hyperplasia: This type of endometrial hyperplasia is associated with an increase in the number of glands and endometrial stroma (figure 17.4A). Some glands are cystically dilated. However, epithelium does not show any atypical features.

Complex endometrial hyperplasia – without atypia: There is an increase in the number of glands which are aligned back to back. Glandular outlines are irregular. Complex proliferation of the epithelium occurs but without any associated atypical features (figure 17.4B).

Complex endometrial hyperplasia – with atypia: Besides the above mentioned changes associated with complex endometrial hyperplasia, epithelium also shows atypia (hyperchromatism, mitotic figures, etc). Figure 17.4C shows histopathological changes in case of complex endometrial hyperplasia – with atypia, whereas figure 17.4D shows replacement of normal uterine endometrium with frank invasive cancer.

Patients with a history of unopposed estrogen exposure should be first evaluated by transvaginal ultrasound examination. Biopsy is unnecessary when the endometrial thickness is less than 5 mm. Indications for biopsy are enumerated in table 17.7.

Flow chart 17.3: Management of endometrial hyperplasia

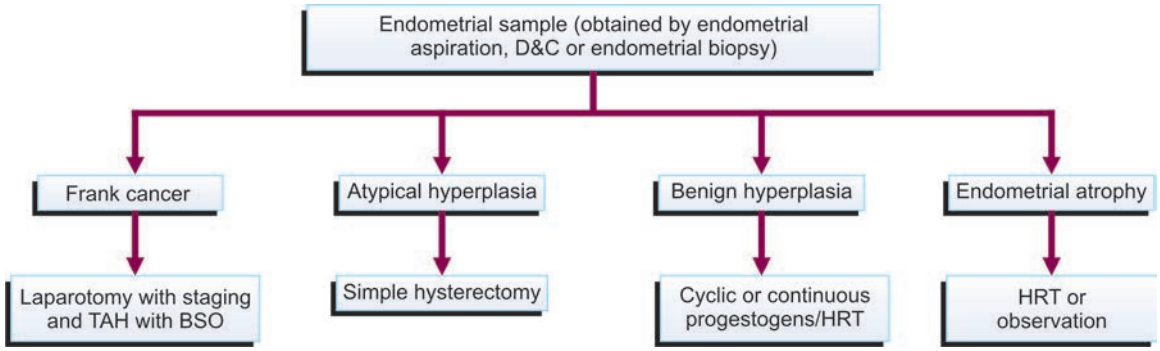


Table 17.7: Indications for biopsy in patient with the history of unopposed exposure to estrogens

Clinical history suggestive of long term estrogen exposure even in the presence of normal endometrial thickness
Endometrial thickness greater than 12 mm despite of low clinical disease suspicion

Biopsy is indicated when the clinical history suggests long-term estrogen exposure even when the endometrial thickness is normal (5–12) mm or when the thickness is greater than 12 mm (even when clinical suspicion of the disease is low). Treatment of endometrial hyperplasia has been shown in flow chart 17.3. Simple endometrial hyperplasia can be corrected using cyclic progestin therapy with medroxyprogesterone acetate, 10 mg daily or norethistherone acetate 5 mg daily for 14 days. Hyperplasia with atypia is best treated surgically. Women who respond to the medical treatment must be encouraged to have regular check-ups as recurrence of hyperplasia can commonly occur. Endometrial hyperplasia with atypia (especially atypical adenomatous hyperplasia) generally is considered equivalent to an intraepithelial malignancy and hysterectomy is usually advised. Any biopsy that reveals endometrial carcinoma requires a prompt immediate referral to a gynecologic oncologist. If no tissue is present on endometrial biopsy, the endometrium is most probably atrophic and requires treatment with estrogens.

Procedure of endometrial sampling

Endometrial sampling is performed without any prior cervical dilatation and comprises of the following steps:

- Firstly, the patient is placed in the lithotomy position and then a bimanual examination is conducted in order to asses the uterus (size, position, presence of masses, etc).
- The cervix is then visualized with help of a Sim's speculum and a tenaculum (which is applied over the anterior lip of cervix).
- The cervical os is cleaned with help of betadine solution.

Fig. 17.5: Endometrial biopsy curette

- A uterine sound is then inserted gently through the cervical os until the sound passes easily to the fundus. The distance from the fundus to the external cervical os can be measured with the help of gradations on the uterine sound and is usually equal to 6 to 8 cm. This helps in assessing the position and size of the uterine cavity and minimizing the risk of perforation.
- When the position and size of the uterine cavity have been assessed, the endometrial biopsy curette (figure 17.5) is inserted gently inside the uterine cavity until any significant resistance is felt (figure 17.6A). The endometrial biopsy curette is a narrow metal cannula having serrated edges with side openings on one end and syringe attached for suction at the other end.
- While inside the uterine cavity, the cannula is rotated several times in order to scrape off the endometrial lining (figures 17.6B and C).
- This procedure should be repeated at least four times and the device rotated by 360° to ensure adequate coverage of the area.
- These endometrial scrapings are then sucked into the syringe.
- When adequate amount of endometrial curetting have been obtained, the curette is removed and samples are sent for microscopic examination.

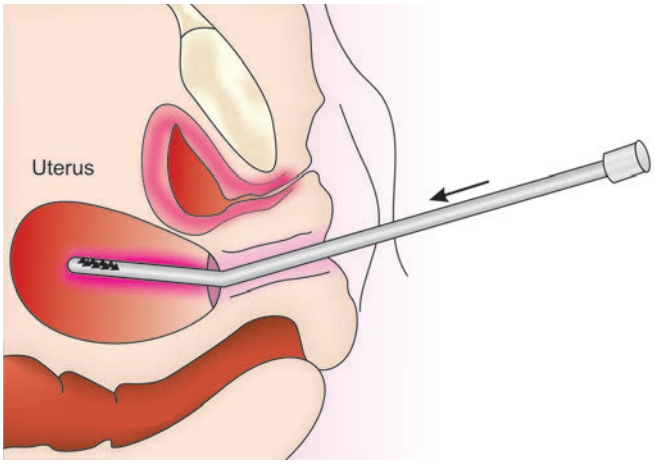


Fig. 17.6A: Placement of the EB curette inside the uterine cavity

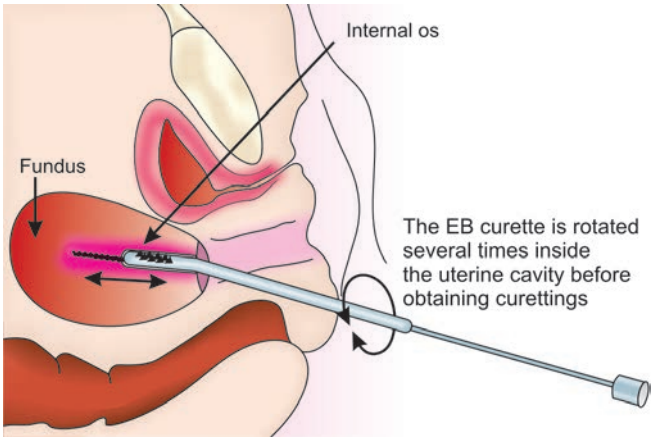


Fig. 17.6B: Before obtaining the endometrial curettings, the EB curette is rotated several times inside the uterus

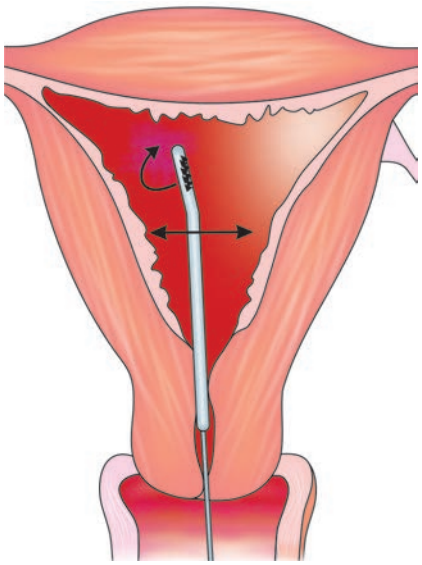


Fig. 17.6C: Transverse section of endometrial cavity showing the EB curette

- One set of sample is sent in normal saline for assessment of AFB. Other set of sample is sent in acetone for assessment of histopathology.

Normal endometrial tissue may be described as proliferative or preovulatory (under the effect of hormone estrogen) and secretory or postovulatory endometrium (under the effect of hormone progesterone). Hormone therapy can be offered to patients with abnormal vaginal bleeding who have normal endometrial tissue on biopsy. If the biopsy is normal but the patient continues to experience excessive vaginal bleeding, further diagnostic work-up is required. Abnormal pathology on histopathalogical examination must be treated as follows:

- Most individuals with simple hyperplasia without any atypia can be managed with hormonal manipulation [medroxyprogesterone (Provera), 10 mg daily every five days for three months] or with close followup. Most authors recommend a follow-up endometrial biopsy after 3 to 12 months, regardless of the management strategy.
- Atypical complex hyperplasia is a premalignant lesion that progresses to cancer in 30% to 45% of women. Some physicians treat complex hyperplasia with or without atypia with hormonal therapy (medroxyprogesterone, 10 to 20 mg daily for up to three months). However most physicians recommend a D&C procedure to exclude the presence of endometrial carcinoma and consider hysterectomy for complex or high-grade hyperplasia.
- Biopsy specimens that suggest the presence of endometrial carcinoma (75% are adenocarcinoma) should prompt consideration of referral to a gynecologic oncologist for definitive surgical therapy.

Endometrial biopsy should not be performed in the presence of a normal or ectopic pregnancy. All patients with the potential for pregnancy should be considered for pregnancy testing prior to the performance of the procedure.

Complications

Though endometrial biopsy is largely a safe procedure, it can be associated with certain complications which are tabulated in the table 17.8.

Bacteremia can occur after endometrial sampling (antibiotic prophylaxis must be given to patients at risk of endocarditis). Since post-procedure bacteremia has been noted, some authors recommend considering antibiotics in postmenopausal women at risk for endocarditis. The risk for infection

Table 17.8: Complications of endometrial biopsy

Prolonged bleeding
Infection, bacteremia, sepsis and acute bacterial endocarditis
Uterine perforation
Intraoperative and postoperative cramping

Table 17.9: Indications for D&C
When an adequate sample cannot be obtained on EMB
Cervical os is stenotic
Medical treatment fails to control severe bleeding
Persistent or recurrent bleeding between 20 & 40 years of age and the clinical suspicion of malignancy is high
Diagnosis of endometrial polyps, intrauterine mucous fibroids, areas of endometritis, hyperplasia or cancer or lost IUDs
Bleeding recurs following a negative report on endometrial biopsy/aspiration

Table 17.10: Complications of D&C
Uterine perforation
Cervical damage due to use of large dilators, resulting in the development of cervical incompetence
Postoperative infection or intrauterine adhesions

appears to be small, but some physicians recommend tetracycline, 500 mg twice daily, for four days following the procedure.

17

Dilatation and Curettage (D&C)

The procedure of D&C involves obtaining scrapings from the endometrium and the cervix and is usually performed under general anesthesia. Not only does it help in detecting the site of malignancy but also gives an idea regarding the spread of malignancy. The sample obtained on D&C is larger than the one obtained by an endometrial biopsy. D&C helps in an extensive sampling of the uterine cavity and has the advantage of being both a diagnostic and a therapeutic procedure. It has a higher sensitivity than endometrial biopsy, especially with smaller in-situ lesions. Its indications are enumerated in table 17.9 below.

This procedure involves the gradual dilatation of the cervix to < 8 cm under general anesthesia, followed by the use of small sharp curette for systematic, thorough, gentle sampling of all parts of the uterine cavity including tubal osteal areas. A few complications can occur with D&C and are listed in table 17.10 below.

D&C helps in diagnosing the various conditions listed in table 17.11. This provides adequate guidance regarding the likely etiology responsible for producing AUB and the treatment to be initiated. Previously, it had been believed that the D&C also has a therapeutic effect. However, it is now recognized that though the first period or two after a D&C may be late or lighter, it does not provide adequate long-term improvement in controlling AUB. Thus, the gynecologists must use D&C as a diagnostic procedure and not as a form of treatment modality. However, D&C can be used for emergency control of severe or persistent bleeding, particularly that associated with hyperplastic endometrium. The main disadvantages associated with the procedure include: Small lesions can be missed and it is associated with a low sensitivity rate (65%) for detection of intrauterine pathology. Though the curretings are subjected to microscopic examination, their naked eye features can also suggest malignancy. For example, malignancy is suspected if the curettings are profuse; friable; appear as cheesy lumps rather than strips and are dark in color. Failure of the uterine wall to give a grating feeling in response to curettage also raises the suspicion of malignancy.

Table 17.11: Advantages of D&C
Diagnosis of organic disease, e.g. tuberculosis
Diagnosis of uterine pathology, e.g. endometritis, polyp, carcinoma, fibroids, etc.
Diagnosing the type of endometrial histopathology: Hyperplastic, proliferative, secretory, irregular ripening, irregular shedding, atrophic endometrium, etc.
Therapeutic effect (controversial)
Arrest of severe or persistent bleeding, particularly that associated with hyperplastic endometrium

Endometrial Aspiration

Endometrial aspiration can be done as an outpatient procedure without anesthesia. It is performed using a plastic cannula, which is less likely to perforate the senile uterus invaded by growth in comparison to the metallic curette. The diagnostic accuracy of this procedure is 92% to 98% when compared with subsequent D&C. Endometrial aspiration is often combined with endocervical curettage to rule out cervical pathology.

Procedure (figure 17.7)

The method is usually performed as an outpatient procedure, without requirements for general anesthesia. It can be done with the help of devices like, pipelle curette, Sharman curette, Gravlee jet washer, Isac cell sampler, vabra aspirator, etc.

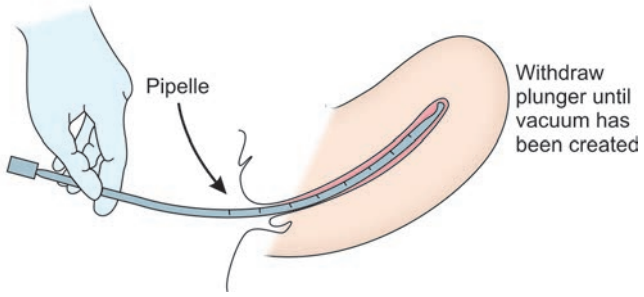


Fig. 17.7: Endometrial aspiration

Table 17.12: Indications for hysteroscopy and biopsy

Women with erratic/irregular menstrual bleeding
Medical therapy has failed to control the bleeding
Transvaginal ultrasound suggestive of intrauterine pathology such as polyps or submucous fibroids

Table 17.13: Advantages of hysteroscopy over D&C

Diagnosis of polyps, submucous fibroids, hyperplasia, etc.
The whole uterine cavity can be visualized with hysteroscopy; very small lesions such as polyps can be identified & biopsied or removed at the time of hysteroscopy.
Biopsy of the suspicious areas can also be carried out.
Hysteroscopy is more sensitive than fractional D&C, especially at diagnosing polyps and submucosal leiomyomas.
In combination with EB, hysteroscopy has almost 100% accuracy in diagnosing endometrial dysplasia and cancer.
Bleeding from ruptured venules & echymoses can be readily identified.

The sample produced by the newer slim endometrial suction currettes (pipelle) is similar to that produced by older devices, while at the same time causing much less pain and trauma.

Fractional Curretage

This method involves taking three samples, one from endocervical canal and others from lower and upper segments.

Cervical Cultures and Papanicolaou Smear

Cervical cultures and a Papanicolaou smear are appropriate initial steps to evaluate for the presence of sexually transmitted diseases or cervical dysplasia.

Hysteroscopy

Hysteroscopy with biopsy can be regarded as the "gold standard" investigation for the diagnosis of AUB. Hysteroscopy with biopsy provides the most comprehensive evaluation of the endometrium and is recommended for use in any woman with equivocal or suspicious findings on biopsy or ultrasonography. Some of the indications for use of hysteroscopy are described in table 17.12. Hysteroscopy allows for direct visualization of the endometrial cavity along with the facility for directed biopsy. Therefore, it serves as a better option in comparison to D&C alone. Some of the advantages of hysteroscopy over D&C are described in table 17.13.

However there are the following disadvantages associated with the use of hysteroscopy: It is a more invasive procedure, is associated with significant financial cost, as well as more physical discomfort in comparison to endometrial biopsy or D&C. Also, hysteroscopy may not be always available, especially in the primary setup.

Table 17.14: Indications for hysterectomy

Failure of medical treatment
Family is completed
Histopathological evidence of atypical hyperplasia or cancer

Rx Treatment/Gynecological Management

There are medical, surgical and combined methods for treating AUB. The choice of approach depends on the patient's age (belonging to reproductive or perimenopausal age group), etiology and severity of bleeding, patient's fertility status, need for contraception and treatment options available at the care site. Typical algorithms for the treatment of AUB in both the women belonging to reproductive age groups and perimenopausal age groups has been described before in flow charts 17.1 and 17.2 respectively. Besides using general measures like treatment of iron deficiency and maintenance of menstrual calendar, various medical and surgical modalities of treatment are available and would be described below.

Medical Treatment

Medical treatment is the option of choice in young women (< 20 years of age) presenting with atypical bleeding. In these cases, surgery is rarely indicated. Medical treatment with conjugated estrogens is also indicated in cases of acute, heavy and uncontrollable bleeding. Various medical modalities for treatment for AUB are discussed in details in chapters 18 and 19.

Surgical

Surgical options used for treatment of AUB can be of two types: Uterine conservative surgery (endometrial ablation) and hysterectomy.

- *Endometrial ablation:* Endometrial ablative techniques have been discussed in details in chapter 19.
- *Hysterectomy:* Hysterectomy can be performed by the following routes: Abdominal, vaginal or laparoscopic. Various indications for hysterectomy are enumerated in table 17.14. The advantages of hysterectomy are that it helps in providing complete cure; there is no requirement for future long term medical treatment and it ensures the removal of any missed underlying pathology. Disadvantages associated with hysterectomy are that it is a major surgery, which requires hospital admission and is associated with high rates of mortality and morbidity.

Important Questions and Answers

Q.1. In the previously mentioned case study what does the patient's history suggest? How is it significant regarding her current situation?

Ans. The history of the patient suggests that she most probably suffered from chronic anovulation as a result of polycystic ovarian disease. She was most probably prescribed clomiphine citrate for ovulation induction. Chronic avoluation is likely to cause unopposed endometrial stimulation with estrogen, resulting in development of endometrial hyperplasia and/or cancer in the long run. There are also other factors in the patient's history such as nulliparity, high BMI, high blood pressure and the patient belonging to perimenopausal age group, which point towards a high risk for development of endometrial malignancy.

Q.2. What should be the next line of management in the above mentioned case study?

Ans. The most serious concern in postmenopausal and perimenopausal women with abnormal uterine bleeding is endometrial carcinoma. Since the woman in the previously mentioned case study belongs to the perimenopausal age group, and also has numerous other factors associated with a high risk for development of endometrial cancer, investigations must be mainly directed towards ruling out endometrial cancer. This mainly involves the assessment of endometrial thickness using transvaginal sonography and study of endometrial cytology using endometrial biopsy, aspiration, D&C or hysteroscopic guided D&C.

Q.3. In the above mentioned case study the endometrial biopsy which was performed revealed endometrial hyperplasia with atypia. What would be the next line of management?

Ans. Management of endometrial hyperplasia has been shown in flow chart 17.3. Since the patient has completed her family and belongs to the perimenopausal group, there is no need to preserve the uterus in this woman. The most appropriate treatment for atypical endometrial hyperplasia in this patient would be simple hysterectomy.

Q.4. Describe the staging of endometrial cancer.

Ans. Staging of endometrial cancer is described in the table 17.15.

Q.5. What are the treatment modalities of choice for endometrial cancer?

Ans. The treatment of endometrial cancer has been summarized in table 17.16.

For patients with stage I and II A, the treatment of choice is an extrafascial total abdominal hysterectomy and bilateral salpingoophorectomy with lymph node sampling. Removal

Table 17.15: Staging of endometrial cancer

Stage		*Characteristics*
Stage I (grade 1, 2 or 3)	IA	Limited to the endometrium
	IB	Invasion of half or less than one half of the myometrium
	IC	Invasion of one half or more than one half of the myometrium
Stage II (grade 1, 2, or 3)	IIA	Endocervical glandular involvement only
	II B	Cervical stromal invasion
Stage III (grade 1, 2, or 3)	IIIA	Invasion of serosa and/or adnexa and/or positive peritoneal cytology
	IIIB	Vaginal metastases
	IIIC	Metastases to pelvic and/or paraaortic lymph nodes
Stage IV (grade 1, 2, or 3)	IVA	Invasion of bladder and/or bowel mucosa
	IVB	Distant metastases, including intraabdominal metastases and/or inguinal lymph nodes

Table 17.16: Treatment of endometrial cancer

Cancer stage	*Treatment*
Stage I and II A	Extrafascial total abdominal hysterectomy and bilateral salpingoophorectomy with lymph node sampling. The procedure also involves peritoneal cytology, thorough exploration of abdomen and pelvis and biopsy of extrauterine lesions.
Stage II tumors	Radical hysterectomy with bilateral salpingoophorectomy with pelvic lymphadenectomy or use of the same standard surgical approach as described for stage I disease, followed by appropriate pelvic or extended field external and intravaginal irradiation.
Stage III tumors	TAH with bilateral salpingoophorectomy with selective lymphadenectomy, biopsies of suspicious areas, omental biopsy and debulking of tumor followed by radiotherapy.
Stage IV tumors	Palliative chemotherapy, radiotherapy and progestogens

Table 17.17: Indications for pelvic lymph node sampling

The tumor histology is known to be clear cell type, serous, squamous or poorly differentiated grade III endometroid type
Cut section shows that the myometrium has been invaded to more than half of its thickness
The tumor has extended to the cervix or isthmus
Size of the tumor is greater than 2 cm
There is evidence of extrauterine disease

Table 17.18: Indications of radiotherapy

Post-operative vaginal irradiation
Stage 1A G3 tumors
Stage 1B G1 and G2 tumors
Stage 1B G3 and stage IIA (G1 and G2) tumors
External pelvic irradiation
Tumors in stage 1C (all grades), stage II A (G3) and stage IIB (all grades), stage IIIA (all grades) or with lymphovascular space invasion
Selected IV A patients
All patients with positive lymph nodes
Patients with documented paraaortic and common iliac lymph node involvement

of a vaginal cuff is usually not required in these cases. The removed tumor specimen is examined for tumor size, depth of myometrial invasion and extension into the cervix. Sampling of the pelvic lymph nodes may be done in selective cases. Indications for pelvic lymph node sampling are enlisted in table 17.17. In these conditions, lymph node sampling must be done even if the lymph nodes are clinically negative. LAVH with bilateral salpingoophorectomy and laparoscopic retroperitoneal lymph node sampling is being tried at certain centers in place of the conventional abdominal surgery. Surgery alone may serve as an appropriate treatment option for patients with stage 1A (G1 and G2) tumors in whom there is no evidence of invasion of the lymphovascular space, cervix or isthmus, peritoneal cytology is negative and there is no evidence of metastasis. In all the other patients, some form of adjuvant radiotherapy is indicated. Indications for postoperative vaginal irradiation are enumerated in the table 17.18. This method helps in bringing about a significant reduction in the incidence of vaginal vault recurrence. However, radical hysterectomy has no place in the management of early stage endometrial cancer.

For stage II tumors, radical hysterectomy with bilateral salpingoophorectomy and pelvic lymphadenectomy is the most commonly used treatment modality. However, some gynecologists prefer to use the same standard surgical approach as described for stage I disease, followed by appropriate pelvic or extended field external and intravaginal irradiation. Both the methods are associated with similar cure rates.

For stage III growths, the goal of surgery is TAH and bilateral salpingoophorectomy with selective lymphadenectomy, biopsies of suspicious areas, omental biopsy and debulking of tumor followed by radiotherapy. Stage IV cancers are usually non-operapable. Treatment has to be individualized in those with stage IV tumors. Usually, a combination of surgery, radiotherapy, hormone therapy or chemotherapy is required. Chemotherapy with doxorubicin in the dosage of 60 mg/m^2 and other drugs including cisplatin and paclitaxel is also being tried. Medroxyprogesterone acetate administered in the dosage of 1 gram weekly acts as an adjuvant to chemotherapy.

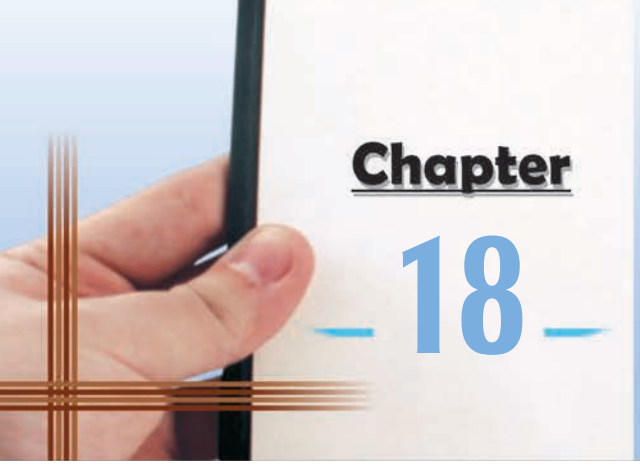
Patients with stage 1BG3 and stage IIA (G1 and G2) tumors are given either pelvic irradiation or vaginal cuff irradiation. For those with tumors in stage 1C (all grades), stage II A (G3) and stage IIB (all grades), stage IIIA (all grades) or those with lymphovascular space invasion, external pelvic irradiation of 50 Gy is recommended in addition to vaginal irradiation. This may also be suitable for selected IV A patients. Various indications for radiotherapy are listed in table 17.18.

Patients with documented paraaortic and common iliac lymph node involvement are additionally given extended field irradiation in the dosage of 45 Gy. Patients with stage IV disease with intraperitoneal spread may require whole abdominal irradiation along with systemic chemotherapy.

Bibliography

1. Baughan DM. Challenges in the management of the patient with dysfunctional uterine bleeding. Family Practice Recertification. 1993;15:68-78.
2. Baughan DM. Office endometrial aspiration biopsy. Fam Pract Res. 1993;15:45-55.
3. Bayer SR, DeCherney AH. Clinical manifestations and treatment of dysfunctional uterine bleeding. JAMA. 1993;269:1823-8.
4. Bremer CC. Endometrial biopsy. Female Patient. 1992;17: 15-28.
5. Chuong CJ, Brenner PF. Management of abnormal uterine bleeding. Am J Obstet Gynecol. 1996;175(3 pt 2):787-92.
6. Claessens EA, Cowell CL. Acute adolescent menorrhagia. Am J Obstet Gynecol. 1981;139:277-80.
7. Dysfunctional uterine bleeding. In: Speroff L, Glass RH, Kase NG, eds. Clinical gynecologic endocrinology and infertility. 5th ed. Baltimore: Williams and Wilkins;1994:531-46.
8. Goldstein SF, Zeltser I, Horan CK, Snyder JR, Schwartz LB. Ultrasonography based triage for perimenopausal patients with abnormal uterine bleeding. Am J Obstet Gynecol. 1997; 177:102-8.
9. Good AE. Diagnostic options for assessment of postmenopausal bleeding. Mayo Clin Proc. 1997;72:345-9.

10. Grimes DA. Diagnostic dilation and curettage: A reappraisal. Am J Obstet Gynecol. 1982;142:1-6.
11. Holbert TR. Transvaginal ultrasonographic measurement of endometrial thickness in postmenopausal women receiving estrogen replacement therapy. Am J Obstet Gynecol. 1997;176: 1334-8.
12. Karlsson B, Granberg S, Wikland M, Ylostalo P, Torvid K, Marsal K, et al. Transvaginal ultrasound of the endometrium in women with postmenopausal bleeding—a Nordic multicenter study. Am J Obstet Gynecol. 1995;172:1488-94.
13. Kaunitz AM, Masciello A, Ostrowski M, Rovira EZ. Comparison of endometrial biopsy with the endometrial pipelle and vabra aspirator. J Reprod Med. 1988;33:427-31.
14. Kaunitz AM. Endometrial sampling in menopausal patients. Menopausal Med. 1993;1:5-8.
15. Langer RD, Pierce JJ, O'Hanlan KA, Johnson SR, Espeland MA, Trabal JF, et al. Transvaginal ultrasonography compared with endometrial biopsy for the detection of endometrial disease. N Engl J Med. 1997;337:1792-8.
16. Laughead ML, Stones LM. Clinical utility of saline solution infusion sonohysterography in a primary care obstetric gynecologic practice. Am J Obstet Gynecol. 1997;176:1313-6.
17. Lerner JP, Timor-Tritsch IE, Monteagudo A. Use of transvaginal sonography in the evaluation of endometrial hyperplasia and carcinoma. Obstet Gynecol Surv. 1996;51:718-25.
18. Lewis BV. Hysteroscopy for the investigation of abnormal uterine bleeding. Br J Obstet Gynaecol. 1990;97:283-4.
19. Livengood CH, Land MR, Addison A. Endometrial biopsy, bacteremia and endocarditis risk. Obstet Gynecol. 1985;65: 678-81.
20. Loffer FD. Hysteroscopy with selective endometrial sampling compared with D&C for abnormal bleeding: The value of negative hysteroscopic view. Obstet Gynecol. 1989;73:16-20.
21. Mettlin C, Jones G, Averette H, Gusberg SB, Murphy GP. Defining and updating the American Cancer Society Guidelines for the cancer-related checkup: Prostate and endometrial cancers. CA Cancer J Clin. 1993;43:42-6.
22. Nesse RE. Managing abnormal vaginal bleeding. Postgrad Med. 1991;89:208;213-14.
23. Reagan MA, Isaacs JH. Office diagnosis of endometrial carcinoma. Prim Care Cancer. 1992;12:49-52.
24. Saidi M H, Sadler R K, Theis V D, Akright B D, Farhart S A, Villanueva G R. Comparison of sonography, sonohysterography and hysteroscopy for evaluation of abnormal uterine bleeding. Journal of Ultrasound in Medicine. 1997;16(9):587-91.
25. Silver MM, Miles P, Rosa C. Comparison of Novak and Pipelle endometrial biopsy instruments. Obstet Gynecol. 1991;78(5 pt 1):828-30.
26. Smith-Bindman R, Kerlikowske K, Feldstein VA, Subak L, Scheidler J, Segal M, et al. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. JAMA. 1998;280:1510-7.
27. Spencer CP, Cooper AJ, Whitehead MI. Management of abnormal bleeding in women receiving hormone replacement therapy. BMJ. 1997;315:37-42.
28. Stovall TG, Ling FW, Morgan Pl. A prospective, randomized comparison of the Pipelle endometrial sampling device with the Novak curette. Am J Obstet Gynecol. 1991;165(5 pt 1):1287-90.
29. Stovall TG, Photopulos GJ, Poston WM, Ling FW, Sandles LG. Pipelle endometrial sampling in patients with known endometrial carcinoma. Obstet Gynecol 1991;77:954-6.
30. Widrich T, Bradley LD, Mitchinson AR, Collins RL. Comparison of saline infusion sonography with office hysteroscopy for the evaluation of the endometrium. Am J Obstet Gynecol. 1996;174:1327-34.



Chapter

18

Menorrhagia due to Leiomyomas

Case Study

A 33-year-old G2P1 Patient presented with complaints of excessive menstrual bleeding since last six months. Despite of heavy bleeding during the periods, the periods were otherwise regular. The patient was prescribed ibuprofen, but did not show any response to treatment. A D&C was done a month ago which revealed benign pathology. Pelvic examination revealed an irregularly enlarged uterus (about six weeks in size). The mass was contiguous with the cervix and could not be moved away from the cervix. An ultrasound examination was done, which showed presence of a submucous fibroid about 4 cm in diameter.

Introduction

Menorrhagia (Greek: Meno – uterus; rhegnunai – to burst forth), is the medical terminology which describes the occurrence of heavy or prolonged bleeding during menstrual periods. The bleeding despite of being excessive or heavy occurs at regular intervals. Menorrhagia is a common symptom and presents as a significant healthcare problem in both the developed and the developing world. Two-thirds of the women with menorrhagia may suffer from iron deficiency anemia, which may be responsible for causing reduced hemoglobin, hematocrit and serum iron levels. Menorrhagia has become a significant problem, which may be responsible for nearly 50% cases of women undergoing hysterectomy. Menorrhagia needs to be distinguished clinically from other common abnormal bleeding patterns including metrorrhagia (flow at irregular intervals), menometrorrhagia (frequent, excessive flow at irregular intervals), polymenorrhea (bleeding at intervals > 21 days) and dysfunctional uterine bleeding (abnormal uterine bleeding without any obvious structural or systemic abnormality). A normal menstrual cycle is 21–35 days in duration in which the bleeding lasts for an average of 7 days (ranging between 4–10 days), with flow between 25 and 80 mL. Clinically, menorrhagia is defined as total blood loss exceeding 80 mL per cycle or menstrual period lasting longer than 7 days.

Pathogenesis

The volume of blood lost at the time of menstruation is controlled by local uterine vascular tone, hemostatic mechanism within the endometrium and regeneration of endometrium. The relationship between the vasodilatory mediators and vasoconstrictor mediators may be altered in patients with menorrhagia. Vasculature imbalance is theorized to be the result of a discrepancy between the vasoconstricting and aggregating actions of prostaglandin F_2 (alpha) and thromboxane A_2 and the vasodilating actions of prostaglandin E_2 and prostacyclins on the myometrial and endometrial vasculature. Increased endometrial fibrinolysis may be of importance in cases of menorrhagia.

Etiology

Etiology of menorrhagia is divided into four categories i.e., organic, endocrinologic, anatomic and iatrogenic (table 18.1). In this chapter special emphasis would be given to menorrhagia resulting due to uterine fibroids.

Uterine Myomas

Myomas (fibromyomas, leiomyomas or fibroids) are well circumscribed benign tumors developing from uterine myometrium, most commonly encountered among women of reproductive age group (30–45 years), with their prevalence ranging between 20% to 40%. The chances of having uterine fibroids increases until 50 years of the age and then declines sharply.

A typical myoma is a pale, firm, rubbery, well-circumscribed mass distinct from neighboring tissues and has a whorled appearance due to presence of interlacing fibers of myometrial muscle, separated by varying amount of connective tissue fibers (figures 18.1A and B). The fibroid is surrounded by a connective tissue capsule, which helps in fixing the tumor to the myometrium. The vessels supplying blood to the tumor lie in the capsule and send radial branches into the tumor. As a result, the central portion of the fibroid receives the least blood supply and is the first to undergo degeneration. On the other hand, the calcification usually starts at

Table 18.1: Causes of menorrhagia

Organic causes	*Endocrinologic causes*	*Anatomic causes*	*Iatrogenic causes*
Genitourinary infections	Thyroid dysfunction: Hypothyroidism and hyperthyroidism	Uterine fibroids	IUDs (copper T 380 A/para gaurd)
Bleeding disorders	Adrenal gland dysfunction	Endometrial polyps	Steroid hormones: Medroxy progesterone and other progestins (when stopped), prednisone
Organ dysfunction: Hepatic or renal failure	Prolactin producing tumors of the pituitary gland	Endometrial hyperplasia	Chemotherapy agents (paclitaxel, docetaxel, etc)
Sexual abuse resulting in bleeding from urethra or rectum	PCOS	Pregnancy complications (miscarriages)	Medications (e.g., anticoagulants like aspirin, warfarin, heparin, etc.)
Coagulation disorders like Von Willebrand disease; factor II, V, VII, and IX deficiencies; prothrombin deficiency; idiopathic thrombocytopenia purpura (ITP); and thromboasthenia	Obesity	Adenomyosis	
	Vasculature imbalance	Cancer (uterine, ovarian, cervical cancer)	

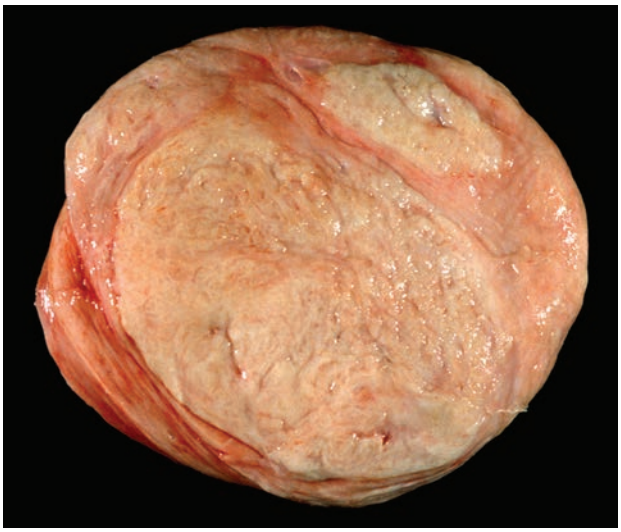


Fig. 18.1A: Macroscopic appearance of a leiomyoma appearing as a pale, firm, rubbery, well-circumscribed mass

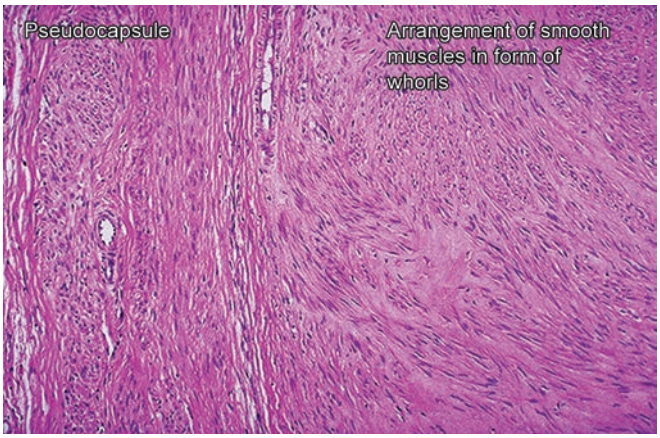


Fig. 18.1B: Histological appearance of a fibroid showing presence of interlacing smooth muscle fibers surrounded by varying amount of connective tissue

the periphery and extends inwards along the blood vessels. Fibroids can be single or multiple and may range in size from that of a small seedling to that of bulky masses which can distort and enlarge the uterus. Small fibroids often remain undiagnosed as they rarely produce any symptoms. Though most leiomymas are situated in the body of the uterus, they may be confined to the cervix, specially the supravaginal portion in nearly 1% to 2% cases. The characteristic symptom of leiomymas is menorrhagia; the duration of menstrual period may be normal or prolonged and the blood loss is usually heaviest on 2nd and 3rd day. The nearer the leiomyomas are to the endometrial cavity, the more likely are they to produce menorrhagia. Normally a woman with leiomyomas would never experience amenorrhea even of short duration, unless she is pregnant or past the menopause. In fact, women with fibroid are likely to have a late menopause.

Types of Fibroids

There are three types of fibroids (figure 18.2). Of the different types of fibroids, the commonest are intramural (interstitial) fibroids, which are present in nearly 75% cases, followed by submucous (15%) and subserous fibroids (10%).

Submucosal fibroids: Also known as subendometrial fibroids, these fibroids grow beneath the uterine endometrial

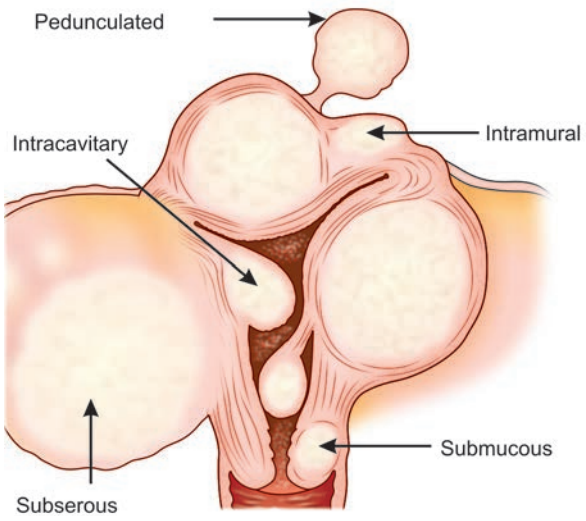


Fig. 18.2: Different types of leiomyomas

lining. This type of fibroid is thought to be primarily responsible for producing prolonged, heavy menstrual bleeding.

Intramural fibroids: These fibroids are the commonest type and are located in the middle of myometrium.

Subserosal fibroids: Also known as the pedunculated fibroids, these fibroids grow beneath the serosa, the outer uterine covering. These types of fibroids are the least common type. Sometimes they may develop a pedicle and extrude out from the surface in form of pedunculated fibroids. Both submucous and subserosal fibroids can be pedunculated.

Mechanism of Production of Menorrhagia by the Fibroids

The mechanism by which endometrial polyps or fibroids cause menorrhagia is not well understood. Some of the factors associated with fibroids which may be responsible for producing menorrhagia are increased size of endometrial cavity resulting in an increase in the bleeding surface, associated endometrial hyperplasia, hyperestrogenism and probably interference with contractions of the uterine muscles. The mechanism of fibroid associated menorrhagia is unknown. It is likely to be related to vascular defects which may be due to imbalance in production of various vasodilators and vasoconstrictors.

History

As previously mentioned, one of the important causes of menorrhagia in women belonging to the reproductive age group is leiomyomas (provided that any pregnancy related complication has been ruled out). The main symptoms attributable to leiomyomas are excessive or prolonged menstrual bleeding. Excessive bleeding, if remains untreated over a long period of time can result in the development of anemia. Anemia can manifest itself by producing symptoms such as palpitations, lassitude, loss of weight, etc.

On the other hand, irregular bleeding is usually not a characteristic symptom of myomas. Therefore, in cases with irregular bleeding, endometrial disease must be ruled out. Pedunculated submucous myomas which become infected or ulcerated may sometimes produce acyclical bleeding. Other circumstances under which the leiomyomas may produce irregular bleeding include presence of sacromatous changes in the leiomyoma, a coincidental pregnancy state, a coincidental carcinoma of the uterus or an endometrial polyp. The association between endometrial cancer and leiomyomas is real, though not direct. The same type of the patient may be subject to both the diseases because both the diseases are related to hyperestrogenism. Therefore, every women suffering from leiomyomas who has continuous or irregular bleeding should be subjected to endometrial aspiration to rule out the presence of endometrial cancer before her treatment is planned.

Other symptoms related to leiomyomas include symptoms related to pressure on adjacent organs. These may include symptoms such as backache (due to the pressure on spinal nerves); urinary symptoms, such as increased diurnal frequency (due to bladder irritability); low backache; rectal tenesmus and constipation (due to pressure on rectum), etc. Cervical or broad ligament fibroids can sometimes produce ureteric obstruction.

Fibroids are usually not painful. They may give rise to acute pain under exceptional circumstances, such as torsion of pedunculated fibroids, degeneration, infection and/or expulsion of pedunculated submucous tumors through cervix. Rarely, a fibroid can cause acute pain when it outgrows its blood supply, thereby causing necrosis. Spasmodic dysmenorrhea may result when expulsion of a pedunculated submucous tumor stimulates uterine contractions. Congestive dysmenorrhea may also occur due to associated pelvic congestion. Sometimes, as the small submucosal fibroids enlarge, they can stretch the endometrium, causing heavy menstrual bleeding and severe pain as the uterus tries to expel the mass. Red degeneration of fibroid (described later in the chapter) during pregnancy can also produce pain.

Besides abnormal bleeding patterns, uterine myomas can also cause infertility or give rise to certain problems during pregnancy. The problems which fibroids can produce during pregnancy are described later in this chapter. Presently, it is not yet known for sure whether infertility is the cause or the effect of leiomyomas. The effect of uterine fibroids on the woman's fertility pattern has been discussed in details in

chapter 26. Uterine fibroids could be responsible for infertility by interfering with the implantation of the fertilized ovum, by distorting the endometrial cavity and by causing disturbances of ovulation. Nearly 40% women conceive following myomectomy. Despite of the above mentioned symptoms, majority of the fibroids are asymptomatic.

Therefore, in suspected cases of fibroids, detailed history regarding the nature of bleeding, presence of any pressure symptoms, infertility and any complications during pregnancy, related to the presence of fibroids needs to be elicited. Questions which need to be asked regarding the nature of bleeding, amount of bleeding, duration of bleeding, pattern of bleeding and timing of bleeding have already been described in chapter 17. Other details which must be elicited while taking history include the following:

- *Patient's age*: As previously mentioned, patient's age can provide important pointer towards the diagnosis of underlying pathology. Uterine leiomyomas are typically more common in patients in the age group of 35–40 years.
- *Obstetric history*: Uterine fibroids are commoner in nulliparous women in comparison to the multiparous women.
- *History of contraceptive use (intrauterine device or hormones)*: Commonly, an intrauterine device (IUD) causes increased uterine cramping and menstrual flow.
- *Presence of any coagulation related disorder*: It is important to rule out the presence of any coagulation related disorders by taking the history of excessive bruising or bleeding on minor trauma and family history of known bleeding disorders. This is especially important in a young patient who does not stop bleeding during her first menses. This is a very common presentation for an undiagnosed bleeding disorder (e.g. Von Willebrand's disease) in a young girl.
- *Symptoms of thyroid dysfunction*: The alteration of the thyroid function may produce menstrual abnormalities like amenorrhea or oligomenorrhea (hypothyroidism) or menorrhagia (hyperthyroidism).
- *History of intake of any medications*: Intake of drugs like hormones or anticoagulants may typically cause bleeding.
- *Plans regarding future fertility and contraception*: These should be ascertained in order to decide appropriate patient management.
- History of undergoing pap smears in the past.

Risk Factors

History related to risk factors which can result in the development of fibroids also needs to be taken.

- *Heredity:* Genetic factors are likely to play an important role in the pathogenesis of fibroids. Patient with a positive family history of fibroid, especially in the first degree relatives (mother or sister) is especially at an increased risk of developing fibroids.

Many chromosomal abnormalities have been detected in cases of leiomyomas, the commonest being translation between the long arms of chromosomes 12-14, the second commonest being deletion on the long arm of the chromosome Y.

Race

Black women are more likely to have fibroids than the women of other racial groups. Furthermore, fibroids occur in black women at a younger age and tend to be larger and more numerous.

High estrogen levels

High estrogen levels predispose a woman to develop fibroids. Some factors which may be responsible for an increased risk of fibroids related to hyperestrogenism are as follows:

- Exposure to OCPs at the age of 13–16 years is associated with a high risk of development of uterine fibroids. However, use of oral contraceptive pills in middle age group acts as a protective factor.
- Obesity increases the risk probably due to higher levels of endogenous estrogens.
- Smoking reduces the risk of fibroids by decreasing the levels of endogenous estrogens.
- Child bearing during the reproductive years (25–29) provides greatest protection against myoma development by producing amenorrhea (thereby reduced estrogen levels) during pregnancy.

There is a positive association between fibroids and the pelvic inflammatory disease.

General Physical Examination

Signs of anemia: Abnormal blood loss, if allowed to continue over a long period of time can result in the development of anemia.

Specific Systemic Examination

An abdominal and pelvic examination should be performed in women presenting with heavy menstrual bleeding. Pelvic examination should be preferably avoided in the women under the age of 20.

ABDOMINAL EXAMINATION

In case of a large fibroid, the mass may be palpable per abdomen. However, a leiomyoma has to attain the size of

approximately 12–14 weeks before the abdominal swelling becomes palpable per abdominally. It may be difficult to detect the leiomyomas, smaller than this on abdominal examination. In case of uterine fibroids, the mass usually appears to be arising from the pelvis, i.e. it may be difficult to get below the mass. The mass is usually well defined, having a firm consistency and a smooth surface. It is usually movable from side to side, but not from above downwards. If the fibroid has undergone cystic degeneration, it may appear soft and cystic in consistency, rather than hard. Presence of multiple fibroids can result in an irregular appearance of the mass. The mass is nearly always dull to percussion because the intestines usually lie behind and besides the mass. The mass is rarely tender on touch. In case of a single subserous leiomyoma with a long pedicle, it may be difficult to recognize its connection with the uterus. In such cases, it might be difficult to distinguish the fibroid from an ovarian tumor.

PELVIC EXAMINATION

The method of conducting the pelvic and bimanual examination has been discussed in details in chapter 16. Bimanual examination helps in assessment of uterine size, shape and contour. Presence of an enlarged, irregularly shaped, nontender, mobile uterus with firm consistency is suggestive of fibroids in women aged 30–50 years. On bimanual examination, it is found that the tumor either replaces the uterus or is attached to the cervix. This is an important point because if the mass were lateral or moved apart from the cervix, the most likely diagnosis would have been presence of an adnexal mass.

Differential Diagnosis

Pregnancy

Pregnancy must always be ruled out in a woman of reproductive age group, presenting with an abdominal lump. A urine pregnancy test and an ultrasound examination help in confirming the diagnosis of pregnancy.

Adenomyosis

Adenomyosis is a condition associated with presence of endometrial tissue within the uterine myometrium. In cases of diffuse adenomyosis, the uterus is symmetrically enlarged to the size between 12–14 weeks. Cases of focal adenomyosis are associated with asymmetrical uterine enlargement. In these cases, it may be difficult to differentiate adenomyosis from uterine fibroids. Adenomyosis is often associated with pain and uterine tenderness. Therefore presence of menorrhagia along with dysmenorrhea is more suggestive of adenomyosis in comparison to fibroids. MRI helps in establishing the exact diagnosis and differentiating between fibroids and adenomyosis.

Benign Ovarian Tumor

At times, it may become particularly difficult to differentiate between a subserous fibroid and a benign ovarian mass. Furthermore, a subserous fibroid may not be associated with menorrhagia. The two can be differentiated on a pelvic examination as explained in chapter 24.

Bicornuate Uterus

One horn of a bicornuate uterus may often be mistaken for a myoma. Ultrasound examination may help confirm the diagnosis.

Management

Presently, the main modality of curative treatment in a patient with leiomyomas is surgery. Medical therapy does not help in curing myomas. It can just provide symptomatic relief and help in reducing the size of the tumor by decreasing its blood supply. The management plan of a patient diagnosed with fibroid uterus, presenting with menorrhagia is described in flow chart 18.1.

Investigations

Only investigations which are required in a case of leiomyomas are described next. Investigations which may be required to be carried out in the case of abnormal bleeding based on history and clinical examination are described in chapter 17.

Complete Blood Count along with Platelet Count and a Peripheral Smear

The CBC with platelet count must be conducted to rule out presence of anemia.

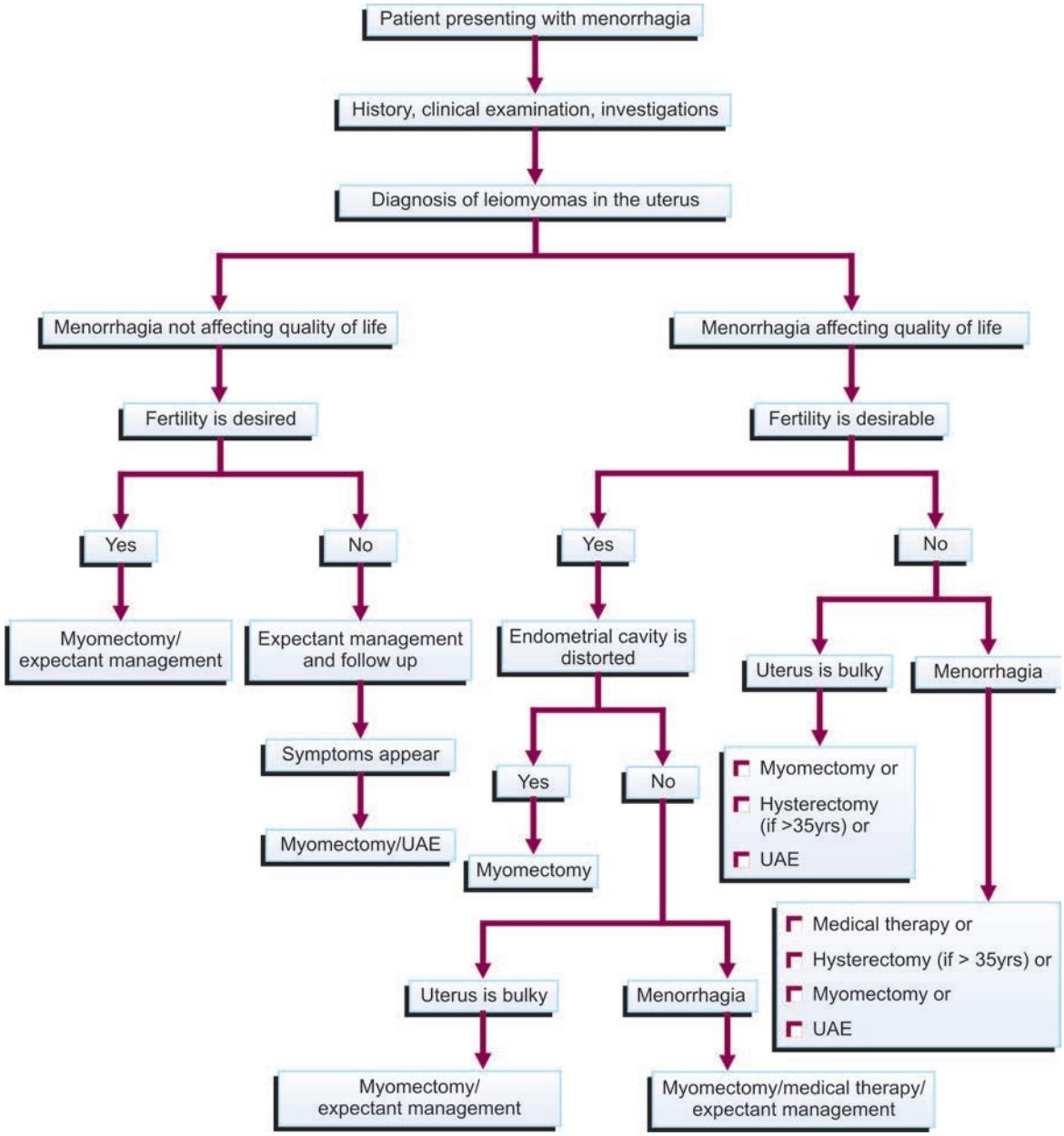
Imaging Studies

Imaging modalities such as ultrasound (both transabdominal and transvaginal ultrasound) and MRI are noninvasive investigations, which play an important role in the management of patients with leiomyomas.

Ultrasound Examination

Nowadays, ultrasound examination (both transvaginal and transabdominal ultrasound) has become the investigation of choice for diagnosing myomas. The advantages of ultrasound imaging are good patient tolerance, noninvasive nature of the investigation, relatively low cost, easy availability and high

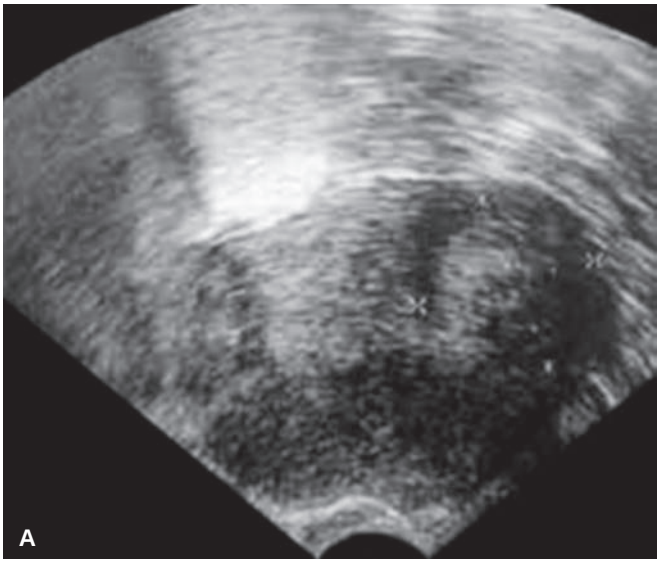
Flow chart 18.1: Management plan of a patient presenting with fibroid uterus presenting with menorrhagia

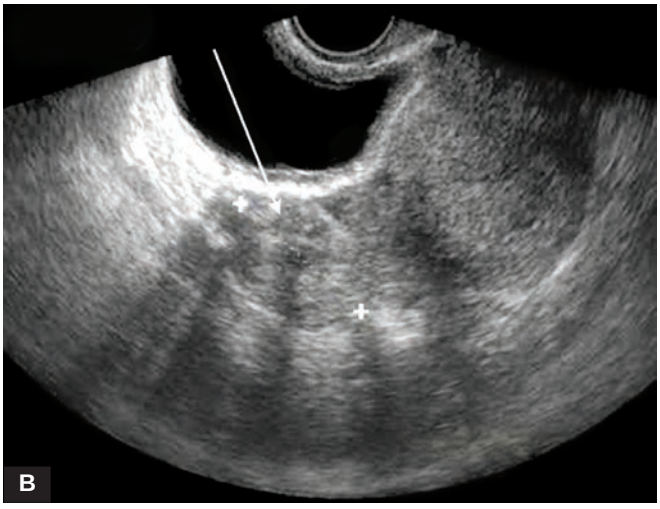


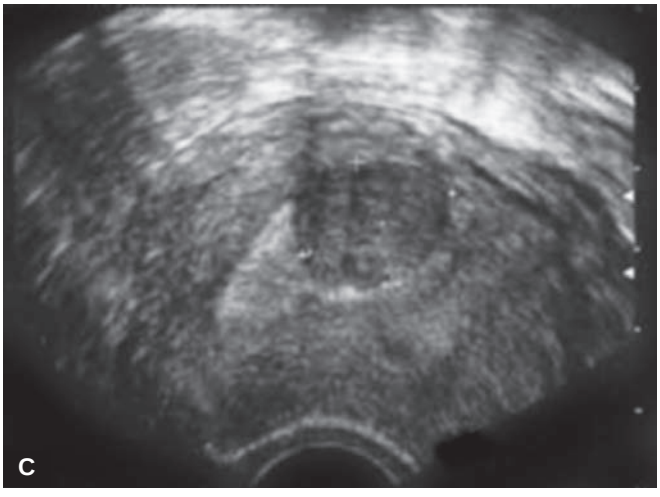
accuracy rates. Ultrasound examination helps in assessing the overall uterine shape, size and contour; endometrial thickness; adnexal areas and presence of hydronephrosis. It helps in detection of small, focal, irregular or eccentrically located endometrial lesions. Pre-operative finding on sonography can guide the gynecologist while performing surgery, hysteroscopy, laparoscopy, etc. Ultrasound examination can help in assessing the size, location and number of uterine fibroids. It may be sometimes very difficult to differentiate between submucous myomas and endometrial polyps on ultrasound examination. In these cases, the investigations such as saline-infusion-sonography (SIS) and hysteroscopy help in arriving at the correct diagnosis. Though MRI is an investigation which helps in accurately establishing the definitive diagnosis of myomas, the high cost associated with its use, prevents its widespread use in clinical practice. Presently, the ultrasound examination forms the most commonly used investigation modality for initial evaluation.

Transvaginal ultrasound

Transvaginal sonography can help in detecting myomas as small as 2.5 cm within the uterus (figures 18.3A to C). Most







Figs 18.3A to C: (A) Intramural fibroid (B) Pedunculated fibroid having a diameter of 3.74 cm (C) Submucous fibroid protruding inside the endometrial cavity

new transvaginal probes offer variable frequency transducers with frequencies between 5.0 and 7.5 MHz. The higher the frequency used, the better is the resolution of the image. However, with the use of higher frequency ultrasound probes, the field of view largely gets restricted. As the uterus enlarges, a lower-frequency transducer must be used to visualize the organ. The 7.5 MHz vaginal probe works best with a normal or minimally enlarged uterus. The 5.0 MHz vaginal probe usually images a uterus up to the size of 12 weeks' gestation. If the uterus is larger than this, transabdominal imaging with a 2.5 or 3.5 MHz probe is required.

Various studies have found the sensitivity of TVS in detection of leiomyomas to range from 90% to 100% and specificity to range from 80% to 94%.

Though transvaginal ultrasonography is associated with higher resolution in comparison to transvaginal sonography, it may not always be useful in distinguishing between a submucosal fibroid, endometrial polyp and adenomyosis. A newer technique, called saline infusion sonography (SIS) or sonohysterography, uses saline infusion into the endometrial cavity to enhance the detection of fibroids and polyps.

Sonohysterography (saline infusion sonography)

Saline infusion sonography (SIS) involves infusion of fluid inside the endometrial cavity in order to enhance the evaluation of endometrial cavity and adnexa at the time of ultrasound examination. As previously described, one of the major advantage of sonohysterography is its ability to differentiate polyps from submucous leiomyomas. SIS has been demonstrated to cause improved evaluation of the endometrial cavity and assessment of tubal patency. SIS also helps in detection of endometrial pathology such as uterine synechiae, endometrial polyps (figure 18.4) and submucous leiomyomas. One of the major limitations of sonohysterography has been the assessment of tubal patency.

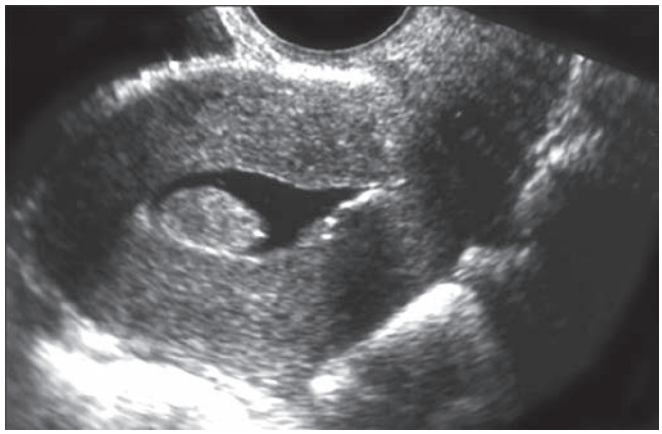


Fig. 18.4: SIS demonstrating a uterine polyp

Procedure: The technique of sonohysterography is relatively simple. Before performing SIS, the possibility of pregnancy must be excluded. Patients with a history of pelvic inflammatory disease should be treated prophylactically with antibiotics before performing the procedure.

The cervix is cleaned with an antiseptic swab.

A 5 French sonohysterogram catheter can be inserted into the lower uterine segment or cervical canal in most menopausal patients without using tenaculum or prior cervical dilatation.

The catheter should be flushed with normal saline prior to insertion in order to avoid the production of air bubbles during the procedure.

After the insertion of the catheter inside the uterine cavity, approximately 10 ml of saline is infused inside.

The vaginal probe ultrasound is inserted, and the sonohysterogram is performed, while the saline is being infused inside the uterine cavity.

The cavity should be assessed in multiple transverse and longitudinal planes.

The procedure can cause vagal episodes, particularly in nulliparous women who have not had any children in the past. In such cases, premedication with nonsteroidal antiinflammatory drugs (NSAIDs) such as ibuprofen or naproxen is recommended.

MRI

Though the use of MRI is not routinely recommended, it is useful in mapping the size and location of leiomyomas (figures 18.5 and 18.6) and in accurately identifying adenomyosis. Though MRI gives images with better resolution, due to its high cost, MRI is usually reserved for only special cases. MRI is usually performed in cases in which the diagnosis is not clear on ultrasound examination. Other pelvic pathology such as ovarian neoplasms can also be identified on MRI. MRI is preferable to CT for imaging myomas as it does not expose the patients to ionizing radiations.

MRI is a highly accurate technique for evaluating uterine leiomyomas, adenomyosis and uterine anomalies. MR images clearly delineate the myometrium, junctional zone and endometrium, allowing highly accurate mapping of the size, location and degree of myometrial involvement of uterine leiomyomas (figures 18.5 and 18.6). It is much more accurate in identifying and mapping adenomyosis. The major limitations of MRI is the high cost involved.

In case the patient has risk factors for endometrial cancer or she is in the perimenopausal age group or gives history of intermenstrual and postcoital bleeding, endometrial biopsy and Pap smear are required to rule out carcinoma endometrium and carcinoma cervix respectively.

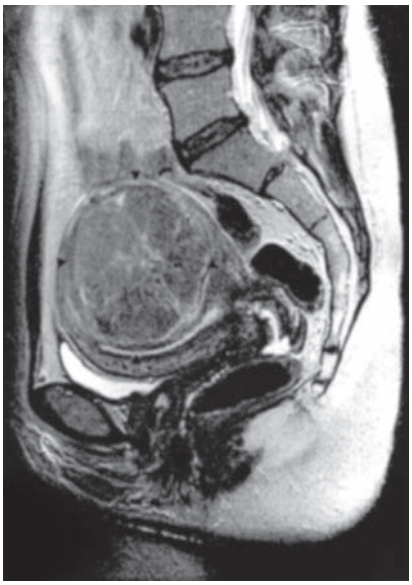


Fig. 18.5: T1-weighted MR image showing an intramural fibroid of size 8 cm

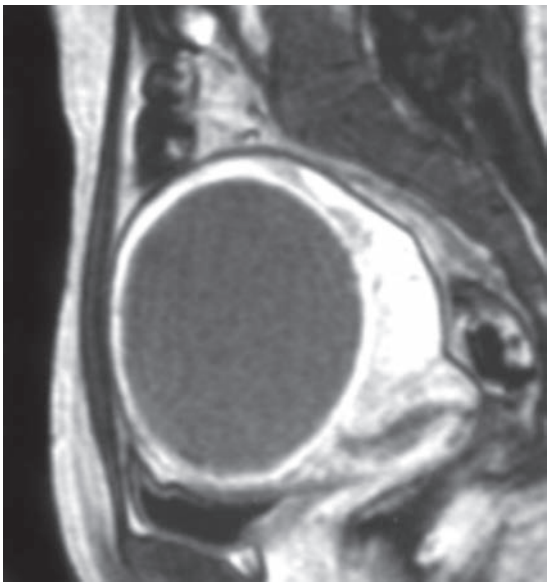


Fig. 18.6: 43-year-old woman with large submucosal fibroid. Enhanced T1-weighted MR image obtained 4 months after uterine artery embolization shows that uterine fibroid decreased to 9 cm in maximum diameter (46% tumor volume reduction) and was not enhancing. Muscular layer of the uterus is enhanced.

Rx *Treatment/Gynecological Management*

Specific treatment for menorrhagia is based on a number of factors including:

- Overall health and medical history
- Extent of the condition
- The effects of the fibroids on the patient's lifestyle

- Personal preference
- Patient's age
- Desire for future fertility
- Duration and severity of the heavy bleeding
- Underlying cause of the condition

In case the patient is diagnosed with fibroid uterus, the ultimate treatment depends on factors such as the number of fibroids, size of fibroids, the proximity of the fibroids to the endometrial cavity and severity of symptoms caused by them. The closer the fibroids are to the endometrial cavity, the more they are likely to be symptomatic. Even if the diagnosis of fibroids has been made, it does not necessarily imply that they are the cause of bleeding. The menstrual periods may be heavy even if the fibroids were not present. It may be sometimes appropriate to offer treatments used for dysfunctional uterine bleeding even in the presence of the fibroids. Since abnormal uterine bleeding can result from other causes, such as endometrial cancer and hormonal problems (dysfunctional uterine bleeding), it is important that women with fibroids, especially the women in the perimenopausal age group, who experience abnormal vaginal bleeding receive a thorough evaluation for endometrial cancer.

The various treatment options which can be used in a woman with fibroid uterus are enumerated in table 18.2 and described in flow chart 18.2. In case of uterine fibroids, skilled judgment is required to decide whether surgical treatment options such as myomectomy or hysterectomy would be required or use of medical treatment options like tranexamic acid would be appropriate. Medical management should be tailored towards alleviation of symptoms like bleeding and pain.

If the woman has completed her family and does not wish to preserve her uterus, hysterectomy can be done. Myomectomy is an option for women, who desire future pregnancy or wish to preserve their uterus. Removal of fibroids that distort the uterine cavity may be indicated in infertile women, where no other factors have been identified, and in women about to undergo in vitro fertilization treatment. However, the women undergoing myomectomy should be counseled regarding the chances of occurrence of massive bleeding during myomectomy and the risk for conversion to hysterectomy at the time of surgery. Once the decision regarding myomectomy has been taken, the next step is deciding the route of myomectomy: Hysteroscopic, laparoscopic or

Flow chart 18.2: Treatment options for a patient diagnosed with fibroid uterus

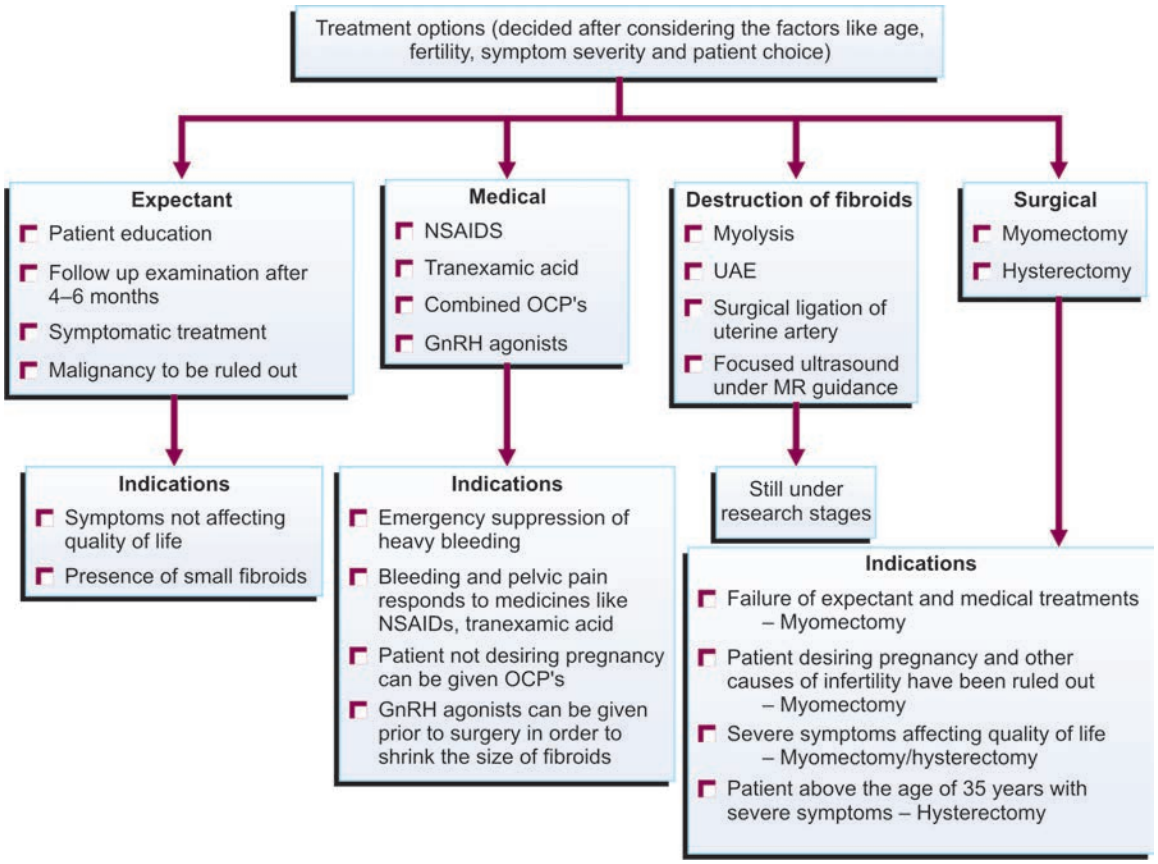


Table 18.2: Treatment options for uterine myomas in women with fibroids

Conservative management	Asymptomatic women with small fibroids
Medical management	Not curative
Surgical management (myomectomy and hysterectomy)	Definitive treatment
Destruction of fibroids (myolysis, uterine artery embolization, uterine artery ligation, focused ultrasound)	Limited evidence as these procedures are still under research stage

abdominal. Hysteroscopic myomectomy should be considered as first-line conservative surgical therapy for the management of symptomatic intracavitary or submucosal fibroids. A hysteroscopic myomectomy is usually preferred in cases of submucosal fibroids showing minimal myometrial involvement. Laparoscopic myolysis (destruction of myoma via diathermy) may present an alternative to myomectomy. It may also serve as an alternative to hysterectomy for selected women with symptomatic intramural or subserous fibroids who wish to preserve their uterus but do not desire future fertility. Uterine artery embolization (UAE) may be offered as an alternative to hysterectomy in selected women with symptomatic uterine fibroids who wish to preserve their uterus. Women choosing uterine artery occlusion for the treatment of fibroids should be counseled about the relative newness of the procedure and absence of adequate literature regarding the possible risks, long-term efficacy, fecundity, pregnancy outcomes and patient satisfaction associated with UAE.

CONSERVATIVE TREATMENT

Most women with uterine fibroids do not require any treatment. Their tumors either are asymptomatic or the symptoms (such as pelvic pain or menorrhagia) can be controlled with common medications such as over-the-counter pain medication for control of pain and iron supplements in presence of symptoms related to anemia. Patient counseling and education forms an important component of the conservative management and comprises of the following:

- The patient must be reassured that the bleeding related to fibroids is a common, benign cause of bleeding and nothing to worry about.
- Patient must be provided information regarding various treatment options, including the probable expectations and adverse effects. Patient must be reassured that in case she experiences failure with one treatment option, other options are available, which can be used.
- Patient must be periodically assessed with either pelvic examination or ultrasound examination to determine whether fibroids are changing in size or if she is developing symptoms that would require surgical treatment. Periodic assessment is especially important if the patient is planning a pregnancy.
- Advice to maintain a menstrual calendar: Women who have abnormal blood loss must be encouraged to chart their menstrual blood loss every month. Amount of bleeding (scanty, moderate and heavy) and occurrence of menstrual cramps and pain must also be noted.

MEDICAL TREATMENT

Though the definitive treatment for uterine fibroids is sugery, medical therapy is sometimes instituted with the following aims:

Aims of Medical Management

- Alleviation of symptoms
- Improvement of hemoglobin status before surgery
- Emergency suppression of heavy bleeding
- Minimizing the size and vascularity of uterine fibroids prior to surgery. This helps in facilitating the laparoscopic or hysteroscopic surgery.

Acute menorrhagia requires prompt medical intervention. Emergency suppression of an episode of heavy prolonged menstrual bleed can be achieved by norethisterone 15 mg/day or medroxyprogesterone acetate in a dose of 30 mg/day for 3 weeks. Conjugated equine estrogens are also used for emergency control of bleeding. Medical therapy must be tailored according to each individual, taking into consideration factors like the patient's age, coexisting medical diseases, family history and desire for fertility. For more details regarding medical therapeutic options for control of menorrhagia, refer to chapter 19. Medical therapeutic options for control of menorrhagia in a patient with leiomyomas are described in table 18.3.

Prostaglandin synthetase inhibitors

NSAIDs (typically menfenamic acid) may be particularly useful when bleeding is associated with pelvic pain and dysmenorrhea. Various NSAIDs, including mefenamic acid have been shown to significantly reduce menstrual blood loss by inhibiting the enzyme prostaglandin synthetase, which is involved in production of prostaglandins. Imbalance between various levels of prostaglandins is thought to be responsible for the pathogenesis of menorrhagia. Side effects associated with their use include nausea, vomiting, gastric discomfort,

Table 18.3: Medical options available for treatment of menorrhagia

Antispasmodic agents: NSAIDS, buscopan (menstruating days only)
Hemostatic agents: Ethamsylate, Tranexamic acid (menstruating days only)
Combined oral contraceptive pills (day 5–25)
Progestogens (e.g. Norethisterone e.g. primolut N, dydrogesterone (duphaston) and medroxyprogesterone (provera)) (day 5–25)
Hormone replacement therapy (HRT)
Androgens: Danazol, GnRH therapy (daily continuous therapy)
Mirena (levonorgestrel intrauterine system)

diarrhea and dizziness. Rarely, it can cause hemolytic anemia or thrombocytopenia. However, mefenamic acid has been observed to be less effective than hemostatic agents (tranexamic acid) in reducing the amount of blood loss (20% vs. 54%), but in general it has a lower side effect profile. Mefenamic acid is administered in the dose of 500 mg TDS during menses. Other analgesic drugs belonging to the class of NSAIDs, including drugs like naprosyn, ibuprofen, indomethacin and diclofenac may also prove to be effective in reducing pelvic pain and dysmenorrhea.

Hemostatic agents

Tranexamic acid: Under normal circumstances, clotting of blood requires conversion of fibrinogen into fibrin. Fibrinolytic substances (fibrinolysins) in the blood are responsible for breakdown of blood clot, resulting in prolonged bleeding. Hemostatic agents like tranexamic acid help in reducing the blood loss by inhibiting this fibrinolytic activity, thereby sealing the bleeding vessels. The tranexamic acid is administered in the intravenous dosage of 10–15 mg/kg body weight 2–3 times a day or 0.5–1 gm per day orally in divided doses, leading to a total of 3–6 gm/day for the first 3 days of the cycle. Side effects due to tranexamic acid are dose related and may include symptoms like nausea, vomiting, diarrhea and dizziness. Rarely, there may be transient color vision disturbance, or intracranial thrombosis.

Ethamsylate: This drug helps in achieving hemostasis by reducing capillary bleeding. It helps in increasing the capillary wall strength and increasing platelet adhesion. It is used orally in the dosage of 250–500 mg three times a day.

Gonadotropin releasing hormone agonists

Mode of action: Gonadotropin releasing hormone (GnRH) is released by the hypothalamus and stimulates the release of the gonadotropins like, FSH and LH by the pituitary gland. These hormones then trigger the ovary to secrete hormones like estrogen and progesterone, which in turn stimulate ovarian follicular development. Administration of GnRH agonists simulates the action of GnRH in the body. However continuous exposure to GnRH agonists desensitizes the pituitary gonadotrophs resulting in loss of gonadotropin release thereby causing a reduction in estrogen production. Therefore, following an initial gonadotropin release associated with rising estradiol levels, gonadotropin levels eventually fall off to castrate levels, with resultant hypogonadism. Therefore due to the use of GnRH agonists, medical oophorectomy or medical menopause is produced.

As previously described, estrogen helps in promoting the growth of fibroids. As a result, treatment with GnRH agonists, by reducing estrogen production may cause nearly 50% reduction in the initial volume of the myoma within 3 months of therapy. Maximum fibroid shrinkage usually occurs after 3 months of treatment. Therefore, GnRH agonist treatment should be restricted to a 3 to 6 months interval. GnRH agonists are at times prescribed before surgery for uterine fibroids. They help in reducing the blood loss at the time of surgery by shrinking the tumor size, thereby eliminating the need for blood transfusions at the time of surgery. This form of medical castration is also effective in inducing amenorrhea in patients with DUB by breaking the ongoing cycle of abnormal bleeding in many anovulatory patients. Use of GnRH agonists in woman of childbearing age can help to shrink the size of fibroid tumors, thereby eliminating the need for a hysterectomy, thus preserving fertility. Alternatively, their use may allow a simpler surgical procedure like laparoscopic hysterectomy, thereby avoiding abdominal surgery.

Dosage and some commonly used formulations (table 18.4): GnRH agonists are available in various forms including nasal spray, subcutaneous injections, slow release intramuscular injections and subdermal pellets. Some of the commonly used preparations of GnRH agonists include leuprolide acetate, goserelin, zoladex, buserelin, nafarelin, triptorelin, etc.

Table 18.4: Some commonly used GnRH agonists in gynecological practice

Name of the administration	*Route of*	*Dosage of GnRH agonist*
Buserelin	Intranasal	900–1200 µgms per day
Leupronelin	Subcutaneous Intramuscular	0.1–1.0 mg/day 3.75 mg/month
Naferelin	Intranasal	400–800 µgm/day
Goserelin (zoladex)	Subcutaneous	3.6 mg/month
Triptorelin	Intramuscular	2–4 mg/month
Histrelin	Subcutaneous	10 µgm/kg/day

Side effects: GnRH agonists are usually used on a short-term basis due to high costs and severe adverse effects. Side effects associated with GnRH agonists are common to menopause and may include side effects like hot flashes, mood swings, depression, weight gain, headaches and vaginal dryness. These side effects are usually reversible upon cessation of treatment. The most important side effect of concern in the women using GnRH agonists is osteoporosis. A prolonged hypoestrogenic state associated with their use leads to bone demineralization resulting in osteoporosis. Therefore, these women should not be prescribed these drugs for more than 6 months. Certain approaches which may be used to protect the women against osteoporosis include the following:

- Use of add-back therapy: In this therapy, estrogen and progestin are added in a dosage, which is high enough to maintain bone density, but too low to counter-balance the beneficial effects of the GnRH agonists.
- Addition of a bone-protective drug like bisphosphonates, calcium supplements, etc.

Since the use of GnRH agonists does not result in sterility, the danger of conception, although rare, is present. Furthermore, if a woman becomes pregnant during their use, there is some risk for birth defects. Therefore, the women should be advised to use barrier contraception during the entire course of GnRH agonist therapy. GnRH agonists are not indicated in women who are pregnant or are trying to become pregnant while using the drug. Before using these drugs, the gynecologist should be certain that there is no underlying malignancy, particularly leiomyosarcoma, endometrial cancer, etc. The use of these drugs can delay the detection and treatment of the malignancy and can result in some severe complications.

Exogenous progestins and oral contraceptive agents (OCP's)

Use of exogeneous progestins and OCPs can partially suppress estrogen stimulation, reducing the growth of uterine fibroids. Use of these drugs for controlling menorrhagia is described in details in chapter 19. The levonorgestrel intrauterine system (Mirena) was initially developed intitially as a highly effective and reversible method of contraception. However its use has also been observed to provide excellent reduction in the amount of menstrual blood loss. Mirena is described below in details.

The levonorgestrel intrauterine system (figure 18.7)

The levonorgestrel intrauterine system (IUS) helps in reducing the amount of menstrual blood loss by causing the local release of the progestogen, levonorgestrel within the uterine cavity. The dose of progestogen released within the uterine cavity is equivalent to two progestogen only tablets each week (which is approximately equivalent to 15–20 μg of levonorgestrol/day). This dose of progesterone helps in thinning the endometrial lining, thereby helping in considerably reducing the volume of menstrual blood loss. Menstrual bleeding may eventually stop while the IUS is in place. The IUS provides effective contraception for a period of five years and must be removed or replaced after the expiry of this period. However, IUS should not be used in presence of large uterine fibroids which distort the uterine cavity. Use of IUS can result in the development of side effects like change in menstrual bleeding pattern, such as frequent, prolonged or heavy bleeding; spotting, light, scanty bleeding, irregular bleeding or cessation of bleeding; development of ovarian cysts; weight gain; edema; headache; depression; nervousness; mood swings; nausea; pain including lower abdominal pain, back pain, breast pain, dysmenorrhea; acne; vaginal discharge including cervicitis, genital infections, etc.

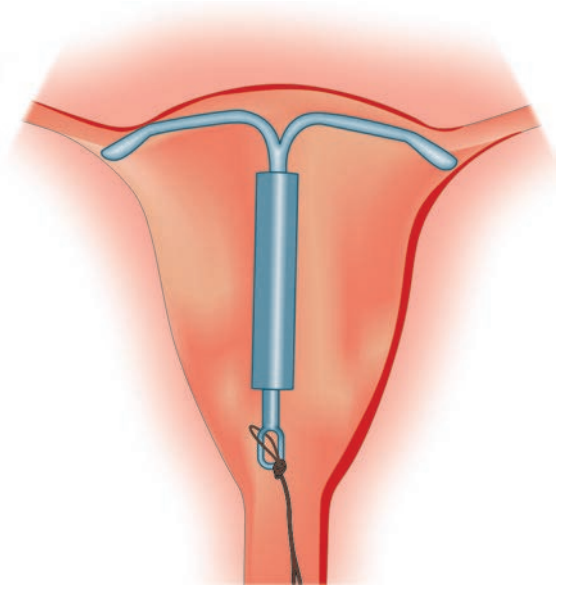


Fig. 18.7: The levonorgestrel intrauterine system (Mirena)

Other side effects related to the use of IUS include the following:

- Break through bleeding in the first few cycles
- 20% develop amenorrhea within 1 year
- Presence of functional ovarian cysts

Special indications for use of IUS include the following:

- Intractable bleeding associated with chronic illness
- Ovulatory heavy bleeding

Antiprogestins

Antiprogestins like mifepristone can also help in reducing fibroid growth. They are administered in the dose of 5 to 50 mg once a day for a period of 3 to 6 months.

Selective estrogen receptor modulators (e.g., raloxifene)

Some studies have shown that the use of SERMs help in reducing the size of fibroids and improving clinical outcomes. However, well designed, randomized studies in future are required to establish definite evidence regarding the benefit of SERMs in treating women with uterine fibroids.

Danazol

This is an androgenic agonist, with strong antigonadotropic activity, due to which it can inhibit LH and FSH. As a result, it can suppress fibroid growth, but is also associated with a high rate of adverse effects, such as weight gain, acne, hirsutism, edema, hair loss, deepening of the voice, flushing, sweating, vaginal dryness, etc and is thus often less acceptable to patients. For detailed description regarding danazol, refer to chapter 23.

Conjugated equine estrogen (Premarin)

Conjugated equine estrogens are effective in controlling acute, profuse bleeding. This drug helps in controlling bleeding by exerting a vasospastic action on capillary bleeding by increasing the level of various clotting factors in the blood including fibrinogen, factor IV and factor X and improving platelet aggregation and capillary permeability. Estrogen also induces formation of progesterone receptors, making subsequent treatment with progestins more effective.

This drug helps in controlling acute bleeding, but does not treat the underlying cause. Therefore appropriate long-term therapy should be administered depending on the underlying pathology, once the acute episode has been controlled. These agents are administered intravenously in a dose of 25 mg every 4 hourly in patients with acute bleeding, for a maximum of 48 hours. If the bleeding slows down, the patient is followed up with estrogen-progestin therapy for 7 days. This may be followed up with OCPs for 3 months.

A D&C procedure may be necessary if no response is noted within 24 hours following the use of premarin. D&C should not be routinely used for treatment of menorrhagia because it provides only short-term relief, typically lasting for about 1–2 months. This procedure is used best in conjunction with hysteroscopy to evaluate the endometrial cavity for pathology. For detailed description of the procedure of D&C, refer to chapter 16.

Endometrial Ablation

Endometrial ablation does not have much role in controlling bleeding related to leiomyomas uterus. While large intrauterine myomas serve as a contraindication for these procedures, a woman with small fibroids (< 3cm) can be treated using endometrial ablation. These techniques may be also useful in controlling menorrhagia related to dysfunctional uterine bleeding in the women wishing to conserve their uterus. For detailed description of endometrial ablation techniques, refer to chapter 19.

SURGICAL OPTIONS

Surgery forms the definite treatment modality for uterine leiomyomas. The three main surgical options, which can be used in the women with leiomyoma uterus include: Myomectomy, hysterectomy and more recently uterine artery embolization (UAE). Women should be informed that having a UAE or myomectomy would potentially allow them to retain their fertility. Some indications, when the gynecologist needs to resort to surgery in case of a woman with leiomyomas uterus are enumerated in the table 18.5 below.

Besides acting as the definitive cure for myomas, surgical management is also used in the following circumstances:

- Control of excessive uterine bleeding.
- Control of pain and symptoms related to excessive pelvic pressure.
- Infertility with distortion of endometrial cavity or tubal occlusion.
- Menorrhagia not responding to conservative or other medical treatment modalities.
- There is a high clinical suspicion of malignancy.
- Growth of fibroid continues even following the menopause.
- Menorrhagia results in severe iron deficiency anemia.
- Recurrent pregnancy losses (all the other causes have been ruled out and uterine fibroids appear to be the most likely cause of recurrent miscarriages).

Hysterectomy

Hysterectomy, a major surgical operation involving the removal of the woman's uterus helps in providing definitive cure for uterine leiomyomas. Hysterectomy can be performed in three ways: Abdominally, vaginally and in some

Table 18.5: Indications for surgery in patients with myomas

Presence of large fibroids (greater than 3 cm in diameter)
Severe bleeding, having a significant impact on a woman's quality of life, which is refractory to drug therapy
Persistent or intolerable pain or pressure
Urinary or intestinal symptoms due to presence of a large myoma
History of infertility and future pregnancy is desired
History of recurrent spontaneous abortions and future pregnancy is desired
Rapid enlargement of a myoma (especially after menopause) raising the suspicion of leiomyosarcoma (a rare cause)

Table 18.6: Indications for hysterectomy

The woman no longer wishes to retain her uterus and fertility
Patient wishes for amenorrhea
Other treatment options (medical, myomectomy, UAE, etc) have failed or are contraindicated

Table 18.7: Disadvantages of hysterectomy

High risk of complications (risk of intraoperative hemorrhage, damage to other abdominal organs, etc.)
Requirement of general or regional anesthesia
The recovery time varies from two to eight weeks
Early onset of menopause
Possible requirement for hormone replacement therapy in future

cases laparoscopically. Recovery time varies from two to six weeks. This procedure is more expensive and is associated with greater mortality and morbidity in comparison to other surgical procedures (myomectomy, UAE, etc). The mortality rate for hysterectomy ranges from 0.1–1.1 cases per 1000 procedures. The morbidity rate usually is 40%. Hysterectomy should be considered only when any of the indication mentioned in table 18.6 occur.

As mentioned before, hysterectomy is a major surgery, which is associated with numerous complications including high rates of morbidity and mortality. Some other disadvantages of hysterectomy are enumerated in table 18.7. The removal of the uterus can frequently result in significant physical strain and psychological stress. Thus, prior to the decision of hysterectomy, the gynecologist should have detailed discussion with the patient regarding the advantages and disadvantages of the surgical procedure, its impact on sexual feelings, fertility and bladder function, probable treatment complications, the woman's expectations and issues related to menopause and their psychological impact. Removal of healthy ovaries should not be routinely undertaken during the surgery.

Removal of ovaries should only be undertaken with the express wish and consent of the woman. Removal of the ovaries at the time of hysterectomy may be considered in the women with a significant family history of breast or ovarian cancer or those suspected of developing future ovarian malignancy. Women should be informed about the risk of possible loss of ovarian function and its consequences, even if their ovaries are retained during hysterectomy. The women should be counseled regarding the possible requirement for hormone replacement therapy (HRT) following oophorectomy.

Next step is to decide the route of surgery: Vaginal route (vaginal hysterectomy), abdominal route (abdominal hysterectomy) or laparoscopic route [laparoscopic hysterectomy or laparoscopic assisted vaginal hysterectomy (LAVH)]. Usually vaginal hysterectomy is preferred over abdominal hysterectomy. Compared with abdominal hysterectomy, vaginal hysterectomy is associated with reduced rate of morbidity (shorter hospital stay and faster recovery) and other complications. Laparoscopic hysterectomy or LAVH is also associated with reduced rates of morbidity and complications (post-operative pain, hospital stay and recovery period) in comparison with abdominal hysterectomy. However LAVH may not be widely available as its performance requires specific laparoscopic training and skills. Various factors must be taken into consideration before deciding the route of surgery. Some of the factors, which need to be taken into account, are listed in table 18.8.

Table 18.8: Factors to be taken into consideration before deciding the route of surgery

Presence of other gynecological conditions or diseases
Uterine size
Location, number and size of uterine fibroids
Mobility and descent of the uterus
Size and shape of the vagina
History of previous abdominal surgery

When abdominal hysterectomy is decided upon, then both types of abdominal hysterectomies: The total method (removal of the uterus and the cervix) and subtotal method (removal of the uterus and preservation of the cervix) should be discussed with the woman.

Myomectomy

Surgical removal of myomas from the uterine cavity is termed as myomectomy. Although myomectomy allows preservation of the uterus, present evidence indicates a higher risk of blood loss and greater operative time with myomectomy in comparison to hysterectomy. Numerous techniques are used nowadays for performing myomectomy. These include the following: Performing a myomectomy through an abdominal incision (figure 18.8), vaginal incision, with help of a laparoscope (figure 18.9) or with help of a hysteroscope (figure 18.10). Removal of the myoma relieves symptoms in more than 75% of women. Summary of ACOG practice bulletin (2000) regarding the management of leiomyomas is enumerated in table 18.9.

There are times, when myomectomy is associated with uncontrollable bleeding and thus needs to be converted into an abdominal hysterectomy during the time of planned surgery.Therefore, if myomectomy is selected as the therapeutic option, the women should be counseled about small risk of reoperation and the risk of conversion to hysterectomy.

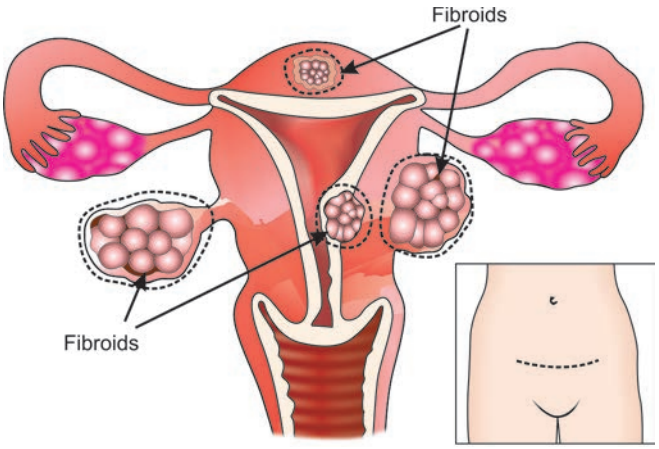


Fig. 18.8: Abdominal myomectomy

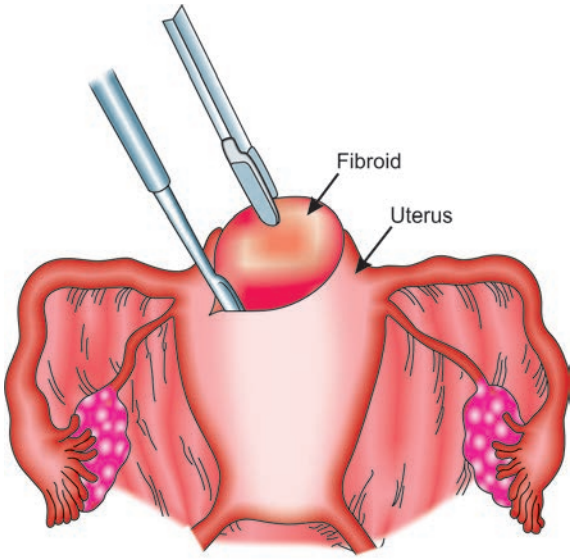


Fig. 18.9: Laparoscopic myomectomy

Table 18.9: Summary of ACOG practice bulletin (2000) for management of leiomyomas

Evidence level A (based on well designed, randomized controlled trials)

Hysterectomy is the definitive cure for symptomatic leiomyomas; however abdominal myomectomy is a safer and more effective option in women who wish to become pregnant.

Use of GnRH agonists and vasopressin pre-operatively at the time of myomectomy helps in reducing the amount of blood loss.

Evidence level C (based on evidence from expert committee reports or opinions and/or clinical experience of respected authorities)

Safety of laparoscopic myomectomy has yet not been established in women planning pregnancy.

Hysteroscopic myomectomy is an effective option for women with submucous fibroids.

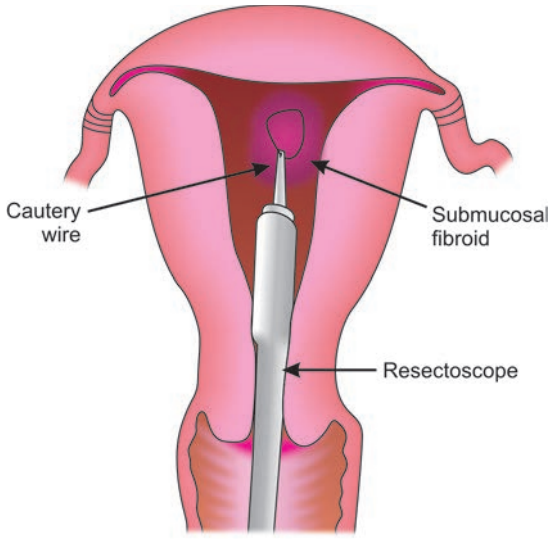


Fig. 18.10: Hysteroscopic myomectomy

Besides ACOG (2000), RCOG (1998) also suggests that the present evidence does not establish the safety and efficacy of laparoscopic myomectomy for women planning pregnancy. Hysteroscopic myomectomy has been considered as an effective option for controlling menorrhagia in women with submucous fibroids.

Some of the indications for myomectomy are listed in table 18.10. Myomectomy is a viable therapeutic alternative to hysterectomy in women with symptomatic myomas, who desire fertility. If the myoma (especially the submucosal or intramural type) is large in size (> 5 cm), most studies recommend that it must be removed. Large submucosal or intramural myomas not only may cause distortion of endometrial cavity, they may also result in menometrorrhagia. Both these factors have been shown to result in reduced fertility. Large myomas may also result in complications for the future pregnancies (miscarriage, preterm delivery, etc).

Any symptomatic myoma (for e.g. myoma which causes menometrorrhagia) also needs to be treated. However, finding of a small asymptomatic leiomyoma in an infertile woman is not an indication for immediate myomectomy. Uncertainty regarding surgery exists mainly for asymptomatic women along with the presence of mostly large intramural or subserous myomas in the uterus.

Table 18.10: Indications for myomectomy

Women with symptomatic myomas, desiring fertility
Large myomas (especially the submucosal or intramural type)
Any symptomatic fibroid, (which causes menometrorrhagia) also needs to be treated
When IVF is indicated (especially if the myoma results in the distortion of the uterine cavity)

Success rate of IVF is most significantly affected by presence of intramural or submucosal fibroids which distort the uterine cavity. Therefore presence of intramural or submucous myomas which distort the endometrial cavity in a woman undergoing IVF is also an indication for myomectomy. However, if the myoma does not distort the endometrial cavity, the indications for myomectomy are not so clear. The available evidence does not support myomectomy before ART in patients with asymptomatic myomas that do not significantly distort the uterine cavity or cause abnormal uterine bleeding.

Due to a high rate of myoma recurrence, a myomectomy is generally not recommended for women who have completed child bearing, yet continue to suffer from excessive heavy menstrual periods and from pelvic pressure and pain due to fibroids.

Risks Associated with Myomectomy

Risks associated with myomectomy are enumerated in table 18.11. Since there are numerous risks associated with myomectomy, the expected benefits of myomectomy must be weighed against the risks associated with the procedure, before carrying out this surgery. The most important complication associated with myomectomy is intraoperative blood loss. Thus crossmatched blood must be made available for transfusion. Also, anemia must be corrected before performing the elective myomectomy. Use of GnRH agonists prior to surgery may help in preventing anemia by reducing the blood loss related to menorrhagia. Before performing myomectomy, it is important to counsel the patient regarding the possibility that intraoperative findings may contraindicate myomectomy and require that hysterectomy be performed instead.

If pregnancy is desired, there is a risk of uterine rupture after myomectomy during delivery. This can occur irrespective of the route for myomectomy (abdominal, laparoscopic or hysteroscopic myomectomy) due to excessive dissection of myometrial muscles during the surgery.

Development of post-operative adhesions following myomectomy is an important complication of myomectomy. This complication has been shown to occur more with laparoscopic as compared to the abdominal procedure. In order to reduce the risk of development of post-operative intestinal adhesions, incisions over the peritoneal aspect of the posterior uterine wall must be avoided during surgery.

Recurrence of myomas post-operatively is another complication associated with myomectomy (more with laparoscopic as compared to the abdominal procedure). A small myoma at the time of surgery may get overlooked and not get removed. This may result in future recurrence of myoma post-operatively.

Table 18.11: Risks associated with myomectomy

Increased post-operative blood loss
Hysterectomy may be required during the surgery, if myomectomy appears dangerous or difficult
Increased risk of uterine rupture at the time of delivery
Need for mandatory cesarean section in case the patient achieves pregnancy
Increased risk for post-operative adhesions
Recurrence of myoma post-operatively

Deciding the Type of Myomectomy to be Performed

Myomectomy can be performed abdominally, laparoscopically or hysteroscopically. If myomectomy is being performed to regain fertility, the next question, which requires to be answered is, what type of myomectomy would be associated with best pregnancy outcome? Abdominal, laparoscopic or hysteroscopic? These various options are discussed below:

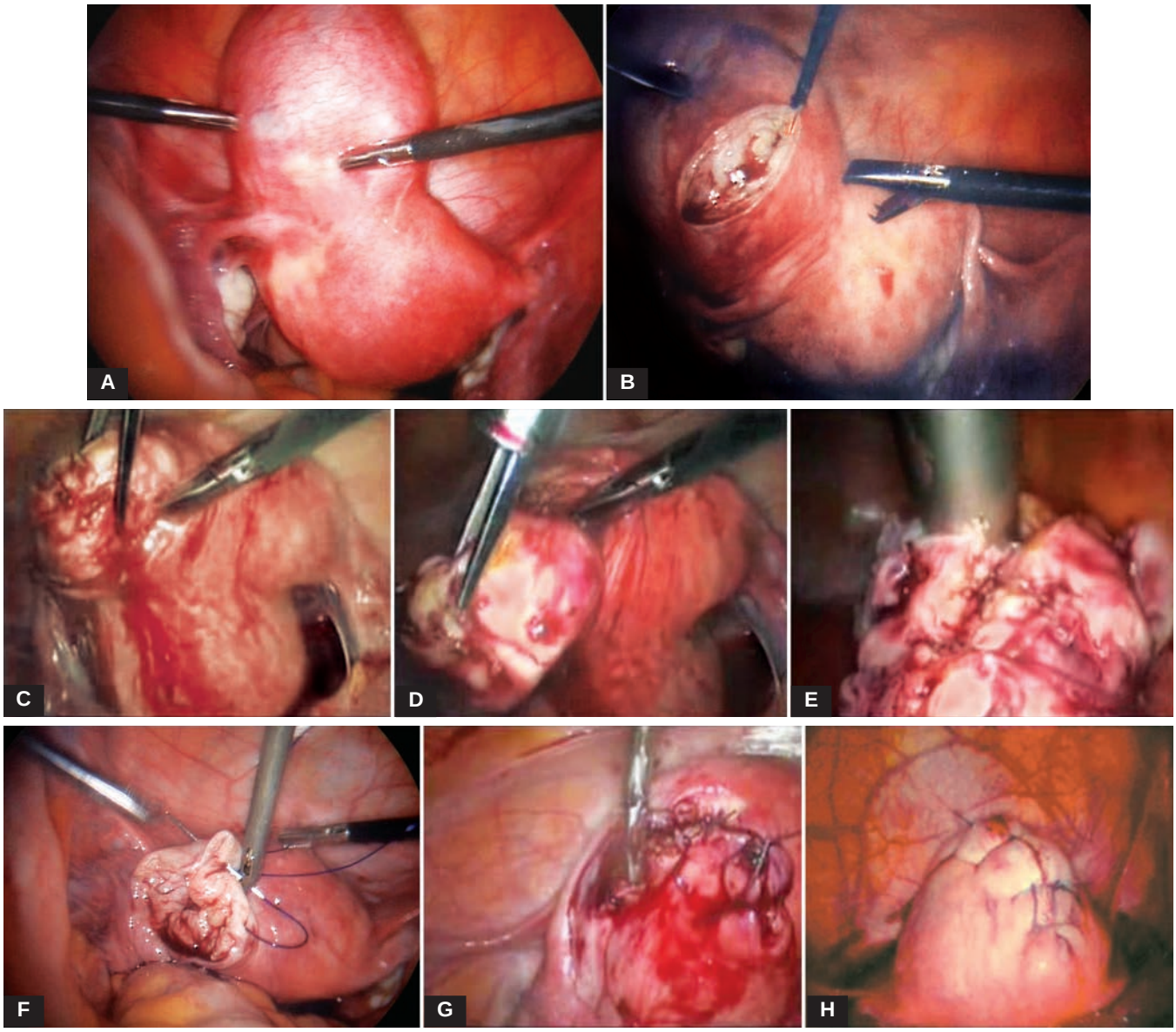
Abdominal myomectomy

The advantage of abdominal myomectomy is that large fibroids can be quickly removed. The surgeon is able to feel the uterus, which is helpful in locating myomas that may be deep in the uterine wall or are very small in size. The disadvantage of a laparotomy is that it requires an abdominal incision. The main complication of myomectomy is that it weakens the uterine musculature. As a result, a woman who becomes pregnant after a myomectomy may require a cesarean delivery to prevent rupture of the uterus at the myomectomy site.

Steps: After inspecting the uterus to determine the number and position of the fibroids, the uterine endometrium overlying the fibroid is cut, following which the fibroids are separated and removed from the normal uterine muscle. After the removal of the fibroids, normal uterine muscle can be sewn back together.

Laparoscopic myomectomy

Fibroids can also be removed by laparoscopy. The challenges of this surgery rest with the surgeon's ability to remove the mass through a small abdominal incision and to reconstruct the uterus. Laparoscopic myomectomy is most commonly used for removing subserosal fibroids. The steps for removal of a subserosal myoma are shown in figures 18.11A to H. Once the fibroids are removed, they are cut into pieces and removed with help of a morcellator. The advantage of laparoscopic myomectomy is that it this can be performed as an outpatient procedure and allows faster recovery in comparison



Figs 18.11A to H: (A) Presence of a subserous fibroid, which is handled laparoscopically (B) An incision given over the surface of fibroid (C) The myoma is gradually shelled out from the underlying myometrium (D) The myoma has been shelled out completely (E) The large fibroid is morcellated and removed from the body (F) Following the removal of myoma the small raw area left after removal is stitched together with vicryl sutures (G) The closure of uterine myometrium is almost complete (H) The myometrial suture line following the completion of surgery

to a conventional laparotomy. One of the disadvantage of the procedure is that extended time may be required for removing large fibroids from the abdomen. Since the surgeon cannot actually touch the uterus, it may be more difficult to detect and remove smaller myomas. Additionally, a uterus repaired laparoscopically is more likely to give away at the time of delivery in comparison to the uterus that is repaired abdominally. This is likely to be problematic in women desiring future pregnancy.

Procedure (figures 18.11A to H): Two or three small, half–inch incisions are made above the pubic hairline and the laparoscopic instruments are passed through these small incisions to perform the surgery. After reaching the uterus, the subserosal fibroid is grasped and freed from its attachments to the normal uterine muscle. In case of a subserosal fibroid attached by a stalk on the uterine surface, once the stalk of the subserosal fibroid has been cut and the fibroid is freed from the uterine surface, the fibroid can be cut up into small pieces

with a specially designed instrument called a morcellator and brought out of the abdomen through a small incision. The deeper the fibroid is embedded into the uterine muscle wall, the more difficulty may be encountered while removing it. In these cases, an incision is given over the surface of the fibroid, following which the fibroid is gradually shelled out from the uterine musculature or removed using a myoma screw. After the myoma has been completely freed from the uterine surface, it is removed using a morcellator. The uterine wall is repaired using laparoscopically applied sutures. Laparoscopic suturing with small instruments requires considerable amount of surgeon skill, experience and judgment. If future fertility is desired, then the strength of the uterine wall repair is important. Thus before undertaking laparoscopic myomectomy in a woman desiring future fertility, factors which are likely to influence uterine wall strength following repair, need to be taken into consideration. These include size of fibroid and closeness of the myoma to the endometrial cavity.

Advantages of laparoscopic myomectomy: Advantages of laparoscopic myomectomy are described in table 18.12. Since laparoscopic myomectomy is a less invasive procedure in comparison to the conventional abdominal myomectomy, it is associated with fewer complications in the operative and post-operative periods, compared to that of the abdominal procedure. Laparoscopic myomectomy results in significantly reduced hospital stay following surgery, reduced surgical morbidity and improved patient's outcome and patient's recovery. Blood loss during surgery is significantly less with laparoscopy.

Complications of laparoscopic myomectomy: Complications of laparoscopic myomectomy are listed in table 18.13. The most important complication following myomectomy is the development of adhesions post-operatively. Development of these post-operative adhesions is particularly important as these adhesions can trap the adnexa, resulting in tubal blockage, etc. Hence, this can impair the woman's fertility, resulting in further problems in women desiring future fertility. Development of adhesions post-operatively is less commonly associated with laparoscopic myomectomy in comparison to abdominal myomectomy. There has been a recent advancement in laparoscopic surgery, associated with the use of special substances, called adhesion barriers, which help prevent the formation of scar tissue after surgery. Small sheets of cloth-like material can be wrapped around the raw areas from surgery and this material prevents nearby tissue from adhering to the site of surgery (figure 18.12). After a few weeks, the material dissolves, leaving the newly healed surgery sites fairly free of adhesions. While the use of these barriers may not be completely perfect in preventing adhesions, they have been shown to help reduce the formation of adhesions.

Table 18.12: Advantages of laparoscopic myomectomy

Less invasive procedure
Fewer operative and post-operative complications (post-operative adhesions, blood loss, paralytic ileus, infection, etc)
Reduced surgical morbidity resulting in improved post-surgical outcomes
Significantly reduced hospital stay and quick recovery
May be performed as an outpatient surgery under general or regional anesthesia

Table 18.13: Complications of laparoscopic myomectomy

Development of uterine rupture during pregnancy (most commonly third trimester)
Development of post-operative adhesions
Recurrence of myoma after myomectomy
The procedure requires more level of skill and training in comparison to the abdominal surgery

As previously mentioned, the operative and post-operative complications associated with laparoscopic myomectomy are much less in comparison to abdominal myomectomy. One of the most important complications associated with any type of myomectomy is the risk of uterine rupture during pregnancy. Though both laparoscopic and abdominal myomectomies can result in uterine rupture, the timing of this drastic complication varies between the two procedures. While, uterine rupture following abdominal myomectomy commonly occurs during labor, that following laparoscopic myomectomy commonly occurs during the third trimester of pregnancy (after 36 weeks).

Some possible reasons for the uterus to rupture following laparoscopic myomectomy are listed in table 18.14.

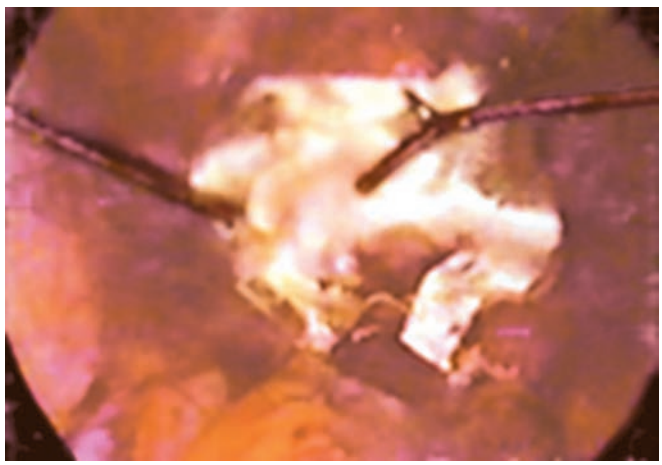


Fig. 18.12: Use of adhesion barriers for prevention of post-operative adhesions

Myomectomy is a very challenging procedure because it may require extensive manipulation and reconstruction of the uterine tissue. Moreover, the uterus is an organ which undergoes remarkable structural changes (hypertrophy and hyperplasia), both during pregnancy and puerperium. Massive enlargement of the uterus during pregnancy can result in weakening of the uterine scar, increasing the risk for uterine rupture.

Besides this natural disadvantage, the microsurgical procedure (laparoscopic myomectomy) is associated with less perfect reconstruction of uterine tissue in comparison to abdominal myomectomy. As a result, the risk of uterine rupture is more with laparoscopic procedure in comparison to abdominal procedure. Also, when the myomas are deeply embedded in the myometrium or are large in size or numerous, proper repair of the uterine wall may not be possible with laparoscopic procedure. Wide use of electrosurgery for obtaining hemostasis during laparoscopic surgery may be another factor involved in reducing the scar strength. Use of electrosurgery may result in poor vascularization, tissue necrosis and adverse effects on scar strength. Excessive bleeding during the surgery can result in hematoma formation, which can weaken the uterine walls by resulting in the formation of fibrous tissue.

During myomectomy, extensive manipulation of uterine tissue is performed. The uterine muscles have an ability to regenerate slowly. If the edges of the wound are accurately sutured, the healing of the uterine wound takes place through regeneration of myometrial muscles. This results in strengthening of the uterine walls. On the other hand, if the edges of the wound are not approximated properly, healing occurs by secondary intention, thereby resulting in the formation of fibrous tissue, which considerably weakens the post-operative scar. Thus, in order to avoid scar rupture during pregnancy, precautions to be taken are listed in table 18.15.

Another possible complication is the recurrence of myoma following surgery. Laparoscopic myomectomy, due to limited exposure may result in less effective removal of the fibroid tissue. This is especially the case if multiple myomas are present in the uterus. Incomplete removal of myoma tissue may result in development of recurrence following laparoscopic myomectomy.

Table 18.14: Possible reasons for uterine rupture following laparoscopic myomectomy

Natural tendency of the uterus to undergo hyperplasia and hypertrophy during pregnancy
Less perfect reconstruction of uterine tissues
Proper repair of the uterine wall may not be possible (especially with large, numerous or deeply embedded uterine myomas
Presence of a hematoma over scar tissue
Wide use of electrosurgery for obtaining hemostasis during laparoscopic surgery

Table 18.15: Precautions to be taken to prevent scar rupture after laparoscopic myomectomy

Proper approximation of the edges of the incision (inverting the edges of the myometrium)
One must never use radiofrequencies to achieve hemostasis during surgery
Long time interval must be planned between surgery and pregnancy (greater than one year)
Elective cesarean section in these patients before 36 weeks

Hysteroscopic myomectomy

Hysteroscopic myomectomy forms the procedure of choice for completely submucosal myomas or those myomas having less than 50% extension into the myometrium.

Hysteroscopic myomectomy can be performed as a simple outpatient procedure where a hysteroscope is placed into the uterine cavity and the leiomyomas are resected out (figures 18.13A to C). The technique of hysteroscopic resection of submucous leiomyomas was first described by Neuwirth and Amin in 1976**.** Since the use of hysteroscope requires instillation of fluid inside the uterine cavity, it is important to

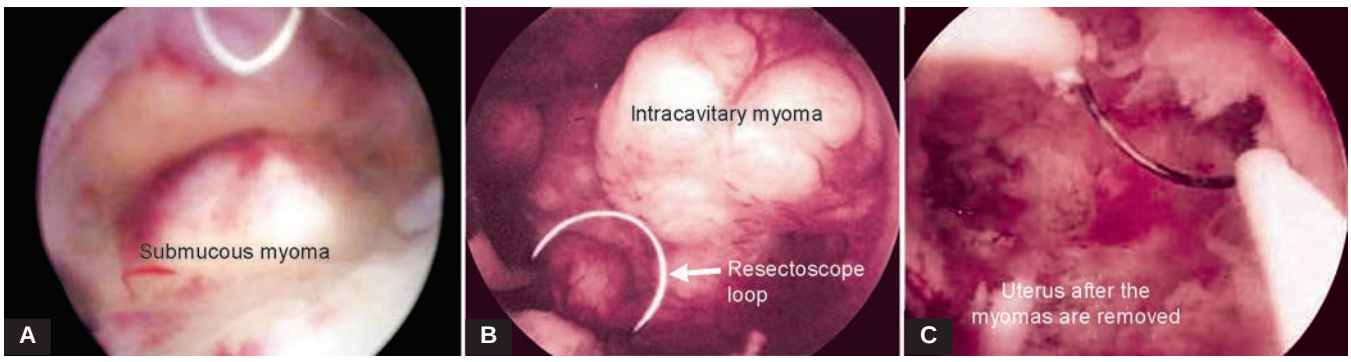


Fig. 18.13A to C: (A) Hysteroscopic view showing presence of a submucous fibroid (B) Beginning of the hysteroscopic resection of submucous fibroid (C) Completion of the hysteroscopic resection of submucous fibroid

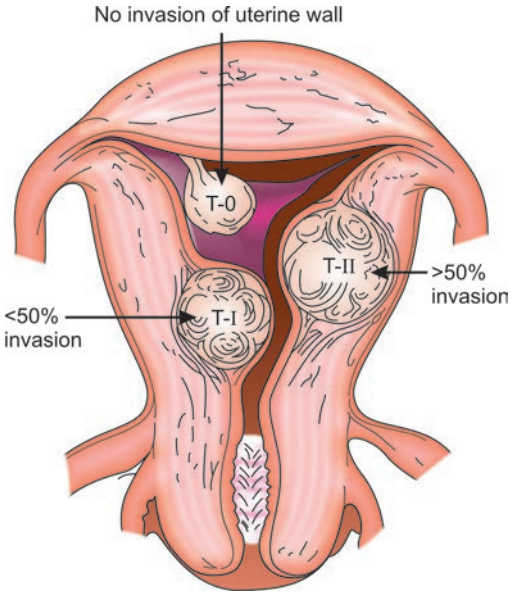


Fig. 18.14: European Society of Hysteroscopy classification of myomas

monitor ongoing fluid balance carefully during hysteroscopic removal of fibroids. According to the European Society of Hysteroscopy, submucous leiomyomas have been classified into three categories depending on the degree of myometrial invasion (figure 18.14). T-0 corresponds to pedunculated submucous leiomyomas. T-I represents submucous leiomyomas with less than 50% invasion into the myometrial wall and T-II those with greater than 50% invasion. Myomas belonging to the categories T-0 and T-1 should be attempted using a hysteroscope. However, hysteroscopic resection should not normally be attempted in fibromyomas belonging to T-2 category. This is so because, when submucous myomas have intramural extensions greater than 50%, hysteroscopic resection may be associated with a higher rate of complication, including increased rate of conversion to laparotomy, higher rates of intravascular extravasation of distending media, prolonged operating times and increased requirement for repeat surgery. Therefore, endoscopic removal of intramural or submucosal leiomyomas larger than 5 cm in diameter or with myometrial involvement greater than 50% should be attempted only by very experienced endoscopists.

DESTRUCTION OF THE FIBROIDS

Several procedures have been designed to treat the myomas by destroying their blood supply instead of removing them.

Myoma Coagulation (Myolysis)

Myoma coagulation, also known as myolysis, is a laparoscopic procedure which helps in shrinking the fibroids without removing them. The procedure is performed laparoscopically, in which either a laser or a cryo needle is passed directly into the fibroid to destroy both the fibroid tissue and the blood vessels feeding it. The destroyed fibroid tissues are eventually absorbed by the uterus. Presently, myoma coagulation is not recommended for women desiring future fertility because the procedure is thought to result in the formation of scar tissue, which is likely to weaken the strength of the uterine wall. Due to this, there are high chances of uterine rupture during the pregnancy in case the woman conceives following myolysis. Although some women who underwent the procedure have conceived and have been uneventfully delivered by cesarean section, the fertility and pregnancy outcomes after laparoscopic myolysis remain unknown. Presently, however the patients undergoing myolysis are advised not to attempt to conceive following the procedure. The indications for myolysis include symptomatic patient presenting with menorrhagia, pelvic pain or pressure symptoms due to fibroids pressing upon the adjacent organs; presence of four or fewer myomas with a size of less than 5 cm; or if the size of the largest subserosal myoma is less than 10 cm in diameter. Other concomitant laparoscopic pelvic surgery such as adhesiolysis, excision of endometriosis or adnexal surgery, can be carried out at the same time. Sometimes, concomitant hysteroscopic endometrial ablation is performed at the end of laparoscopic myolysis to further assist in the treatment of menorrhagia. Complications associated with myolysis include pelvic infection, bacteremia and bleeding. Thus, laparoscopic myolysis may present an alternative to myomectomy or hysterectomy for selected women with symptomatic intramural or subserous fibroids who wish to preserve their uterus, but do not desire future fertility.

Uterine Artery Embolization (UAE)

Uterine artery embolization is a relatively new, novel technique for treatment of uterine fibroids, which was first performed by Ravina, a French Gynecologist in 1995. UAE is a nonhysterectomy surgical technique, which helps in reducing the size of the uterine fibroids by shrinking them, without actually removing them. Besides uterine fibroids, the technique of embolization has been used to treat various other medical pathologies like, inoperable cancers, brain aneurysms, arteriovenous shunts in the lung, etc.

Procedure

The procedure of UAE itself lasts between 1 to 2 hours. Though anesthesia is usually not required, the procedure is usually performed under sedation. The interventional radiologist introduces and manipulates a catheter through the femoral artery into the internal iliac and uterine arteries (figure 18.15). Once the fibroids are visualized on X-ray, an

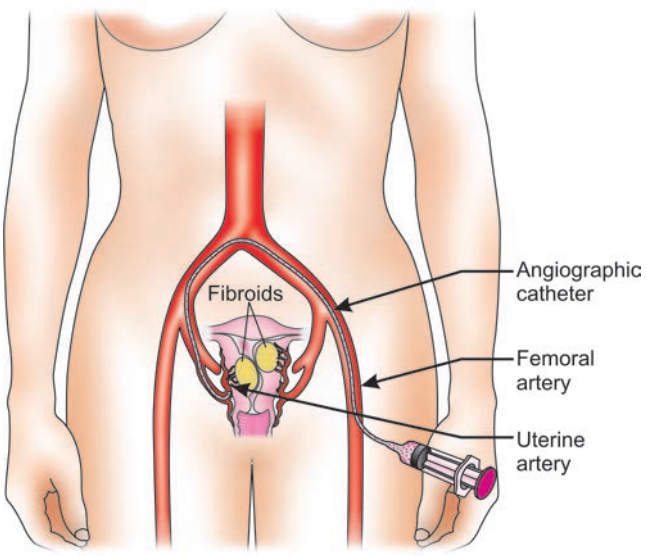


Fig. 18.15: Passing the catheter through femoral artery into the uterine artery

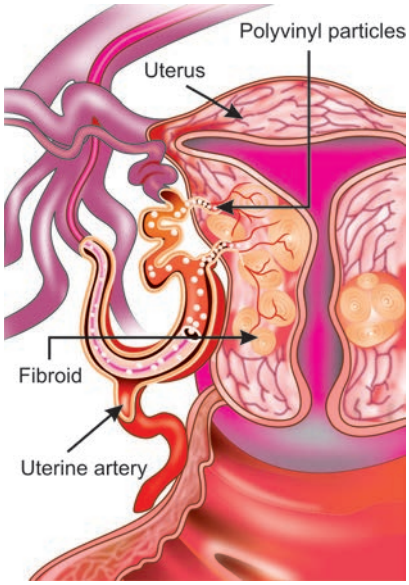


Fig. 18.16: Blocking the blood supply of fibroids

embolizing agent [gelatin microspheres (trisacryl gelatin) or polyvinyl alcohol] is injected, which helps in blocking both the uterine arteries, thereby cutting off the blood supply to the fibroids (figure 18.16). Compared to normal uterine cells, fibroid cells are much more sensitive to low oxygen saturation. Thus, due to the lack of sufficient blood supply, the fibroids become avascular and shrink, ultimately resulting in cell death, their degeneration and eventual absorption by the myometrium. The normal myometrium, on the other hand, receives new blood supply from vaginal and ovarian vasculature. As fibroids begin to undergo necrosis, any active bleeding commonly subsides. The dying cells of the fibroids may release toxins, which may cause irritation of the surrounding tissues, thereby causing pain and inflammation in the first few days following the procedure. Though the rate of recovery usually varies from one woman to the other, it usually takes a few months for the fibroids to fully shrink and the full effect of the procedure to be evident.

Till date, this procedure has been performed in approximately 30,000 women in the United States and another 20,000 women worldwide. As a result, presently there is limited evidence regarding the safety and efficacy of the procedure. The world-wide success rate of the procedure in producing improvement of symptoms has been considered to be approximately 85%. UAE may be the right treatment choice in women in whom the symptomatic relief may be obtained by shrinking the fibroids to a little more than half their present size. However, UAE may not be very helpful for women with extremely large fibroids because they may not shrink enough to make a significant difference in the symptoms. Since the technique of UAE has been available since 1997, there is presently no long-term follow up information. Three to six months following UAE, the uterus and fibroids are likely to have decreased by about 40% in size. About 90% of women who were symptomatic due to the large size of their fibroids would experience a significant improvement in their symptoms. About 10% to 15% of women who have UAE may continue to suffer from menorrhagia and may require some other treatment modality.

Complications

Major complications: Major complications such as pulmonary embolism, arterial thrombosis, groin hematomas, local infections, guide-wire perforation of arteries, allergic reaction to contrast medium, endometritis, ischemia of pelvic organs, sepsis and death are rare events with UAE. These may occur in approximately 0.5% cases of embolization performed for symptomatic fibroids. Till date, only four fatalities have been reported among more than 30,000 procedures which have been performed worldwide.

Early acute abdominal pelvic pain: Nearly all women may experience some degree of acute pain within the first few weeks, often requiring hospitalization with intensive pain management protocols and monitoring. The pain is thought to be due to nonspecific ischemia of the uterus and fibroids. It often responds to pain control with analgesics like opiates and non-steroidal antiinflammatory drugs.

Post-embolization syndrome: Following UAE, some women may develop low-grade fever, leukocytosis, increasing pelvic pain and a vaginal discharge. Many of these women may also experience malaise, nausea and exhaustion.

This combination of these symptoms is known as post-embolization syndrome and is probably related to transient fibroid degeneration and uterine ischemia. The condition is usually self-limiting and symptoms may last from few days to weeks; the patient may be hospitalized for antibiotic therapy. The post-embolization syndrome normally regresses over time. However, if the symptoms seem to worsen over the period of time, an examination and evaluation for infection is important. In presence of severe infection, hysterectomy may be required.

Misembolization: Since the particles that are used for embolization are very small, in a few instances, the particles may travel through blood vessels to areas besides the fibroid tissue, where they are actually intended to go. This is termed as misembolization.

Infection: The incidence of febrile morbidity and sepsis following embolization has been reported to be between 1.0% and 1.8%. Some of the infections, which can occur, include pyometra with endomyometritis, bilateral chronic salpingitis, tubo-ovarian abscess and infection of the myomas. The most frequent pathogen that has been isolated is *Escherichia coli*. Though some women may respond to antibiotic therapy, others may require prolonged hospitalization, intensive therapy and sometimes even hysterectomy. Prophylactic antibiotics have not been shown to be effective and should be used only in women at higher risk of infection.

Affect on fertility: The ovaries may stop functioning in about 5% of the women, following embolization and early menopause may result. This may be a particularly devastating complication for young patients who wish to conceive in future. The ovarian function may cease due to reduced blood supply. The blood supply to the ovaries may be blocked off due to misembolization or as a result of the blockage of uterine artery in women in whom the main blood vessels supplying the ovaries branches off from the uterine artery. As a result, if the uterine artery is blocked, the blood supply to the ovary is also blocked off and the ovaries cease functioning.

Pregnancy outcomes: Though this procedure helps in preserving the uterus, pregnancies following UAE have been reported to be at higher risk in comparison to the general population. Women becoming pregnant following UAE may be at significantly increased risk for postpartum hemorrhage, preterm delivery, cesarean delivery, malpresentation and uterine rupture.

Presently, however there is limited evidence regarding the pregnancy outcomes following UAE. As a result, the women who wish to conceive in future are not recommended to use UAE as treatment option for their fibroids. Better evidence in form of future well-designed, randomized studies is required before UAE can be confidently recommended to the women with fibroids desiring future fertility.

Risk of underlying malignancy: Similar to myolysis, no samples are sent for biopsy in UAE; therefore any underlying malignancy is likely to remain undetected. However this is unlikely to cause any problem because the chances of malignancy in cases of fibroids are extremely low.

Persistent or chronic pain: In 5% to 10% of women, the pain persists for more than 2 weeks. Presence of uterine infection should be ruled out in these cases. Persistent pain in the absence of infection or pain lasting longer than 2 to 3 months may require surgical intervention.

Transcervical fibroid tissue passage: Overall, transcervical fibroid tissue passage may occur in approximately 2.5% of the patients. This may be associated with severe pain, infection or bleeding and is one of the most common complications requiring hospitalization.

Laparoscopic Uterine Artery Ligation

Gynecologists have recently created a surgical technique to surgically ligate off the uterine arteries rather than blocking them with embolization agents using the laparoscope. The advantages of the surgical uterine artery ligation over UAE are that there is a little risk of misembolization to other areas and there is no theoretical risk of premature menopause that may accompany UAE. If, however, some women have a branch of the uterine artery as the only blood supply to the ovaries, then surgical ligation of the uterine artery may cut off blood supply to the ovaries, resulting in an early menopause for these women.

Focused Ultrasound (MRgFUS) for Treatment of Fibroids

This is another new technique for destruction of fibroids, which is still under the research stages. In this technique, ultrasound energy, which uses high-frequency energy in the form of sound waves, is used for destroying fibroids. This energy can be focused on a single point inside a patient's body (for example on a fibroid) so that the heat created by the energy is able to destroy the fibroid cells (figure 18.17). Since the technique uses MRI to focus the ultrasound waves, hence the term "magnetic resonance guided focused ultrasound (MRgFUS)" is used to describe this technique. Still in its early stages of development, focused ultrasound is a noninvasive alternative to treat fibroids. The use of focused-ultrasound is associated with very low risk and rapid recovery. However, presently there is limited evidence regarding the safety and efficacy of the procedure, therefore, it is not recommended for women desiring future fertility. In future, with

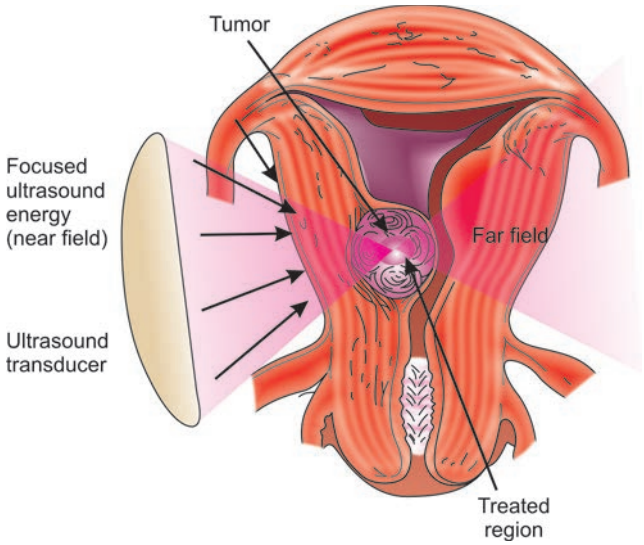


Fig. 18.17: Focused ultrasound (MRgFUS) for treatment of fibroids

the improvement in technology, MRgFUS would probably serve as a proven alternative for women with symptomatic fibroids.

ExAblate 2000 System

This is a new device, approved by the Food and Drug Administration, based on MRgFUS technique which serves as a noninvasive method of treating fibroids, while retaining the uterus. The procedure involves repeated targeting and heating of fibroid tissue, using ultrasound energy while the patient is under continuous MR imaging. The focused ultrasound energy can be used to generate sufficient heat so as to cause protein denaturation and cell death. In this device, magnetic resonance imaging is used for visualizing patient anatomy, mapping the volume of fibroid tissue to be treated, monitoring the temperature of the uterine tissue after heating and monitoring the focused ultrasound beam that heats and destroys the fibroid tissue using high-frequency, high-energy sound waves. The procedure can last as long as three hours. While many fibroids can be treated with this device, fibroids close to sensitive organs such as the bowel or bladder and those outside the image area cannot be treated. Though the device has been shown to successfully treat fibroid related menorrhagia in nearly 70% of the women within six months of treatment, the remaining 30% have been observed to require an alternative surgical treatment for fibroids within a year. This implies that while the ExAblate treatment may succeed in reducing the symptoms from the treated fibroids, there may be a recurrence of fibroids in some women, thereby requiring an additional treatment either with ExAblate or an alternative treatment modality. The device labeling indicates that no more than two treatments should be performed in a two-week period.

Complications

Various complications related with uterine myomas include the following:

- Severe pain
- Infertility
- Toxic shock syndrome
- Anemia

Torsion

Torsion of the pedicle of a subserous pedunculated leiomyoma may interfere first with venous, then with the arterial supply. This may result in an initial extravasation of blood followed by the eventual development of gangrene.

Ascites/Pseudomeigs Syndrome

Very mobile pedunculated subserous tumors may produce ascites by causing mechanical irritation of the peritoneum. Sometimes, ascites may be accompanied by a right sided hydrothorax, resulting in the development of a condition known as pseudo-meigs syndrome.

Infection

A submucous leiomyoma may sometimes become infected and ulcerated at its lower pole.

Secondary Changes (Degeneration)

Certain degenerative changes can occur in a fibroid, which can cause an interference with capsular circulation. As a result of the circulatory disturbances, the tumor becomes painful, tender, softened and enlarged. Some such degenerative changes taking place in the fibroids are described below:

- *Atrophy:* Shrinkage of the fibroid can occur as a result of reduced blood supply of the fibroid, usually following menopause.
- *Hyaline degeneration:* This is the commonest type of degeneration in which, the fibrous tissue cells are replaced by a homogeneous substance which stains pink with eosin. The bundles of muscle fibers become isolated and die off, causing large areas of the tumor to become structureless. Eventually, the liquefaction of hyaline material occurs, leaving behind ragged cavities filled with colorless or blood stained fluid.
- *Calcification:* This type of degeneration may initially occur with the presence of fatty deposits within the

leiomyomas. At a later stage in this process, there is deposition of phosphates and carbonates of calcium along the course of blood vessels. Calcification usually begins at the periphery of the fibroid and can be identified with the help of radiography. At a later stage there may be widespread deposition of calcium throughout the tumor resulting in "wombstone" appearance or a peripheral distribution resulting in an "egg-shell" appearance.

- *Myxomatous/cystic degeneration*
- *Red/carneous degeneration*: This type of degeneration of uterine fibroid usually develops during pregnancy. It may be associated with constitutional symptoms like malaise, nausea, vomiting, fever and severe abdominal pain. The myoma may become soft and necrotic in the center and is diffusely stained red or salmon pink in color. Though the pathogenesis of the condition is not yet clear, it is believed that the purple-red colour of the myoma is probably due to the thrombosis of blood vessels supplying the tumor. The myoma may also develop a peculiar fishy odor due to infection by the coliform organisms. Although the patient may develop mild leucocytosis and a raised ESR, the condition is essentially an aseptic one. It needs to be differentiated from other conditions including appendicitis, twisted ovarian cyst, accidental hemorrhage etc. Ultrasound examination usually helps in establishing the correct diagnosis. On ultrasound examination, the tumor shows a mixed echodense and echolucent appearance. Red degeneration occurring during pregnancy must be managed conservatively. The patient must be advised bed rest and prescribed analgesics to relieve the pain. The acute symptoms subside gradually within the course of 3–10 days and pregnancy then proceeds uneventfully.
- *Sarcomatous change*: Occurrence of malignant changes in a leiomyoma is an extremely rare occurrence. According to Jeffcoate, sarcomatous changes are found in only 0.2% of tumors. Malignancy rarely develops in a woman under the age of 40 years. A suspicion of malignancy must be kept in mind in case of sudden increase in the size of fibroid, sudden development of pain or tenderness in the myoma, systemic upset and pyrexia or postmenopausal bleeding. Macroscopically a sarcomatous tumor appears grayish in color with areas of necrosis and hemorrhage (figure 18.18). The consistency of sarcoma is soft and friable and not firm like that of a fibroid. The malignant process usually begins at the center of the tumor and the diagnosis is made on the histopathological examination of the removed myoma specimen. Sarcomas with a malignant behavior usually have 10 or more mitoses per high power yield; are non-encapsulated and therefore may rapidly spread via the bloodstream.

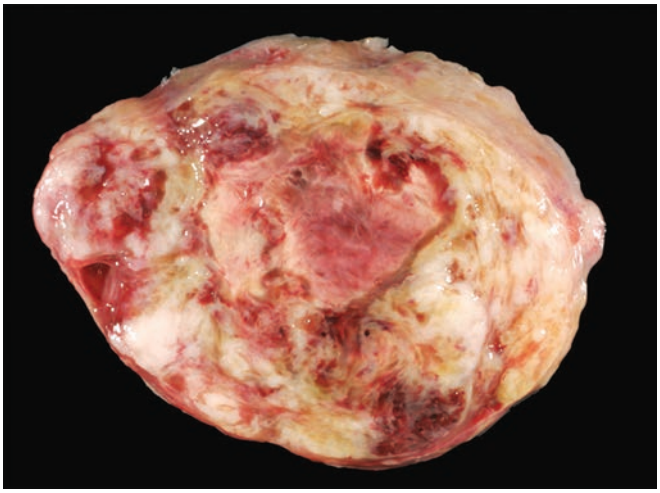


Fig. 18.18: Gross specimen of leiomyosarcoma

Fibroids and Pregnancy

Possible effects of fibroids on pregnancy

Majority of fibroids remain unchanged in size during pregnancy. Most fibroids remain uncomplicated during pregnancy. However, they may show an invariable enlargement during pregnancy due to presence of congestion, edema and degeneration; they usually return back to their original size afterwards. Some possible adverse effects related to the presence of fibroids during pregnancy are as follows:

- Abortion
- Preterm labor
- Preterm prelabor rupture of membranes
- Placental abruption
- IUGR
- Malpresentation
- Obstructed labor
- Cesarean section and cesarean hysterectomy.
- PPH
- Very large sized uterine myomas can cause respiratory embarrassment and urinary retention.

Important Questions and Answers

Q.1. What would be the best treatment option in the above described case study?

Ans. Patient's age, desire for future fertility and number, size and location of uterine myomas are important parameters for deciding the appropriate treatment option. Since the age of woman in the above mentioned case study is 33 years and she desires future fertility, myomectomy appears to be the best treatment option. The route for myomectomy needs to be determined based on many factors including the type

of myomas, degree of myometrial invasion and number of myomas. The severity of the problem and its duration must be taken into account. In this case the woman has a submucosal fibroid of size 4 cm on the ultrasound, having less than 50% myometrial invasion. Therefore the best option appears to be hysteroscopic resection.

Q.2. What are the possible medicolegal pitfalls associated with the case of menorrhagia?

Ans. There are the following possible medicolegal pitfalls associated with the cases of menorrhagia:

- Ruling out pregnancy: If the patient with menorrhagia belongs to the reproductive age group, pregnancy should be ruled out by performing a pregnancy test in order to rule out any pregnancy related complication (threatened or incomplete abortion, ectopic pregnancy or retained products of conception) as the cause of bleeding. After ruling out pregnancy, imaging studies should be ordered.
- Ruling out malignancy: Every high-risk or postmenopausal patient with uterine bleeding first must be evaluated for endometrial or other gynecological malignancy.
- Risk of pregnancy with use of GnRH agonists: When treating patients with progestin therapy or with GnRH therapy, the women must be informed that pregnancy may still be possible since these drugs are not a form of birth control. Since the safety of these drugs on pregnancy is not known, an effective form of contraception must be used in these cases.

Q.3. Is there any link between leiomyomas and cancer?

Ans. Fibroids are benign uterine growths. Furthermore, these fibroids usually do not turn malignant. The rate of malignancy in a fibroid uterus is about 0.5%. Also, the rate of occurrence of uterine leiomyosarcomas is extremely low, with the incidence being about 0.67/1000 women per year. The average age of women who develop fibroids is 38. Although sarcomas can rarely occur in young women, the average age of a woman who develops a sarcoma is 63. So, in a young woman with fibroids, there is not much risk of malignancy. According to a recent study, diagnosis of uterine sarcoma can be reliably made using a combination of a contrast (enhanced) MRI and a blood test called LDH. At the time of the MRI, a liquid dye called gadolinium is injected into a blood vessel. Since the sarcoma contains more blood vessels than normal uterine muscle, an enhanced image would be produced on the MRI. On the other hand, LDH is an enzyme made in muscle cells. The sarcoma is supposed to produce LDH isoenzyme 3 in high quantities. Therefore presence of an abnormal image on contrast MRI and increased LDH-3 levels can imply that a sarcoma is present. However, these tests are still in the research stages and they need to be confirmed by further well designed studies in future before they can be given total acceptance in clinical practice.

Q.4. What should you do if the patient's fibroid is observed to be increasing in size?

Ans. If the patient's fibroids are observed to be growing, she should be called for a repeat pelvic examination after every one to three months. If the fibroid suddenly becomes symptomatic or increases in size, then surgery may be considered. Since, the incidence of sarcomas is so low, it is not clinically justifiable to believe that a growing fibroid indicates malignancy. However, if the patient is postmenopausal, any growth in the uterus may be a cause for concern. In these cases, endometrial carcinoma must be ruled out first.

Q.5. Besides submucous fibroids, what are the other lesions in the uterus that can be diagnosed using a hysteroscope?

Ans. The most common lesions found during diagnostic office hysteroscopy include cervical and uterine polyps, submucous myomata, uterine septae, intrauterine adhesions, endometrial hyperplasia and endometrial cancer.

Q.6. Can fibroids cause infertility?

Ans. The relationship between myomas and infertility is still controversial and has been a subject of extensive debate. Mere presence of myomas in an infertile patient should not be considered as a cause of her infertility. Firstly, she should be investigated for all the other common causes of infertility (including the tubal factor, the ovarian factor, male factor etc). Only after all the other common causes of infertility in a woman have been ruled out, presence of myomas may be considered as the cause for infertility in a woman. Uterine myomas may be present in approximately 27% of infertile women and of these 50% may become pregnant following a myomectomy. The extent to which presence of myomas can influence fertility in a woman depends upon the position of fibroids inside the uterus, the number of fibroids and their size. For detailed description regarding how the presence of myomas can influence fertility, please refer to chapter 26.

Q.7. How can presence of leiomyomas affect pregnancy?

Ans. Presence of leiomyomas in a pregnant patient can result in numerous complications. For example, patient with fibroids during pregnancy may have increased incidence of bleeding in the first trimester, premature rupture of membranes, malpresentations (breech presentation), placental abruption, prolonged labor and high rate of cesarean section.

Q.8. Does growth of uterine fibroids relate to fibrocystic change of breasts?

Ans. No, uterine fibroids and fibrocystic changes of breast are totally different and unrelated conditions. Development of fibroids does not cause an increased likelihood for any other benign or cancerous conditions of the breasts.

Bibliography

1. Ascher SM, Arnold LL, Patt RH et al: Adenomyosis: Prospective comparison of MR imaging and transvaginal sonography. Radiology. 1994;190:803.
2. Berek JS. Abnormal bleeding. In: Berek JS, Olive DL, eds. Novak's Gynecology - Self-Assessment and Review. 12th ed. Philadelphia: Lippincott Williams & Wilkins; 1996:331-98.
3. Bernard JP, Lecuru F, Darles C et al. Saline contrast sonohysterography as first-line investigation for women with uterine bleeding. Ultrasound Obstet Gynecol. 1997;10:121.
4. Bonilla-Musoles F, Simon C, Serra V et al. An assessment of hysterosalpingosonography (HSSC) as a diagnostic tool for uterine cavity defects and tubal patency. J Clin Ultrasound. 1992;20:175.
5. Boujida VH, Philipsen T, Pelle J, et al. Five-year follow-up of endometrial ablation: Endometrial coagulation versus endometrial resection. Obstetrics and Gynecology. 2002;99:988-92.
6. Campbell S, Bourne TH, Tan SL, Collins WP: Hysterosalpingo contrast sonography (HyCoSy) and its future role within the investigation of infertility in Europe. Ultrasound Obstet Gynecol. 1994;4:244.
7. Cicinelli E, Romano F, Anastastio PS. Transabdominal sonohysterography, transvaginal sonography and hysteroscopy in the evaluation of submucous myomas. Obstet Gynecol. 1995;85:42.
8. Cohen BJ, Gibor Y. Anemia and menstrual blood loss. Obstet Gynecol Surv. 1980;35(10):597-618.
9. Cooper KG, et al. A randomised comparison of medical and hysteroscopic management in women consulting a gynaecologist for treatment of heavy menstrual loss. Br J Obstet Gynaecol. 1997;104:1360-66.
10. DeCherney AH, et al. Current Obstetric and Gynecologic Diagnosis and Treatment. 9th ed. New York. McGraw-Hill Medical; 2003.
11. Dodson MG. Use of transvaginal ultrasound in diagnosing the etiology of menometrorrhagia. J Reprod Med. 1994;39(5): 362-72.
12. el Senoun GS, Mousa HA, Mahmood TA. Medium-term follow-up of women with menorrhagia treated by rollerball endometrial ablation. Acta Obstetricia et Gynecologica Scandinavica. 2000;79:879-83.
13. Fleischer AC, Vasquez JM, Cullinan JA, Eisenberg E: Sonohysterography combined with sonosalpingography: Correlation with endoscopic findings in infertility patients. J Ultrasound Med. 1997;16:384.
14. Glasser MH, Zimmerman JD. The HydroThermAblator system for management of menorrhagia in women with submucous myomas: 12 to 20 month followup. J Am Assoc Gynecol Laparosc. 2003;10(4):521-7.
15. Goldberg J, Pereira L, Berghella V. Pregnancy after uterine artery embolization. Obstet Gynecol. 2002;100:869-72.
16. Hillis SD, Marchbanks PA, Peterson HB. Uterine size and risk of complications among women undergoing abdominal hysterectomy for leiomyomas. Obstet Gynecol. 1996;87:539-43.
17. Hricak H, Tscholakoff D, Heinrichs L et al. Uterine leiomyomas: Correlation of MR, histopathologic findings, and symptoms. Radiology. 1986;158:385.
18. Hurskainen R, Teperi J, Rissanen P, et al. Clinical outcomes and costs with the levonorgestrel-releasing intrauterine system or hysterectomy for treatment of menorrhagia: randomized trial 5-year follow-up. Journal of the American Medical Association. 2004;291:1456-63.
19. Istre O, et al. Treatment of menorrhagia with levonorgestrel intrauterine system versus endometrial resection. Fertil Steril. 2001;76:304-9.
20. Kadir RA, Economides DL, Sabin CA, et al. Frequency of inherited bleeding disorders in women with menorrhagia. Lancet. 1998;351(9101):485-9.
21. Learman LA, Summitt RL, Varner RE. Hysterectomy versus expanded medical treatment for abnormal uterine bleeding: Clinical outcomes in the medicine or surgery trial. Obstet Gynecol. 2004;103(5 Pt 1):824-33.
22. Lethaby A, Hickey M. Endometrial destruction techniques for heavy menstrual bleeding (Cochrane review). In: The Cochrane Library. Wiley, Chichester, UK.
23. Lethaby AE, Cooke I, Rees M. Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding (Cochrane review). In: The Cochrane Library. Wiley, Chichester, UK.
24. Long CA, Gast MJ. Menorrhagia. Obstet Gynecol Clin North Am. 1990;17(2):343-59.
25. Mendelson EB, Bohm-Velez M, Joseph N, Neiman HL. Endometrial abnormalities: Evaluation with transvaginal sonography. AJR Am J Roentgenol. 1988;150:139.
26. Narayan R, Goswamy RK. Transvaginal sonography of the uterine cavity with hysteroscopic correlation in the investigation of infertility. Ultrasound Obstet Gynecol. 1993;3:129.
27. National Institute for Health and Clinical Evidence. Heavy menstrual bleeding. January 2007. Clinical guideline CG44. Available at http://www.nice.org.uk/CG44 (accessed June 2009).
28. Nehzat C, Nehzat F, Silfen SL et al. Laparoscopic myomectomy. Int J Fertil. 1991;36:275.
29. Nehzat C. The "cons" of laparoscopic myomectomy in women who may reproduce in the future. Int J Fertil. 1996;41:1.
30. Neuwirth RS, Amin HK. Excision of submucous fibroids with hysteroscopic control. Am J Obstet Gynecol. 1976;126: 95.
31. Parker WH, Fu YS, Berek JS. Uterine sarcoma in patients operated on for presumed leiomyoma and rapidly growing leiomyoma. Obstet Gynecol. 1994;83:414-8.
32. Pritts EA. Fibroids and infertility: A systematic review of the evidence. Obstet Gynecol Surv. 2001;56:483-91.
33. Ravina JH, Herbreteau D, Ciraru-Vigneron N, Houdart E, Aymar A, and Merland JJ. Arterial embololization to treat uterine myomas. Lancet. 1995;46:671-72.
34. Reid PC, Virtanen-Kari S. Randomised comparative trial of the levonorgestrel intrauterine system and mefenamic acid for the treatment of idiopathic menorrhagia: A multiple analysis using total menstrual fluid loss, menstrual blood loss and pictorial blood loss assessment charts. BJOG. 2005;112(8):1121-5.
35. Richman TS, Viscomi GN, DeCherney A et al: Fallopian tube patency assessed by ultrasound following fluid injection. Radiology. 1984;152:507.
36. Royal College of Obstetricians and Gynecologists. The initial management of menorrhagia: Evidence-based guidelines No. 1. RCOG Press, London, UK; 1998.

37. Sawin SW, Pilevsky ND, Berlin JA, Barnhart KT. Comparability of perioperative morbidity between abdominal myomectomy and hysterectomy for women with uterine leiomyomas. Am J Obstet Gynecol. 2000;183:1448-55.
38. Shaw RW. Assessment of medical treatments for menorrhagia. Br J Obstet Gynaecol. 1994;101 Suppl 11:15-8.
39. Showstack J, Lin F, Learman LA. Randomized trial of medical treatment versus hysterectomy for abnormal uterine bleeding: Resource use in the Medicine or Surgery (Ms) trial. Am J Obstet Gynecol. 2006;194(2):332-8.
40. Singh RH, et al. Hormonal management of abnormal uterine bleeding. Clin Obstet Gynecol. 2005;48:337-52.
41. Stewart A, Cummins C, Gold L, et al. The effectiveness of the levonorgestrel-releasing intrauterine system in menorrhagia: A systematic review. BJOG. 2001;108:74-86.
42. Takeuchi AGS, Maruo KST. Usefulness of Gd-DTPA contrast-enhanced dynamic MRI and serum determination of LDH and its isozymes in the differential diagnosis of leiomyosarcoma from degenerated leiomyoma of the uterus. International Journal of Gynecological Cancer. 2002;12:354.
43. Towbin NA, Gviazda IM, March CM. Office hysteroscopy versus transvaginal ultrasound in the evaluation of patients with excessive uterine bleeding. Am J Obstet Gynecol. 1996; 174:1678.
44. Wamsteker K, Emanuel MH. Uterine leiomyomas. In Brosens I, Wamsteker K (eds): Diagnostic Imaging and Endoscopy in Gynecology, pp 185–198. London: WB Saunders, 1997.
45. Wamsteker K, Emmanuel MH, deKruif JH. Transcervical hysteroscopic resection of submucous fibroids for abnormal uterine bleeding results regarding the degree of intramural extension. Obstet Gynecol. 1993;82:736.
46. West S, Ruiz R, Parker WH. Abdominal myomectomy in women with very large uterine size. Fertil Steril. 2006;85:36-9.
47. Widrich T, Bradley LD, Mitchison A, Collins R. Comparison of saline infusion sonography with office hysteroscopy for the evaluation of the endometrium. Am J Obstet Gynecol. 1996; 174:1327.
48. Wilansky DL, Greisman B. Early hypothyroidism in patients with menorrhagia. Am J Obstet Gynecol. 1989;160(3):673-7.
49. Wright RC. Hysterectomy: Past, present and future. Obstet Gynecol. 1969;33(4):560-3.
50. Wu T, Chen X, Xie L. Selective estrogen receptor modulators (SERMs) for uterine leiomyomas. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD005287. DOI: 10.1002/14651858.CD005287.pub3
51. Zupi E, Zullo F, Marconi D, et al. Hysteroscopic endometrial resection versus laparoscopic supracervical hysterectomy for menorrhagia: A prospective randomized trial. American Journal of Obstetrics and Gynecology. 2003;188:7-12.

Chapter

19

Dysfunctional Uterine Bleeding

Case Study

A 28-year-old para 2 patient presented to the gynecological emergency with an episode of irregular menstrual bleeding since past four months.

Introduction

Dysfunctional uterine bleeding (DUB), defined as abnormal bleeding not caused by pelvic pathology, medications, pregnancy or systemic disease, is the most common cause of abnormal uterine bleeding. In these cases, no obvious structural (pelvic or adnexal or extragenital) cause of bleeding can be demonstrated on clinical examination or laboratory evaluation. Bimanual examination of the uterus and adnexa remains normal. The development of DUB is related to an imbalance in the levels of hormones, estrogen and progesterone. Though DUB remains the most common cause of abnormal uterine bleeding, it is largely a diagnosis of exclusion. Diagnosis of DUB is made only after the other causes of AUB including, pregnancy, iatrogenic causes, systemic conditions, and obvious genital tract pathology have been ruled out. Since the development of DUB is related to an imbalance in the levels of naturally produced hormones like estrogen and progesterone, it becomes important to discuss the hormonal changes occurring during a normal menstrual cycle, which would be described below:

Normal Menstrual Cycle

The normal menstrual cycle has been described in details in chapter 16. As gonadotropin releasing hormone (GnRH) is released by the hypothalamus, the pituitary gland synthesizes follicle stimulating hormone (FSH) and luteinizing hormone (LH), which induce the ovaries to produce estrogen and progesterone. These hormones are responsible for development of the two phases of a normal menstrual cycle:

- Follicular phase of normal ovarian cycle (equivalent to the proliferative phase of endometrial cycle), dominated by the hormone estrogen and
- The luteal phase of the ovarian cycle (corresponding to the secretory phase of endometrial cycle), dominated by progesterone.

During the follicular phase of normal ovarian cycle, there is an increase in the blood levels of the hormone, estrogen. During this phase, the maturation of the dominant follicle takes place. At the mid point of a normal cycle ovulation occurs, following which the luteal phase begins. Following the process of ovulation, the ruptured ovarian follicle gets converted into corpus luteum. The main hormone produced by corpus luteum is progesterone, which is the predominant hormone during the luteal phase. During this phase, the endometrium gets transformed for implantation of conceptus in anticipation of the pregnancy. If pregnancy occurs, the rising levels of human chorionic gonadotropin (hCG) stimulate and rescue the endometrium. In case the pregnancy does not occur, the CL undergoes regression. As a result, the levels of estrogen and progesterone rapidly decline causing withdrawal of the functional support of the endometrium. This results in menstrual bleeding, marking the end of one endometrial cycle and beginning of the other. The variations in the cycle length are associated with differences in the length of the follicular phase of the ovarian cycle.

Thus as described above, normal menstruation begins at the end of an ovulatory cycle primarily due to estrogen-progesterone withdrawal. Imbalance between the levels of various hormones involved in the menstrual cycle could be responsible for producing irregular bleeding related to DUB. Dysfunctional bleeding could be related to estrogen withdrawal, estrogen breakthrough, progesterone withdrawal and progesterone breakthrough.

Estrogen breakthrough bleeding

This occurs when excessive estrogen causes undifferentiated proliferation of the endometrium. With insufficient progesterone to provide structural support to the endometrium, portions of the endometrial lining slough off at irregular intervals. The usual progesterone-guided vasoconstriction and platelet plugging does not take place, often resulting in profuse bleeding.

Estrogen withdrawal bleeding

Estrogen withdrawal bleeding results from a sudden decrease in estrogen levels. This type of bleeding is commonly related to anovulation. This type of bleeding can also occur following bilateral oophorectomy, cessation of exogenous estrogen therapy or just prior to ovulation in the normal menstrual cycle. Estrogen withdrawal bleeding is usually self-limited and usually does not recur if estrogen levels continue to remain low.

Progesterone breakthrough bleeding

Progesterone breakthrough bleeding occurs when the progesterone-to-estrogen ratio is high. This may occur with the use of progesterone-only contraceptive methods. In these cases, the lack of estrogen causes the endometrium to become atrophic and ulcerated, thereby resulting in frequent, and irregular bleeding.

ETIOLOGY OF DUB

The etiology of this condition is purely hormonal. DUB can be of two types: Anovulatory and ovulatory type. Anovulation represents a common cause of DUB.

Anovulatory DUB

Anovulatory dysfunctional uterine bleeding is related to disturbances of the hypothalamic-pituitary ovarian axis that results in anovulation, thereby resulting in an irregular, prolonged, and sometimes heavy menstrual bleeding. Nearly 80% cases of DUB are anovulatory in nature. The prevalence of anovulatory cycles is highest in the women under the age of 20 (adolescents) and over the age of 40 years (women belonging to the perimenopausal age group).

Anovulatory bleeding can occur as a result of estrogen withdrawal or estrogen breakthrough. This causes anovulatory bleeding, which is usually heavier than normal menstrual flow. The anovulatory woman is always in the follicular phase of the ovarian cycle and in the proliferative phase of endometrium cycle. In the absence of ovulation, there is no luteal or secretory phase and therefore, the corpus luteum fails to form, resulting in reduced progesterone secretion. Uninterrupted stimulation of the endometrium by estrogen results in its continued growth. The endometrial proliferation occurs to abnormal heights until it becomes fragile. Without the structural support by progesterone, focal areas of bleeding and breakdown occur, resulting in an irregular and prolonged bleeding. Withdrawal of the hormonal support causes vasoconstriction of the spiral vessels resulting in the ischemic necrosis of the endometrium. However, according to the present evidence, the cause of bleeding is the release of lysosomal, and proteolytic enzymes from the surrounding epithelial and stromal cells, rather than focal ischemia.

Table 19.1: Causes of anovulation

Puberty menorrhagia
Bleeding in perimenopausal women
Chronic illness or excessive exercise
Extreme degree of weight loss, eating disorders, stress
Polycystic ovarian disease
Idiopathic chronic anovulation

Anovulatory DUB may also occur in the circumstances enumerated in table 19.1. Puberty menorrhagia and bleeding in perimenopausal age group are important causes of anovulatory DUB. Another cause of anovulation is polycystic ovarian disease, which is usually associated with obesity, increased circulating androgen levels and insulin resistance. Excess androgens are converted to estrogen in peripheral tissues. This unopposed estrogen state increases the risk of endometrial hyperplasia and cancer. In some women, no actual cause of ovulation can be documented. Such women can be considered to be suffering from idiopathic chronic anovulation.

Puberty menorrhagia

Immediately after menarche, the maturation of the hypothalamic-pituitary-ovarian axis may not be complete. In the first 18 months after menarche, the immature hypothalamic-pituitary axis may fail to respond to estrogen and progesterone, resulting in anovulation. As a result, puberty menorrhagia is an important cause of DUB primarily because nearly 80% of menstrual cycles are anovulatory in the first year following menarche. Menstrual cycles usually become ovulatory within two years following menarche. If no cause of menorrhagia can be found on the diagnostic work-up of an adolescent patient, she can be diagnosed as a case of DUB due to puberty menorrhagia.

Perimenopausal DUB

When the menopause is approaching, the estrogen levels may decline, resulting in failure of LH surge and thereby ovulation. Perimenopausal patients who are 40 years or older may be associated with diminishing number and quality of ovarian follicles. Follicles continue to develop but do not produce enough estrogen in response to FSH in order to trigger ovulation. Estrogen continues to be produced, which usually results in late cycle estrogen breakthrough bleeding. In perimenopausal women, it is important to exclude cancer cervix and cancer endometrium, which are particularly very common in this age group and can produce AUB.

Metropathia hemorrhagica (Schroeder's disease)

Though generally seen in postmenopausal women, this special type of menorrhagia may also be sometimes seen in the women under the age of 20 years. The bleeding is mainly of ovulatory type. The problem lies at the level of ovaries and is due to the disturbances of rhythmic gonadotropin secretion. There is slow and steady increase in estrogen levels with no inhibitory feed-back effect on FSH secretion. Since there is no ovulation, the endometrium is primarily under the effect of estrogen. Also, there is prolonged absence of the growth inhibiting hormone, progesterone. Due to this, there are increased estrogen levels with amenorrhea for about 6–8 weeks. After a variable period of amenorrhea, there occurs relative or absolute estrogen deficiency. Relative deficiency sets in because estrogen levels, despite of being normal are not able to sustain the hyperplastic endometrium. Absolute estrogen deficiency eventually sets in when high levels of estrogen start suppressing FHS levels. This in turn causes an absolute decrease in the level of estrogen secretion. As a result, the most common clinical presentation is a period of amenorrhea of about 8–10 weeks followed by an episode of heavy bleeding. In some cases, the episode of heavy bleeding may not be preceded by any amenorrhea, while in some other cases the episode of heavy bleeding may be preceded by menorrhagia.

On macroscopic examination, there may be slight symmetrical enlargement of the uterus up to 8–10 weeks, the size of a pregnant uterus. The ovary may show presence of single or multiple cystic changes. There could be the presence of estrogen containing fluid in these cysts. The ovary may not be clinically palpable. There is no evidence of corpus luteum. On microscopic examination, there could be marked hyperplasia of endometrial components including endometrial stroma, spiral vessels and glands. There is irregularity in glandular size resulting in a "swiss cheese appearance." Glands are largely empty and are lined by columnar epithelium. There is absence of secretory changes due to the lack of progesterone. There could be areas of necrosis in the superficial layers of endometrium with small hemorrhages and leukocytic infiltration. This type of bleeding needs to be differentiated from that due to abortion and ectopic pregnancy. While DUB due to metropathia hemorrhagica is completely painless, the bleeding associated with abortion and ectopic pregnancy is usually associated with pain.

Ovulatory Dysfunctional Bleeding

Although less common than anovulatory bleeding, ovulatory DUB may also sometimes occur. Ovulatory dysfunctional bleeding may include menstrual abnormalities like polymenorrhea, oligomenorrhea, premenstrual spotting (Mittelschmerz syndrome), hypomenorrhea, and menorrhagia. Ovulatory DUB can occur due to the following abnormalities: Shortened proliferative or secretory phase, corpus luteal insufficiency, persistent corpus luteum (Halban's disease), and irregular shedding. These would be described in details below:

Persistent corpus luteum (Halban's disease)

In these cases, the shedding of endometrium is late and occurs in form of large chunks causing membranous dysmenorrhea. Histological picture shows late secretory phase endometrium mixed with menstrual blood and early proliferative phase endometrium.

Luteal phase deficiency

It may be associated with a shortened luteal phase or insufficient progesterone production.

Mittelschmerz syndrome (Midcycle spotting)

This is the type of mid-cycle bleeding, which occurs just before or at the time of ovulation. It results from a physiological fall in estrogen levels, which occur just prior to the LH surge.

Irregular ripening

Inadequate luteal phase functioning could be due to the failure of corpus luteum to develop properly. Irregular ripening could also be related to the inability of the endometrium to respond to progesterone due to reduced sensitivity of endometrium (in presence of a normal corpus luteum). Histological picture shows an endometrium which is "out of phase" or an endometrium with irregular hormonal response. On microscopic examination, mixture of proliferative stroma and secretory endometrial glands are seen. In these cases, the deficient corpus luteal function causes an inadequate support of endometrium with progesterone resulting in an inadequate luteal phase. Breakthrough bleeding occurs before the time the normal menstrual cycles are expected, resulting in polymenorrhea.

Irregular shedding

Irregular shedding or Halban disease can occur as a result of persistent corpus luteum. Though the menstrual periods come on time, the periods itself may be prolonged. The diagnosis is established on endometrial biopsy, which shows persistence of secretory changes along with a proliferative endometrium. The condition is largely self-limited.

History

In the majority of women with true anovulatory bleeding, the cause of bleeding can be established by taking history itself. Characteristics of ovulatory and anovulatory menstrual cycles which can be determined by taking appropriate history are enlisted in table 19.2. Anovulatory bleeding is typically infrequent, irregular, and unpredictable that varies in amount, duration and character. It is usually not preceded by any pattern of premenstrual molimina. Treatment can begin without additional laboratory evaluation or imaging.

Detailed history to be taken in cases of AUB has been described in chapter 17. Important points in the patient's history which may be particularly important in cases of DUB include the following:

- Patient's age,
- Time of last menstrual period and last normal menstrual period

  Detailed history regarding the episode of bleeding has been explained in chapter 17. The specific points which need to be elicited include the following:
  - Intermenstrual intervals between the episodes of bleeding: Number of days following which the bleeding occurs and cycle regularity.
  - Volume of bleeding: Heavy, light, or variable.
  - Duration of the bleeding episode: Normal or prolonged, consistent or variable.
  - Temporal association of the bleeding episode: Whether post-coital, postpartum, or post-pill.
- History of intake of any medications (especially hormonal agents, NSAIDS, or warfarin)
- History of any endocrine abnormalities (thyroid dysfunction)
- Symptoms of pregnancy (morning sickness, breast changes, etc.)
- Symptoms suggestive of coagulopathies
- History of use of hormonal contraceptive agents in the past
- History of trauma
- History of weight gain or loss, galactorrhea, hirsuitism
- History of symptoms suggestive of premenstrual molimina (breast tenderness, edema, mood swings, etc.), and other sysmptoms like dyspareunia, dysmenorrhea, dyschezia, etc.
- Presence of underlying systemic illnesses (renal, hepatic failure, etc.)
- History of Pap smears, previously done must be enquired from the patient. The results of recently done Pap smear tests also need to be documented.

Table 19.2: Characteristics of ovulatory and anovulatory menstrual cycles

Ovulatory menstrual Cycles	*Anovulatory menstrual Cycles*
Regular cycle length	Unpredictable cycle length
Regular bleeding pattern	Unpredictable bleeding pattern: Frequent spotting, infrequent heavy bleeding
Biphasic temperature curve	Monophasic temperature curve
Presence of premenstrual symptoms such as dysmenorrhea, breast tenderness, change in cervical mucus, Mittleschmertz, etc	No premenstrual molimina
Ovulatory cycles may be painful	Anovulatory cycles are painless
Positive result from use of luteinizing-hormone predictor kit	Negative result

General Physical Examination

General physical examination should focus on signs related to excessive blood loss (tachycardia, hypotension), symptoms related to endocrinopathies, including polycystic ovary disease (such as obesity and hyperandrogenism: Acne, hirsutism, deepening of voice), hyperprolactinemia, and hypothyroidism. The following points should be typically looked at the time of general physical examination:

- *Signs suggestive of hypothyroidism or hyperthyroidism*: For signs and symptoms suggestive of hypothyroidism and hyperthyroidism see tables 19.3 and 19.4 respectively.
- *Breast examination*: Breast examination in cases of DUB should specifically aim at the following:
  - Detection of a breast lump: Detection of a tumorous mass could be an indicator of breast malignancy.

Table 19.3: Symptoms and signs of hypothyroidism

Weight gain or increased difficulty losing weight
Fatigue, weakness
Hair loss, coarse, dry hair
Dry, rough, pale skin
Reduced thermogenesis resulting in cold intolerance
Muscle cramps and frequent muscle aches
Constipation
Memory loss
Husky, low-pitched, and coarse voice
Abnormal menstrual cycles, decreased libido
Depression, irritability
Pitting edema in the lower extremities

Table 19.4: Symptoms and signs of hyperthyroidism
Palpitations, nervousness, breathlessness
Heat intolerance
Insomnia
Increased bowel movements
Light or absent menstrual periods
Tachycardia
Tremors in hands
Weight loss
Muscle weakness
Warm, moist skin
Hair loss

History of treatment with tamoxifen (anticancer drug, commonly used in cases of breast malignancy) need to be enquired in such patients. Continuous use of tamoxifen is believed to exert a proliferative estrogen-like effect on the uterus. This could be a cause of AUB in these patients. Abnormal bleeding in women under treatment with tamoxifen could be related to endometrial hyperplasia. This therefore warrants prompt investigation and careful follow-up of these patients.

– Presence of galactorrhea: Hyperprolactinemia is an important cause of amenorrhea and infertility.

Specific Systemic Examination

PELVIC EXAMINATION

Pelvic examination is unnecessary and must not be done in young girls presenting with the history of menorrhagia, who are not sexually active. Pelvic examination may be particularly useful in women belonging to reproductive age group, presenting with DUB. The pelvic examination has been described in details in chapter 16. Gynecologic examination includes inspection of the vagina and cervix for presence of visible lesions [polyps, erosions, tears, malignancy, pregnancy related complications (expulsion of products of conceptions) or infection]. Signs of excessive blood loss must be noted on per speculum examination. On vaginal and bimanual examination, the size, shape, position, and firmness of the uterus should also be examined.

Differential Diagnosis

The most important differential diagnosis in cases of DUB is pregnancy related complications particularly threatened or incomplete abortion and ectopic pregnancy. Various other causes of AUB have been enumerated in chapter 17.

Table 19.5: Laboratory investigations to be considered in case of DUB	
Test	*Indication (to rule out)*
Urine pregnancy test	Pregnancy
CBC with platelet count	Anemia and coagulation defects
PT/aPTT	Coagulation abnormalities
Ristocin cofactor assay	Von Willibrands disease
Pap smear	Cervical cancer
Liver function and/or renal function tests	Hepatic and renal disease
TSH	Thyroid disease
Prolactin level	Pituitary adenoma
LH, FSH, and androgen levels	Polycystic ovary disease
Endometrial biopsy	To rule out endometrial cancer

Excluding Endometrial Carcinoma

All perimenopausal women with persistent abnormal uterine bleeding should be evaluated for the presence of endometrial hyperplasia or carcinoma. Endometrial biopsy is the most widely used and best studied method of excluding endometrial carcinoma in this age group. Detailed description of endometrial biopsy is given in chapter 17. The women having normal findings on endometrial biopsy can be prescribed progesterone withdrawal or low-dose oral contraceptives. If bleeding continues despite hormonal therapy, further investigation is warranted.

Management

Typical algorithm for management of DUB in the women belonging to the reproductive age group and perimenopausal women has been described in flow charts 19.1 and 19.2 respectively.

Investigations

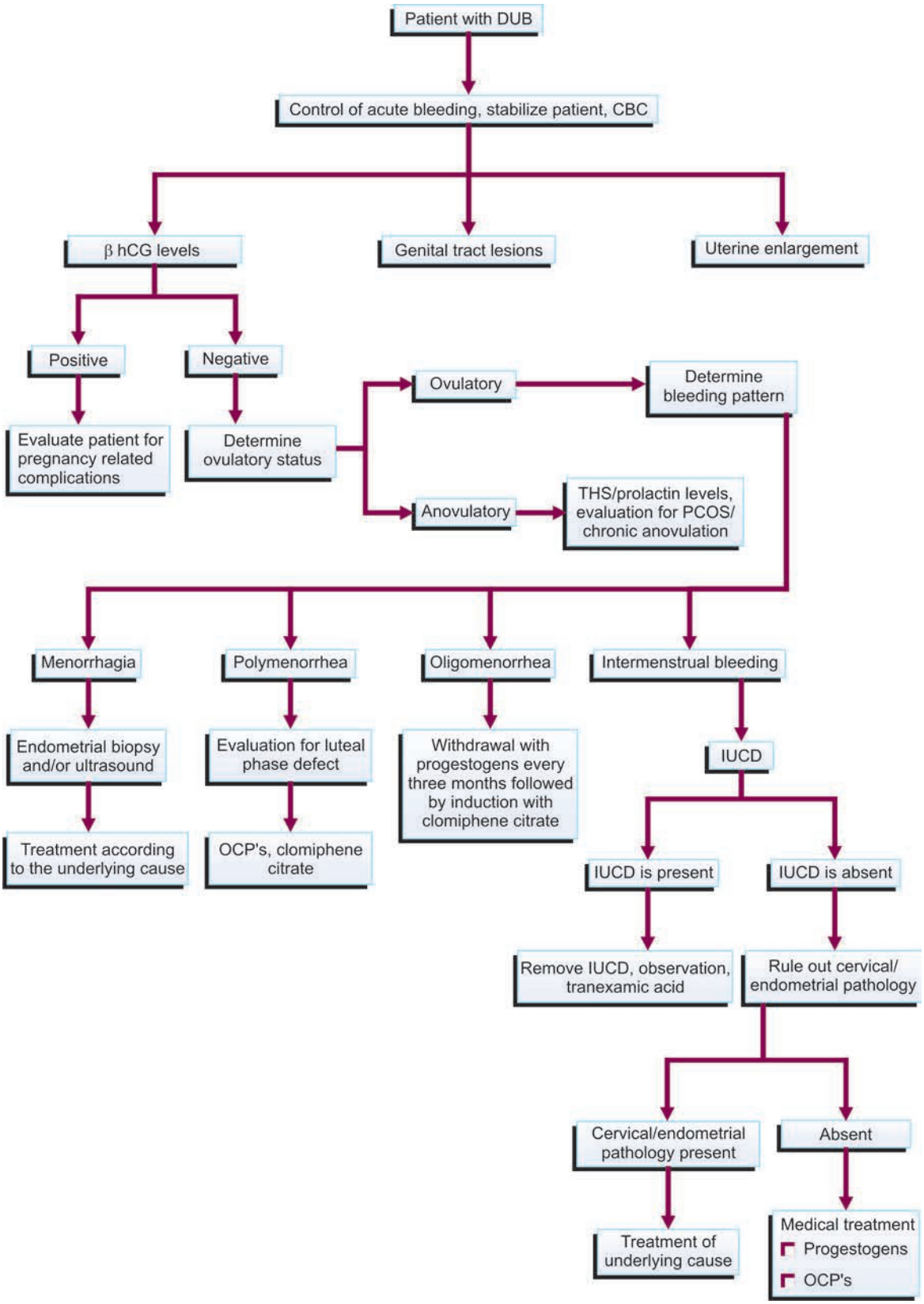
Laboratory investigations to be considered in case of DUB are listed in table 19.5. These are described in details in chapter 17.

Imaging Studies

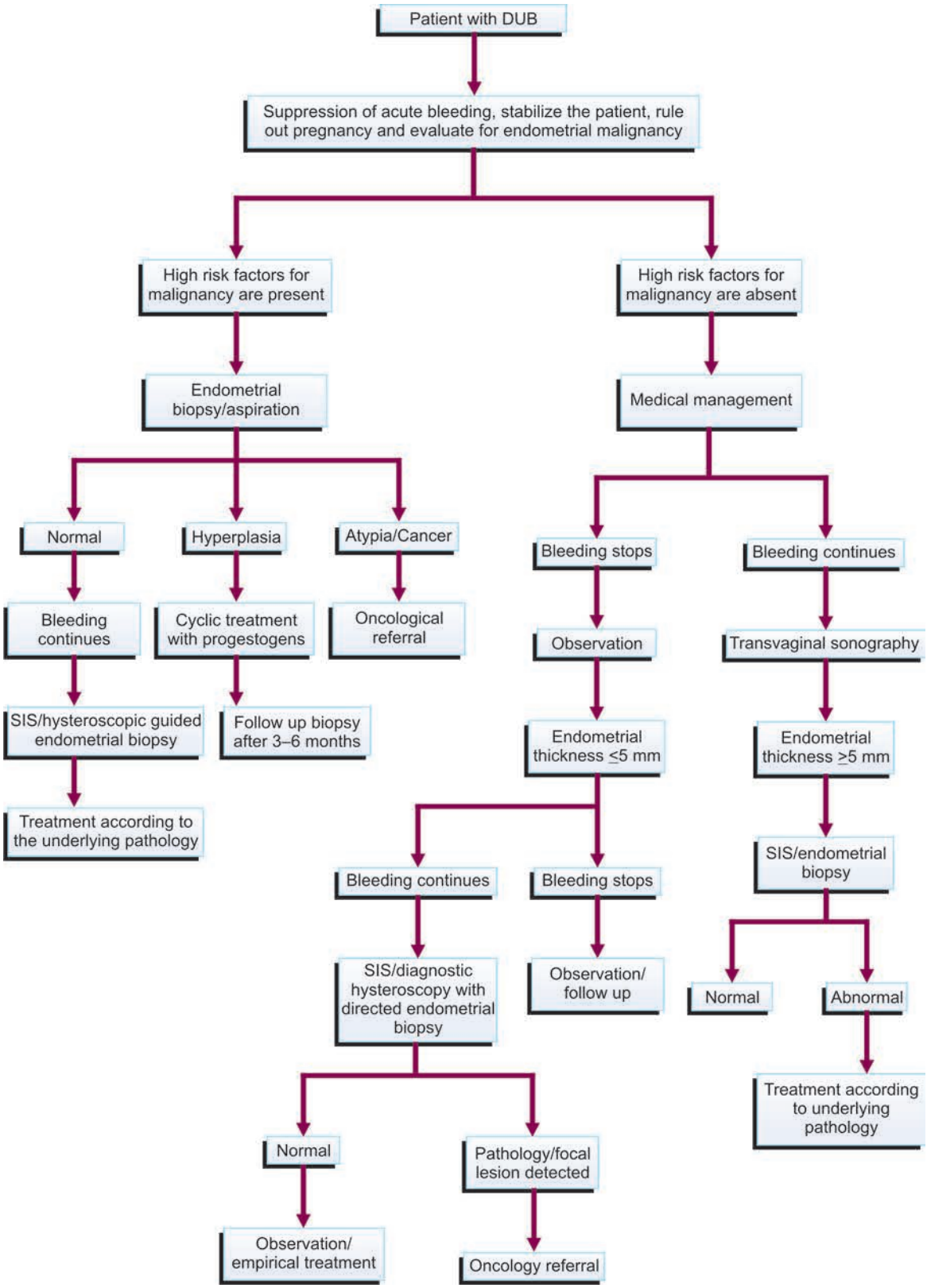
For details regarding the use of imaging studies in a case of AUB, kindly refer to chapter 17.

Presence of secretory endometrium in a woman with AUB having no history of recent exposure to exogenous progestational agents is indicative of recent ovulation. In such cases, anovulatory DUB can be ruled out and one needs to search for an anatomical cause of AUB.

Flow chart 19.1: Treatment of DUB in women of reproductive age group



Flow chart 19.2: Treatment of DUB in perimenopausal women



Endometrial Studies

Refer to chapter 17.

Tests for Ovulation

In order to determine whether or not ovulation has taken place, two tests can be done: Basal Body temperature charting and determination of serum progesterone levels in mid-luteal phase.

Basal body temperature charting

Basal body temperature charting may assist in determining whether or not ovulation has occurred. In this method, the patient is required to consistently take her temperature every day. The women is instructed to start taking her temperature from day 1, which corresponds to the first day of the menstrual periods. She should preferably take her temperature immediately after awakening, before any physical activities have been undertaken. The temperature must be preferably taken at the same time each morning. A sustained rise in basal temperature of 0.3°C to 0.6°C is indicative of ovulation. The increase in basal body temperature following ovulation is related to the thermogenic effect of the hormone progesterone.

Serum progesterone levels

Determination of serum progesterone levels in mid luteal phase can help in establishing ovulation or anovulation. Serum progesterone values greater than 3 ng/ml are indicative of ovulation.

℞ *Treatment/Gynecological Management*

Many cases of DUB may simply represent normal physiological variation of menstrual cycle and thereby resolve with clinical observation. In these cases, the patient must be instructed to maintain a menstrual calendar. The treatment of moderate to severe DUB or that uncontrolled by clinical observation mainly comprises of medical therapy. Endometrial ablation procedures can be used in patients who are unresponsive to medical therapy, those who have completed their families or those with severe DUB. Medical treatment of menorrhagia has been described in details in chapter 18. For severe bleeding, interavenous estrogen therapy (2.5 mg) conjugated equine estrogens every 4 hours until bleeding subsides or for 24 hours can be very effective. When bleeding is less severe, but still quite heavy, treatment can be given with 1.25 mg conjugated estrogen or 2.0 mg micronized estrogen every 4–6 hours for 24 hours. This can be tapered to once a daily dose for another 7–10 days after bleeding has been controlled. Lighter bleeding may respond to a single daily dose (1.25 mg conjugated estrogens or 2.0 mg micronized estradiol) for 7–10 days.

In cases of acute hemorrhage, if the endometrium is thickened, progestogens can also be administered. Norethistrone acetate is usually started in high dosage, administered in the dosage of 10 mg TDS, for 24–48 hours to stop the bleeding. This is gradually tapered down to a dose of 5 mg per day when the bleeding reduces and continued in a dose of 5 mg per day for further 20 days. The patient should be warned about the episode of withdrawal bleeding following the stoppage of therapy. Thereafter, the gynecologist must await the series of events. Sometimes, it will be found that the patient remains amenorrheic for 6–8 weeks. If heavy and prolonged bleeding recurs, another course of treatment may be given to control it. In adolescents, only two-three courses may be required before a normal cycle is spontaneously established. In order to avoid relapse, progestogens may be administered cyclically for a few months after the initial attack of bleeding has been controlled. For this, one of the synthetic progestogens such as dehydrogesterone or medroxyprogesterone acetate in a dosage of 10 mg daily from day 16th to 25th day of the cycle can be used. Cyclical therapy is usually administered for 6–9 cycles. Endometrial aspiration to confirm the reversal of histopathological changes is essential at the end of this period.

Various medical therapies for the control of DUB based on the patient's age are summarized in table 19.6. Treatment of ovulatory and anovulatory menorrhagia is slightly different and would be described below.

Treatment of Anovulatory DUB

If anovulatory bleeding is not heavy or prolonged, no treatment is necessary. All cases of anovulatory DUB represent a progesterone-deficient state. In such patients with irregular cycles secondary to chronic anovulation or oligo-ovulation, progestins help to prevent the risks associated with prolonged unopposed estrogen stimulation of the endometrium. Thus progestins form the mainstay of treatment for anovulatory bleeding, once presence of any uterine pathology has been ruled out. Exogenous progestogens must be prescribed to protect against endometrial cancer; 5–10 mg of medroxyprogestrone acetate can be administered daily for the first 15–16 day of each month for 4–6 months. Progestin therapy helps in controlling anovulatory bleeding in most cases. Some of the commonly used progesterone preparations include medroxyprogesterone (provera) / depot-medroxyprogesterone / megestrol acetate / 19-nortestosterone derivative, etc. Medroxyprogesterone (Provera) is administered in the dose of 5–10mg PO per day for 10 to 12 days of each month for 4–6 months. Depot medroxyprogesterone (150 mg)

Table 19.6: Summary of medical treatment used for control of DUB

Age group	*Treatment*	*Comments*
Premenopausal (adolescents and women belonging to rreproductive age groups)	Oral contraceptives	Low-dose (35 µg) monophasic or triphasic oral contraceptives can regulate cycles, at the same time providing contraception.
	Progestogens	If contraception is not required, medroxyprogesterone acetate can be used to regulate cycles in a dose of 10 mg per day for last 10 days of the cycle (day 16th to day 25th)
	Clomiphene citrate, 50 to 150 mg per day on days 5 to 9 of the cycle	Can induce ovulation in a woman with anovulatory cycles, who desire pregnancy. If there is no response or no pregnancy occurs in 3 to 6 months, referral is appropriate.
Perimenopausal	Medroxyprogesterone, 10 mg per day for 10 days	May use monthly to regulate bleeding patterns.
	Oral contraceptives	Oral contraceptive pills can be continued until a woman has reached menopause and then HRT may be started.
Postmenopausal women (receiving HRT)	Cyclic HRT	Estrogen dose may be increased if intermenstrual bleeding is present, whereas progesterone dose should be increased, if early withdrawal bleeding occurs.
	Continuous combined HRT	Clinician may increase the estrogen dose for 1 to 3 months to stabilize the endometrium. Clinician may also try increasing the progesterone dose. If bleeding continues, consider changing regimen to cyclic HRT or using a different type of estrogen.

or progesterone in oil (100–200 mg) may be given intramuscularly every three monthly to achieve similar effects. These also provide contraception. Combined OCP pills can be used if contraception is also desired. If pregnancy is desired, ovulation induction with clomiphene citrate may be required. The treatment strategy may vary depending on the age group of the woman experiencing anovulatory DUB. This is described below:

Adolescents

In adolescents, the first few menstrual cycles are frequently anovulatory. Thus, it is not unusual for the first few cycles to be irregular and heavy. In case of mild-moderate bleeding, no treatment may be required. In these cases, simple reassurance and supportive therapy (with iron and other hematinic agents) may be all that is required. The patient just needs to be reassured and explained about the cause of bleeding. However, if the adolescent is significantly distressed by the irregularity of her menses or has been anovulatory for more than a year or if the bleeding has been heavy, therapy may be required. Diagnostic procedures are usually not required in young patient. A therapy with progestogens or a combination of progestogens or estrogens (OCPs), given orally would be adequate in most patients. In patients receiving cyclical therapy with estrogens and progesterone, treatment is administered in monthly courses for about 3–6 months. After this, the treatment is discontinued and further evaluation is performed if necessary. In adolescents in whom the bleeding is not severe or those desiring contraception, OCPs may be used as normally prescribed in older women (active pills for 21 days followed by placebo tablets or no pills for the next 7 days).

Women belonging to the reproductive age group

In patients belonging to the reproductive age groups, pathological changes (particularly, pregnancy related complications, fibroids, adenomyosis, endometriosis, PCOS, etc) are more common. As a result, diagnostic procedures, particularly endometrial biopsy or aspiration and pelvic ultrasound are more often required. Hormonal treatment forms the first line therapy in the patients in whom no pathology is detected. In these cases, hormones are to be used in the same dose as that described in young patients above.

Perimenopausal women

In the perimenopausal years, extreme degree of care must be taken towards excluding pathological causes because of the underlying possibility of endometrial cancer. Besides detecting endometrial hyperplasia, endometrial aspiration or biopsy also helps in establishing the histopathology of endometrium, whether proliferative or secretory. For patients with severe bleeding, who are also anemic and whose lifestyle is compromised by persistence of irregular bleeding, D&C may be sometimes used to help in temporarily stopping the bleeding. Eventually, however, an endometrial ablation procedure or an abdominal or vaginal hysterectomy may be required. In case

of co-existent pelvic pathology like co-existent endometriosis, leiomyomas etc., definitive surgery may be required.

Therapy with progestogens

Therapy with progestin helps in causing a 15% reduction in menstrual blood flow when used alone. Progestin works as an antiestrogen by minimizing the effects of estrogen on target cells. They help in achieving medical curettage by converting hyperplastic endometrium into secretory phase endometrium. Normal shedding is precipitated when the treatment is discontinued. Progestogens can be either administered orally or in form of intramuscular injections. During an episode of heavy bleeding, progestogens can also be used in the dosage as previously described.

Progesterone therapy helps in reducing blood loss by nearly 80%. Common adverse effects which can occur with the use of progestogens are weight gain, headaches, edema, breast tenderness, mood swings, nausea, bloating, edema, acne, depression, exacerbation of epilepsy and migraine, loss of libido, etc.

Treatment of Ovulatory Dysfunctional Uterine Bleeding

Medical therapy for ovulatory DUB primarily includes nonsteroidal anti-inflammatory drugs (NSAIDs), the levonorgestrel-releasing intrauterine system (mirena), danazol and GnRH agonists. While the medical therapies like NSAIDS and mirena are commonly used, the use of androgens such as danazol and gonadotropin releasing hormones is largely limited due to high costs and high incidence of side effects. GnRH agonists are commonly used in the treatment of menorrhagia to produce short-term endometrial thinning before ablation is performed.

Oral contraceptive pills (OCPs) are also commonly used both for cycle regulation and contraception in patients with ovulatory DUB.

Medical Treatment

Oral contraceptive pills (OCPs)

Oral contraceptive pills (OCPs) are a commonly used first-line therapy for women with DUB, who desire contraception. OCPs suppress pituitary gonadotropin release, thereby preventing ovulation, and help in causing endometrial atrophy. OCPs help in reducing the menstrual blood loss by as much as 60% by causing endometrial atrophy. Common adverse effects of OCPs include nausea, breast tenderness, breakthrough bleeding, nausea, headache, migraine, weight gain, cholestatic jaundice, hypertension, thrombotic episodes, etc.

In cases of moderately heavy DUB, oral contraceptive pills (OCPs) may be given upto four times a day for 5 to 7 days or until bleeding stops, followed by the rest of the pills to be taken once a day until the pack is finished and withdrawal bleeding occurs. In anovulatory patients, the OCPs are prescribed for additional two months in order to stabilize the epithelium, slough out the excessive endometrial build-up, and provide contraception. In patients with mild DUB, OCPs may be administered in the dose of one pill every day.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDS show an average reduction of 25–35% in menstrual blood flow. Besides the NSAIDs, drugs like hyoscine butylbromide, which help in relaxing the smooth muscles and reducing uterine contractions, may be considered in the management of dysmenorrhea and pelvic pain associated with DUB.

Hemostatic agents

Tranexamic acid, ethamsylate: Refer to chapter number 18 for details.

Antibiotics

Use of antibiotic therapy may prove to be beneficial when there is a clear evidence of pelvic infection. Sometimes subclinical bacteria infection within the uterus may account for some otherwise unexplained menstrual disturbances.

The levonorgestrel intrauterine system (Mirena)

Refer to chapter 18 for details.

Arginine vasopressin derivatives

Arginine vasopressin derivatives like desmopressin (DDAVP) have been used to treat abnormal uterine bleeding in patients with coagulation defects. Desmopressin helps in transiently elevating the levels of factor VIII, Von Willebrand factor and platelet levels in the body. Thus, it can be used for treating patients with coagulation disorders such as type I Von Willebrand disease, mild hemophilia and thrombocytopenia. In adults, it is prescribed in the dosage of 0.3 mcg/kg in 50 mL NS IV injection administered over 15 minutes.

Endometrial Ablation

Endometrial ablation involves destruction of a thin endometrial layer, which helps in controlling the amount of bleeding. In some women, menstrual bleeding does not stop, but is reduced to normal or lighter levels. In most cases, women with heavy bleeding are treated first with medication. The women whose bleeding does not respond to hormonal or

pharmacological therapy and who want to conserve their uterus must be offered endometrial ablation. If ablation does not control heavy bleeding, further treatment or surgery may be required. Some indications for endometrial ablation are described in table 19.7 below.

Endometrial ablation may be offered as an initial treatment for DUB after full discussion with the woman regarding the risks and benefits associated with the procedure and of other available treatment options. The outcome of these techniques would be better if these are performed when the endometrial lining is thin. One option would be to perform the procedure in immediate post menstrual period when the endometrium is in early proliferative phase. Curettage of the endometrium prior to the procedure is likely to serve the same purpose. Though this procedure would also have an added benefit of providing tissue for histological examination, bleeding due to D&C is likely to interfere with the effectiveness of the ablative procedure. Some researchers have advocated the use of medical treatment (OCPs, progesterone or GnRH agonist) for a period of 4–6 weeks prior to the procedure. However, this may prove to be costly and is associated with a delay in periods by 4–6 weeks. Endometrial ablation should be considered in women who have a structurally normal uterus, which is less than 10 weeks in size. It can also be sometimes offered to the women having small uterine fibroids (less than 3 cm in diameter).

Some contraindications for not performing endometrial ablation are listed in table 19.8. Endometrial ablation should not be done in women past menopause or in cases suspected to be suffering from various disorders of the endometrium including endometrial hyperplasia, endometrial cancer, and current or recent infection of the uterus. An endometrial biopsy must be preferably carried out to rule out any malignancy before doing this procedure.

Even though endometrial ablative techniques help in conversation of uterus, these must not be offered to the women planning future pregnancy. Women must be advised to avoid subsequent pregnancy and to use effective contraception, if required, following endometrial ablation. Endometrial ablation must also not be performed in the women who have cu-T in situ.

Table 19.7: Indications for endometrial ablation

Women does not desire future fertility
Failure of medical treatment
Menorrhagia is related only to DUB and no other cause
Menorrhagia is unresponsive to hormonal or pharmacological therapy
Malignant disease of the cervix and/or endometrium has been ruled out
Uterine size is less than 10 weeks
Submucous fibroids < 5 cm
Endometrium is normal with no risk of hyperplasia

Table 19.8: Contraindications for use of endometrial ablation techniques

Presence of endometrial carcinoma or premalignant change of the endometrium, (e.g. adenomatous hyperplasia)
Patient with any anatomic or pathologic condition associated with weakness of the myometrium (e.g. history of previous classical cesarean sections or transmural myomectomy)
A patient with active genital or urinary tract infection at the time of procedure (e.g., cervicitis, vaginitis, endometritis, salpingitis, or cystitis)
A patient with an intrauterine device (IUD) currently in place
A patient who is pregnant or who wants to become pregnant in the future

Table 19.9: Procedures for endometrial ablation

First generation procedures
Hysteroscopic laser ablation
Transcervical resection of the endometrium
Roller ball ablation of the endometrium
Second generation procedures
Cryoablation
Hydrothermal ablation
Laser thermoablation
Microwave ablation
Thermal balloon ablation
Electrosurgical ablation
Photodynamic ablation
Radiofrequency induced thermal ablation

Endometrial Ablation Methods

These methods help in treating DUB by destroying the endometrial lining. These methods for endometrial ablation are mainly of two types: First generation (hysteroscopic) methods and second generation (non-hysteroscopic methods) (table 19.9 and figures 19.1A to F). Hysteroscopic methods include laser and electrosurgical resection (roller ball and TCRE). Electrosurgical method that uses the wire loop to resect out the endometrial lining is called transcervical endometrial resection or TCRE (figures 19.2A and B). The wire loop is around 6 millimeters long and is attached at an angle to a pencil-shaped handle. On the other hand, electrosurgical technique that uses the heated roller ball to burn away the endometrial tissue is called roller ball ablation (figure 19.3). The roller ball is a ball about 2 millimeters wide that rotates freely on its handle. Non-hysteroscopic or the

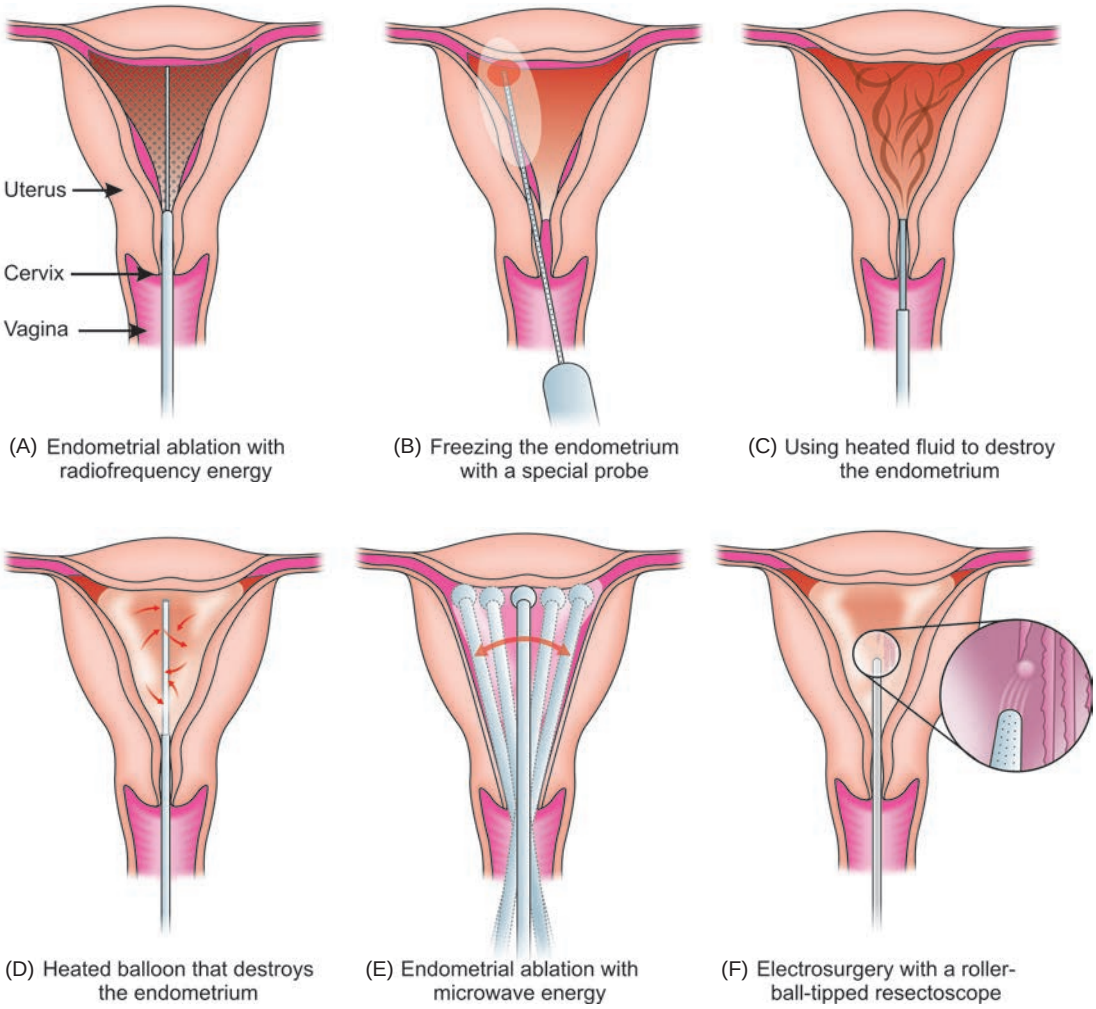


Fig. 19.1: Various techniques for endometrial ablation

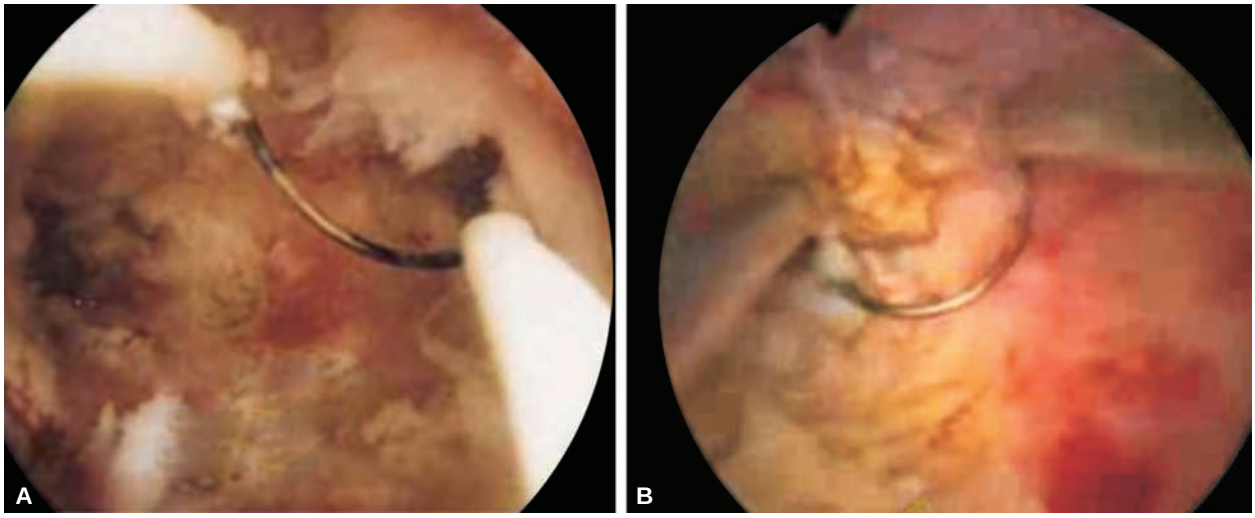


Fig. 19.2: Transcervical resection of the endometrium. (A) Wire loop touching the endometrial surface (B) Wire loop resecting out the endometrium

second generation methods for endometrial ablation include thermachoice, microwave therapy etc.

Though the use of endometrial ablation helps in avoiding hysterectomy, there is nearly 12% probability that endometrial resection would not be able to control DUB, thereby resulting in the future requirement of hysterectomy within the next four years. Endometrial resection/ablation can cause side effects like uterine perforation, fluid overload, hemorrhage, infection, etc. Despite the above mentioned complications associated with endometrial ablation methods, the rate of occurrence of these complications is less than that associated with hysterectomy. Endometrial resection/ablation also helps in avoiding possible ovarian dysfunction, psychological effects and other side effects related to hysterectomy. However, hysterectomy is preferable over endometrial resection if the patient has a large uterus, or some underlying uterine pathology like fibromyomas or severe endometriosis. Presently, hysterectomy remains the most absolutely curative treatment for DUB. The comparison between abdominal hysterectomy and endometrial resection is shown in the table 19.10.

Endometrial ablation in women desiring pregnancy

Endometrial ablation is intended for use only in women who do not desire future pregnancy because the likelihood of pregnancy is significantly decreased following this procedure. Since the procedure does not result in absolute sterility, there have been occasional reports of pregnancy following the procedure. However, the pregnancies following the ablative procedures can be dangerous for both mother and fetus.

Furthermore, patients undergoing endometrial ablation procedures who had previously undergone tubal ligation are at an increased risk of developing post ablation tubal sterilization syndrome which can even require hysterectomy. This can occur as late as ten years following the procedure. Post-ablation-tubal sterilization syndrome is believed to be related to the regeneration of endometrium in the cornual areas of the uterus. Blood from these glands can flow back into the proximal fallopian tubes in cases where the lower uterine segment is extensively scarred. As a result, the proximal oviduct becomes filled with blood and fluid and may cause symptoms similar to those of an ectopic pregnancy.

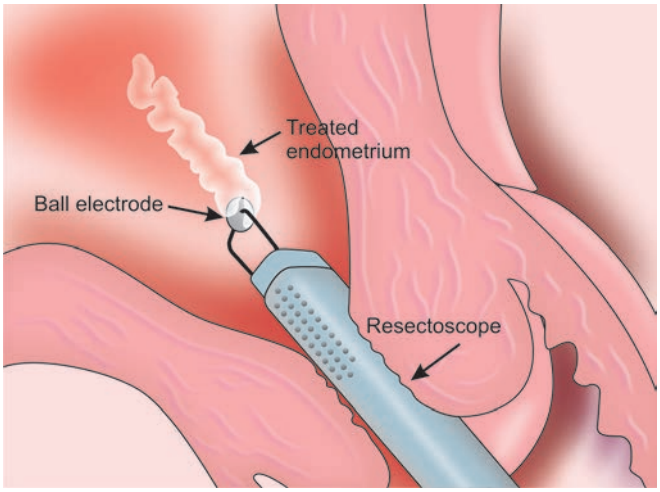


Fig. 19.3: Roller ball endometrial ablation

First Generation Methods

Transcervical resection of the endometrium

Transcervical resection of the endometrium (TCRE) is the first generation endometrial ablation procedure, which has been considered the standard cure for menorrhagia since many years. This procedure requires the use of a resectoscope, which is composed of a hysteroscope with a heated wire loop. Though, the use of resectoscope requires time, skill, and extensive experience, success rates as high as 80–90% can be achieved. The resectoscope has the advantage of being able to remove polyps and some fibroids at the time of ablation. This procedure also has a distinct advantage of providing endometrial tissue for histopathological examination. This procedure can also be done if the endometrium is thick. Additionally, the hysteroscopic resection equipment is considerably less expensive to buy and maintain than in comparison to the laser equipment. However, this procedure is associated with few complications. The main risk associated with TCRE is uterine perforation. Other complications due to the procedure may

Table 19.10: Abdominal hysterectomy vs. endometrial resection

	Abdominal hysterectomy	*Endometrial resection*
Duration of hospital stay	Longer theater times and hospital stay	Day-stay or overnight procedure
Rate of complications	Higher complication rate (45%)	Lower rate of complications (0–15%)
Mortality and morbidity rates	Higher	Lower
Time for resumption of normal activities	Two to three months	Two to three weeks
Overall health care costs	Higher health care costs because of longer theater time and duration of hospital stay	Lower health care costs because of shorter theater time and duration of hospital stay

include complications such as menstrual like cramps, which may last for 1–2 days; watery discharge lasting for about 10 to 14 days; hemorrhage and or hematoma formation; infection; injury to the bowel; risk of fluid overload; endometritis, etc. The potential fluid overload problem can be alleviated by the use of carbon dioxide gas or dextran 70 solution to distend the uterus. The method of doing TCRE is described below:

Procedure:

- This method is usually is done in an operating room under general anesthesia.
- After dilating the cervix, a hysteroscope is inserted inside the uterine cavity, following which a heating device is placed inside the uterine cavity. The heating device composed of a loop which is heated using electricity.
- Using a wire loop, the surgeon cuts away the endometrial lining.
- Fluid is continuously pumped inside the uterine cavity in order to keep it distended while the endometrial resection is being carried out.

Roller ball endometrial ablation

In this procedure, the endometrium is ablated via electrosurgical energy using a roller ball. This type of endometrial ablation essentially is the same as TCRE, except that instead of a wire loop, a heated roller ball is used to destroy the endometrium. Roller ball electrodes are available in two sizes: Small (2.5 mm) and large (5 mm). Roller ball endometrial ablation is an easier technique in comparison to the TCRE and is associated with a lower risk of complications including uterine perforation, fluid absorption and hemorrhage.

Hysteroscopic laser ablation

Endometrial laser ablation requires Nd: YAG (Neodymium–yttrium–aluminum–garnet) laser equipment and optical fiber delivery system. In this method, the uterine cavity is distended using normal saline, Hartmann's solution or Hyskon, following which a laser compatible hysterscope, and 600–800 µm quartz fiber is guided inside the uterine cavity. Laser power density of approximately 4,000–6,000 W/Cm^2 is used to maintain contact with the endometrium. This is known as the dragging technique. Alternatively, blanching technique where the laser fiber is not allowed to come in contact with the endometrium, but destruction is caused by coagulation, may also be sometimes used. Laser ablation helps in destroying nearly 5–6 mm thickness of endometrium. This method is associated with a success rate of approximately 85% and is more effective in patients over the age of 35 years.

Disadvantages of this method include high expense of the equipment, long time required for the procedure and the risk of fluid overload due to excessive fluid uptake from the distending media infusion and irrigating fluid. Following the procedure, 50% may develop amenorrhea and another 30% may develop hypomenorrhea, resulting in an overall success rate of nearly 80%. Amenorrhea may occur in 29% of the patients. There is some concern that cancers could be missed, since no tissue is available for pathologic study.

Second Generation Methods

Thermal balloon ablation

In this procedure, the endometrium may be hysteroscopically ablated via the insertion of a thermal uterine balloon. This procedure uses a thermal balloon device consisting of basic mechanism by which a balloon tipped catheter is introduced inside the uterine cavity and is inflated by a fluid which is either is preheated or heated after filling. One such device is the thermachoice balloon. The use of Thermachoice™ balloon for endometrial ablation has now attained FDA approval. Some experts are concerned about the balloon's ability to reach the cornual areas of the uterus.

Procedure

- A balloon catheter, filled with isotonic sodium chloride solution is inserted inside the endometrial cavity, inflated, and heated to 87°C for 8 minutes.
- The control unit with monitor display is used to adjust intrauterine balloon temperature, pressure and the duration of the treatment.
- The fluid is usually instilled until the pressure reaches between 160 and 180 mm Hg.
- The solution is heated to 87° C for 8 minutes and then the device is removed.

The treatment has been found to be as efficacious as roller-ball ablation with fewer complications. However, uterine balloon therapy cannot be used in irregular shaped uterine cavities because the balloon will not conform to the cavity. This procedure can be effective in woman with regular uterine cavity, because the balloons are of predefined shape and size. Studies report a 90% satisfaction rate and a 25% amenorrhea rate.

Microwave endometrial ablation

This procedure was developed and has been used in Europe since 1996. Microwave endometrial ablation (MEA) uses high-frequency microwave energy to cause rapid, but shallow heating of the endometrium. The device consists of the software controlled unit which provides microwave energy of fixed 9.2 G Hz frequency at 30W power. These microwaves are released into the uterine cavity by means of a 15 cm long,

8 mm diameter applicator which also has a thermocouple at the tip to record the abdominal temperature. The local heating effect by the microwaves (75–80°C) leads to ablation. Microwaves are selected so that they do not cause destruction beyond 6 mm. There is an inbuilt alarm in the system which gets activated, if the temperature exceeds 85°C and the power automatically gets shut off at 90°C. MEA requires 3 minutes of time and only local anesthesia. Its use is now proving to be as effective as TCRE.

Laser thermoablation

Endometrial laser intrauterine thermo therapy (ELITT) is different from the first generation laser endometrial ablation. In this procedure, the cavity is not distended or visualized and ND: YAG laser is not used. This is a blind procedure in which, following the dilatation of cervix to about 7 mm, a handset device with fold away arm design containing three optical diffusers is inserted inside the uterine cavity. The arm of the device opens up inside the uterine cavity, conforming to the uterine shape, there by ensuring the uniform distribution of the laser light. The device should ideally be used in the normal sized, regular uterine cavity. Laser light is absorbed by hemoglobin in the uterine wall, resulting in blood coagulation. Temperature rises up to 102°C inside the uterine cavity but only up to 60°C in the device. If prior treatment with GnRH analogues has been done, this procedure helps in destruction of the entire depth of the endometrium along with 1–3.5 mm of myometrium.

Cryoablation

In this procedure, the cryoprobe is inserted under ultrasound guidance up to the level of uterine fundus and cooled to –90°C. The tip of the probe freezes the uterine lining by perfusing liquid nitrogen. The procedure is performed for approximately 10 minutes. A cycle of two minutes freeze followed by two minutes thaw leads to endometrial destruction until the depth of approximately 4–5 mm. Patients undergoing cryoablation may experience watery vaginal discharge for nearly 1 week following the procedure. Other risks associated with cryoablation include perforation and suboptimal ablation of the entire uterine cavity. Studies indicate that 50–70% of patients may experience complete amenorrhea following the procedure.

Electrosurgical endometrial ablation

Electrosurgical ablation can be performed with a device which consists of coaxial bipolar system, 1.6 mm in diameter. It can be inserted into the opening channel of 5 mm continuous flow hysteroscope and has different types of electrodes tips like spring, twizzle, etc. After uterine distension, the endometrium is touched with the device to complete the circuit and produce electrosurgical ablation.

Photodynamic endometrial ablation

In photodynamic endometrial ablation procedure, chemicals capable of producing photosensitizing effect, e.g. (5-aminolevulinic acid) have been tried to achieve endometrial ablation. This chemical is preferentially taken by the protoporphyrin IX molecules present in the endometrial blood vessels. After four hours following ALA instillation, laser light at a wave length of 635 nm and intensity of 300 MW is delivered for 60 minutes inside the uterine cavity. This helps in achieving endometrial ablation. Presently, the feasibility and clinical usefulness of this procedure has not been established.

Radiofrequency induced thermal ablation

In this procedure, a probe is inserted into the uterus through the cervix. The tip of the probe expands into a mesh-like device that sends radiofrequency energy into the uterine lining. The energy and heat destroys the endometrial tissue, while suction is applied to remove it. Radiofrequency ablation involves destruction of the endometrium using heat produced by the electromagnetic radiations of 27 MHz with power of 550 W, applied for a time period lasting for 20 minutes. The technique has been abandoned due to a high complication rate.

Other methods of endometrial ablation

Others devices for endometrial ablation include novasure, and hydrothermablation (HTA). They all have similar success rates. Novasure uses cautery, while HTA uses hot water which circulates around the cavity slowly and gently ablates the endometrial lining. Each of this method would be described below in details.

Hydrothermal ablation

The HTA Hydrothermablator® is the device used for performing hydrothermal ablation. This is performed as an office procedure under local anesthesia in which preheated normal saline is infused into the uterus via the hysteroscope and is allowed to circulate freely in the endometrial cavity. It is done under direct vision through a hysteroscope. As a result, this technique differs from other second generation techniques by virtue of not being a blind procedure because in this procedure heated normal saline is introduced into the uterine cavity under hyteroscopic monitoring. The solution is heated to 194°F/90°C; once the proper temperature is reached, the hot water circulates for 10 minutes and destroys the endometrial

cells. Vaginal, intestinal and skin burns are the most commonly reported complications. One of the concerns associated with the procedure was about the possibility of fluid leaking out through the fallopian tubes and burning intestines. Though occasional cases of intestinal burns can occur, this has not been proved by the clinical trials. Keeping this in mind, the device is specially engineered to keep the water at a low pressure so that it cannot escape through the tubes. This device helps in attaining intrauterine pressure equal to 40–45 mm of Hg, which is below that in the fallopian tubes (70–75mm of Hg). If the device senses a leak of greater than 10 ml, it automatically shuts off. This helps in preventing any inadvertent thermal injury to the vagina or peritoneal cavity. One treatment cycle over 10 minutes produces endometrial destruction of about 5 mm depth. The procedure is reported to have a satisfaction rate of about 87%. Since the water circulates freely throughout the entire uterine cavity, the shape of the cavity does not affect the results. As a result, the device is very effective for women with fibroids and irregularly shaped endometrial cavities or enlarged uterine cavities. Hydrothermal ablation takes about 10 minutes and the results are excellent.

Novasure

It is a simple, safe procedure that removes the lining of the uterus to reduce or eliminate bleeding. It offers the following advantages: The procedure takes approximately 4 minutes and comprises of a simple, 90-second treatment cycle; it has been proven to be a safe and effective therapy; requires no pretreatment; it is a convenient procedure which can be performed at any time during the menstrual cycle; is associated with rapid recovery and has an excellent success rate.

Novasure system is also based on electrosurgical power setting consisting of a computerized power generator and a hand piece which does not require hysteroscopic guidance. The hand piece has a catheter that carries metallic membrane electrode supported over an expandable skeleton. It is inserted inside the uterine cavity in a collapsed state and is then expanded. The generator applies suction to draw the endometrium in contact with the electrode and then the current is passed. This helps in destroying adequate depth of the endometrium.

Important Questions and Answers

Q.1. What would be the next line of management in the above mentioned case study?

Ans. The initial step is to stabilize the patient. Depending on the severity of her bleeding, she can be administered either oral or parenteral conjugated estrogens to control the initial episode of bleeding. Once the bleeding episode has been controlled, the patient is to be prescribed oral progestogens (10 mg daily) for last 15 days of cycle. This when administered over a period of 4–6 months would help in regularizing the cycle.

Q.2. What treatments for DUB are there for a young woman?

Ans. Teenagers and young women wishing to retain their fertility generally require medical treatment. The combined oral contraceptive pill is frequently an effective first choice for younger patients particularly when there is need for contraception. Teenagers with heavy periods may be having anovulatory cycles; progestogens prescribed in the second half of the cycle may prove to be effective. Tranexamic acid, two or three tablets taken three or four times daily, on the usually heavy period days is otherwise a sensible first choice. When pain accompanies the heavy loss, a nonsteroidal anti-inflammatory agent may be appropriate. Mefenamic acid 500 mg three times daily is a popular selection.

Q.3. How can you decide the best treatment option for menorrhagia?

Ans. It is essential that clinician should be aware of the options available. Age and fertility requirements are the first concern. Next the severity of the problem and its duration must be taken into account. Other factors, such as pelvic pain or premenstrual syndrome may also influence the decision.

Bibliography

1. Andersson K, Mattsson LA, Rybo G, Stadberg E. Intrauterine release of levonorgestrel—A new way of adding progestin in hormone replacement therapy. Obstet Gynecol. 1992;79:963-7.
2. Apgar BS, DeWitt D. Diagnostic hysteroscopy. Am Fam Physician. 1992;46(5 Suppl):19S-36S.
3. Baughan DM. Changes in the management of patients with dysfunctional uterine bleeding. Fam Pract Recertification. 1993;15:68-78.
4. Bayer SR, DeCherney AH. Clinical manifestations and treatment of dysfunctional uterine bleeding. JAMA. 1993;269:1823-8.
5. Brooks PG, Clouse J, Morris LS. Hysterectomy vs. resectoscopic endometrial ablation for the control of abnormal uterine bleeding. A cost-comparative study. J Reprod Med. 1994;39:755-60.
6. Brooks PG, Serden SP, Davos I. Hormonal inhibition of the endometrium for resectoscopic endometrial ablation. Am J Obstet Gynecol. 1991;164:1601-8.
7. Brooks PG, Serden SP. Endometrial ablation in women with abnormal uterine bleeding aged fifty and over. J Reprod Med. 1992;37:682-4.
8. Campion MJ, Reid R. Screening for gynecologic cancer. Obstet Gynecol Clin North Am. 1990;17:695-727.
9. Chamberlain G, Freeman R, Price F, Kennedy A, Green D, Eve L. A comparative study of ethamsylate and mefenamic

acid in dysfunctional uterine bleeding. Br J Obstet Gynaecol. 1991;98:707-11.
10. Copperman AB, DeCherney AH, Olive DL. A case of endometrial cancer following endometrial ablation for dysfunctional uterine bleeding. Obstet Gynecol. 1993;82:640-2.
11. DeVore GR, Owens O, Kase NL. Use of intravenous premarin in the treatment of dysfunctional uterine bleeding: A double blind randomized control study. Obstet Gynecol. 1982:59:285-91.
12. Dijkhuizen FP, Mol BW, Brolmann HA, et al. The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis. Cancer. 2000;89(8):1765-72.
13. Dockeray CJ, Sheppard BL, Bonnar J. Comparison between mefenamic acid and danazol in the treatment of established menorrhagia. Br J Obstet Gynecol. 1989;96:840-4.
14. Dodson MG. Use of transvaginal ultrasound in diagnosing the etiology of menometrorrhagia. J Reprod Med. 1994;39: 362-72.
15. Fayez JA. Dysfunctional uterine bleeding. Am Fam Physician. 1982;25:109-15.
16. Garry R, Shelley-Jones D, Mooney P, Phillips G. Six hundred endometrial laser ablations. Obstet Gynecol. 1995;85:24-9.
17. Gilman CJ. Management of early-stage endometrial carcinoma. Am Fam Physician. 1987;35:103-12.
18. Hall P, Maclachlan N, Thorn N, Nudd NWE, Taylor CG, Garrioch DB. Control of menorrhagia by the cyclo-oxygenase inhibitors naproxen sodium and mefenamic acid. Br J Obstet Gynecol. 1987;94:554-8.
19. Horowitz IR, Copas PR, Aaronoff M, Spann CO, McGuire WP. Endometrial adenocarcinoma following endometrial ablation for postmenopausal bleeding. Gynecol Oncol. 1995;56:460-3.
20. Hui SK, Lee L, Ong C, et al. Intrauterine lignocaine as an anaesthetic during endometrial sampling: A randomised double-blind controlled trial. BJOG. 2006;113(1):53-7.
21. Johnson CA. Making sense of dysfunctional uterine bleeding. Am Fam Physician. 1991;44:149-57.
22. Karlsson B, Granberg S, Wikland M, Ylostalo P, Torvid K, Marsal K, Valentin L. Transvaginal ultrasound in women with postmenopausal bleeding - A Nordic multicenter study. Am J Obstet Gynecol. 1995;172:1488-94.
23. Livengood CH 3rd, Land MR, Addison WA. Endometrial biopsy, bacteremia, and endocarditis risk. Obstet Gynecol. 1985;65(5):678-81.
24. Madari S, Al-Shabibi N, Papalampros P, et al. A randomised trial comparing the H Pipelle with the standard Pipelle for endometrial sampling at 'no-touch' (vaginoscopic) hysteroscopy. BJOG. 2009;116(1):32-7.
25. Meyer W, Walsh B, Grainger DA, Peacock LM, Loffer FD, Steege JF. Thermal balloon and rollerball ablation to treat menorrhagia: A multicenter comparison. Obstet Gynecol. 1998; 92:98-103.
26. Neese RE. Abnormal vaginal bleeding in perimenopausal women. Am Fam Physician. 1989;40:185-92.
27. Nutis M, Garcia KM, Nuwayhid B, et al. Use of ultrasonographic cut point for diagnosing endometrial pathology in postmenopausal women with multiple risk factors for endometrial cancer. J Reprod Med. 2008;53(10):755-9.
28. Oehler MK, MacKenzie I, Kehoe S, et al. Assessment of abnormal bleeding in menopausal women: an update. J Br Menopause Soc. 2003;9(3):117-20.
29. Oehler MK, Rees MC. Menorrhagia: an update.; Acta Obstet Gynecol Scand. 2003;82(5):405-22.
30. Rosenfeld J. Treatment of menorrhagia due to dysfunctional uterine bleeding. Am Fam Physician. 1996;53:165-72.
31. Seamark CJ. Endometrial sampling in general practice. Br J Gen Pract. 1998;48(434):1597-8.
32. Serden SP, Brooks PG. Treatment of abnormal uterine bleeding with the gynecologic resectoscope. J Reprod Med. 1991; 36:697-9.
33. Shaw RW. Assessment of medical treatments for menorrhagia. Br J Obstet Gynaecol. 1994;101 Suppl 11:15-8.
34. Thomas EJ, Okuda KJ, Thomas NM. The combination of a depot gonadotropin releasing hormone agonist and cyclical hormone replacement therapy for dysfunctional uterine bleeding. Br J Obstet Gynaecol. 1991;98:1155-9.
35. Williams AR, Brechin S, Porter AJ, et al; Factors affecting adequacy of Pipelle and Tao Brush endometrial sampling. BJOG. 2008;115(8):1028-36.
36. Wortman M, Daggett A. Hysteroscopic management of intractable uterine bleeding. A review of 103 cases. J Reprod Med. 1993;38:505-10.

Section 5

Abnormalities of Vagina and Cervix

- Vaginal Discharge
- Cancer Cervix (Postcoital Bleeding)

Chapter 20

Vaginal Discharge

Case Study

A 23-year-old unmarried lady presented to the gynecological OPD with the complaints of vaginal discharge since last 4–5 days. She described the discharge as being white in color and curd-like in consistency. It was associated with significant itching and discomfort which greatly interfered with her normal routine and disturbed her sleep. The patient does not give history of ever having any sexual partner or indulging in any kind of sexual activity. There is no past medical history of diabetes or any other medical disorder in the past. The patient does give history of taking a seven-day course of the antibiotic erythromycin, which was prescribed to her by a general practitioner for throat infection, a few days back.

Introduction

Vaginal discharge is one of the most common presenting complaints faced by the gynecologists in clinical practice. The most important challenge for the gynecologist is to differentiate between the pathological and physiological causes of discharge (table 20.1). A normal vaginal discharge consists of 1–4 mL of fluid that is white or transparent and odorless. This physiologic discharge is formed by sloughing epithelial cells, normal bacteria and vaginal transudate. If a pathological cause of discharge is suspected, the gynecologist needs to diagnose the exact cause for vaginal discharge. Some common causes of pathological vaginal discharge are described in table 20.2. Healthy women belonging to the reproductive age groups may normally produce some amount of physiological vaginal discharge. The quality and quantity of vaginal discharge may vary even in the same woman over different phases of menstrual cycle. In most cases, women develop a sense of their own vaginal discharge and learn to identify what is acceptable or excessive for them. The amount of physiological vaginal discharge can vary in the same woman. Some of the factors which can influence the amount of physiological discharge include the following: Woman's age, pregnancy, use of hormonal preparations (OCP's, etc) and the woman's personal habits and level of hygiene.

Physiological vaginal discharge is commonly encountered among women belonging to the reproductive age group and varies in amount and consistency during the various phases of the menstrual cycle. For example the cervical

Table 20.1: Differentiating between physiological and pathological causes of vaginal discharge

Physiological vaginal discharge	*Pathological vaginal discharge*
Does not usually cause any discomfort to the patient (except for hygiene problems)	Usually causes significant distress and irritation to the patient
Translucent to whitish in color	May vary in color from dirty white to yellowish green
Is not associated with itching	May be associated with itching
Not foul smelling	May be foul smelling
Amount of discharge may vary in different phases of menstrual cycle	Amount of discharge does not vary in different phases of menstrual cycle
Discharge is usually not adherent to the vaginal walls	Discharge is usually adherent to the vaginal walls and pools up in the dependent areas of vagina

Table 20.2: Causes of pathological vaginal discharge

Infective discharge	*Other causes for discharge*
Vulvovaginal candidiasis	Retained tampon or condom
Vaginitis caused by *Trichomonas vaginalis, Chlamydia trachomatis,*	
STD *(Neisseria gonorrheae)*	Chemical irritation
Bacterial vaginosis	Allergic responses
Acute pelvic inflammatory disease	Ectropion
Post-operative pelvic infection	Endocervical polyp
Post-abortal/postpartum sepsis	Intrauterine device
Less common causes	
Human papillomavirus	Atrophic changes
Primary syphilis	Physical trauma
Mycoplasma genitalium	Vault granulation tissue
Ureaplasma urealyticum	Vesicovaginal fistula
Escherichia coli	Rectovaginal fistula
	Neoplasia (cervical, vulvar, vaginal or endometrial)

discharge becomes profuse just prior to ovulation. During this phase the discharge is watery, transparent and can be stretched for nearly 7–8 cm between the two fingers of the examining hand. Following ovulation, the amount of cervical discharge greatly diminishes in quantity, becomes thicker in consistency, yellowish-whitish in color and loses its capacity of stretching.

PATHOLOGICAL VAGINAL DISCHARGE

Vulvovaginitis can be considered as one of the most common causes for pathological vaginal discharge, irritation and itching in women. Vulvovaginitis commonly results due to inflammation of the vagina and vulva and is most often caused by bacterial, fungal or parasitic infection. Nearly 90% of cases of vaginitis are secondary to bacterial vaginosis, vulvovaginal candidiasis and trichomoniasis. Of these different types of vaginitis, vulvovaginal candidiasis is one of the commonest infective causes of vaginal discharge that affects nearly 75% of women at some time during their reproductive lives. On the other hand, bacterial vaginosis, despite of being asymptomatic in most of the cases is one of the most common diagnoses in women attending genitourinary medicine clinics. The characteristic features of different types of vaginitis are summarized in table 20.3 and would be described in details later in the chapter. Different types of vaginal discharge are shown in figure 20.1. Other important causes for vulvovaginal discharge include, atrophic/contact vaginitis and sexually transmitted diseases, which would also be described later in the chapter.

Vulvovaginal itching generally is not a normal finding in healthy women; if this symptom is present, especially in presence of vaginal discharge, vulvovaginitis (especially candidal) must be specifically ruled out. In absence of vaginal discharge, other dermatologic conditions (e.g., lichen sclerosis and rarely, vulvar cancer) should also be considered.

Pathophysiology

The normal vaginal epithelium undergoes cornification under the influence of estrogen. This thickening of the vaginal epithelium helps in protecting women against infection. Normal vaginal epithelium is inhabited by the bacteria, *Lactobacilllus acidophilus*, which produces hydrogen peroxide. This is not only toxic to the pathogens present in the vagina; it also helps in maintaining the healthy vaginal pH between 3.8 and 4.2. Vaginitis occurs either due to alteration of vaginal flora by the introduction of pathogens or due to the changes in the vaginal environment that allow pathogens to proliferate. Vaginal pH may increase with age, phase of menstrual cycle, sexual activity, hormone therapy, contraception choice, pregnancy, presence of necrotic tissue or foreign bodies and use of hygienic products or antibiotics. This change in vaginal pH may encourage the growth of pathogenic microorganisms. Changes in the vaginal environment, such as an increase in glycogen production in pregnancy or altered estrogen and progesterone levels from the use of oral contraceptives, may also encourage the growth and development of *C. albicans.*

Bacterial Vaginosis

Bacterial vaginosis is one of the most important causes of vulvovaginitis. Initially, this was termed as bacterial vaginitis. However, later it was discovered that the condition was primarily caused due to the alteration of normal vaginal flora, rather than due to any specific infection. Thus the term bacterial vaginosis is now being preferably used over vaginitis. The normal vaginal epithelium contains numerous bacteria called *Lactobacillus acidophilus*. These bacteria release hydrogen peroxide, which is toxic to other aerobic and anaerobic bacteria. Bacterial vaginosis typically is associated with a reduction in the number of the normal hydrogen peroxide-producing *Lactobacilli* in the vagina.

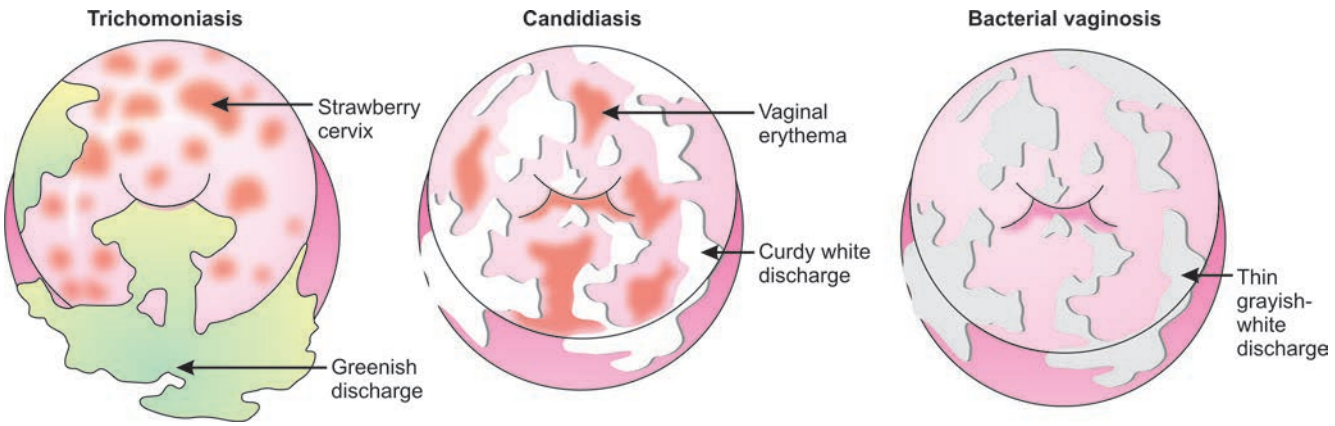


Fig. 20.1: Different types of vaginal discharge

Table 20.3: Features of the most common causes of vaginitis

Basis of diagnosis	*Bacterial vaginosis*	*Vulvovaginal candidiasis*	*Trichomoniasis*
Signs and symptoms	Thin, grayish to off-white colored discharge; unpleasant "fishy" odor, with odor especially increasing after sexual intercourse. The discharge is usually homogeneous and adheres to vaginal walls.	Thick, white ("curd like") discharge with no odor	Copious, malodorous, yellow-green (or discolored) discharge, pruritus and vaginal irritation, dysuria, no symptoms in 20% to 50% of affected women
Physical examination	Normal appearance of vaginal tissues; grayish-white colored discharge may be adherent to the vaginal walls.	Vulvar and vaginal erythema, edema and fissures Thick, white discharge that adheres to vaginal walls	Vulvar and vaginal edema and erythema, "strawberry" cervix in up to 25% of affected women. Frothy, purulent discharge
Vaginal pH (normal = <4.5)	Elevated (>4.5)	Normal	Elevated (>4.5)
Microscopic examination of wet-mount and KOH preparations of vaginal discharge	"Clue cells" (vaginal epithelial cells coated with coccobacilli) Few lactobacilli, occasional motile, curved rods, belonging to *Mobiluncus* species	Pseudohyphae, mycelial tangles or budding yeast cells	Motile trichomonads Many polymorphonuclear cells
"Whiff" test (Normal = no odor)	Positive	Negative	Can be positive
Additional tests	Amsel's criteria (table 20.4) is positive in nearly 90% of affected women with bacterial vaginosis	KOH microscopy, gram stain, culture	DNA probe tests: Sensitivity of 90% and specificity of 99.8% Culture: Sensitivity of 98% and specificity of 100%

Source: Carr PL, Felsenstein D, Friedman RH. Evaluation and management of vaginitis. J Gen Intern Med 1998;13:335-46, and Sobel JD. Vaginitis. N Engl J Med 1997;337:1896-903.

The resultant change in pH allows proliferation of organisms that are normally suppressed, such as *Hemophilus vaginalis*, *Gardnerella mobilicus*, *Mycoplasma hominis*, *Gardnerella vaginalis*, *Peptostreptococcus* species, etc. These organisms may produce metabolic byproducts, such as amines, that further increase the vaginal pH and cause exfoliation of vaginal epithelial cells. These amines are also responsible for the characteristic malodorous discharge in bacterial vaginosis. Bacterial vaginosis is not dangerous, but it can cause disturbing symptoms. Certain factors have been identified that increase the chances of developing bacterial vaginosis. These include multiple or new sexual partners, vaginal douching and cigarette smoking. However, the role of sexual activity in the development of the condition is not fully understood and bacterial vaginosis can still develop in women who have not had sexual intercourse.

Clinical presentation

Women with bacterial vaginosis have a broad spectrum of clinical presentations.

- The classic presentation is a vaginal discharge with its characteristic odor and a clinical examination that is otherwise normal.
- There is presence of white milky, nonviscous discharge which is adherent to the vaginal wall. pH of the discharge is more than 4.5.
- A fishy odor is produced when the discharge is mixed with 10% KOH solution due to production of aminometabolites from various organisms (amine or Whiff's test).
- There is no or minimal vaginal irritation.
- Presence of clue cells: The epithelial cells acquire a fuzzy border due to adherence of bacteria.

Bacterial vaginosis is mainly diagnosed using Amsel's criteria, with three of the four findings required to establish its diagnosis (table 20.4).

Diagnosis

Microscopic examination

Presence of clue cell: A typical sign of bacterial vaginosis on microscopic examination is presence of an unusual vaginal cell known as "clue cell" (figure 20.2). Clue cells are believed to be the most reliable diagnostic sign of bacterial vaginosis. Clue cells are vaginal epithelial cells, which are studded with bacteria on their surface. This results in the obscuration of their borders. In addition to clue cells, women with bacterial

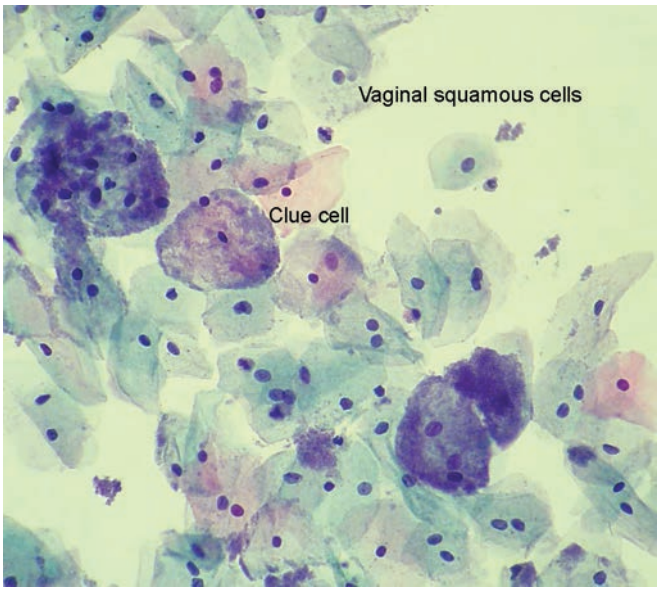


Fig. 20.2: Clue cells

Table 20.4: Amsel's diagnostic criteria for bacterial vaginosis

Thin, homogeneous discharge
Positive "Whiff" test
Presence of "clue cells" on microscopic examination
Vaginal pH >4.5

vaginosis have fewer of the normal vaginal bacteria, called *Lactobacilli*. A vaginal pH greater than 4.5 is also suggestive of bacterial vaginosis.

Whiff test (figure 20.3)

This test is diagnostic of bacterial vaginosis and is performed using potassium hydroxide (KOH) solution. The test is said to be positive if there is production of a typical fishy odor when KOH comes in contact with discharge of a woman with bacterial vaginosis.

Amsel's criteria

Amsel's criteria (table 20.4) helps in establishing the diagnosis of bacterial vaginosis in nearly 90% of affected women. Three of the above mentioned four criteria must be met in order to establish the accurate diagnosis of bacterial vaginosis. Of the various criteria mentioned, presence of clue cells on microscopic examination is a highly significant criterion.

Treatment

Treatment for bacterial vaginosis consists of antibiotics. A few antibiotics are routinely used. These include the following:

Metronidazole: The World Health Organization has recommended metronidazole as the first line therapy for the

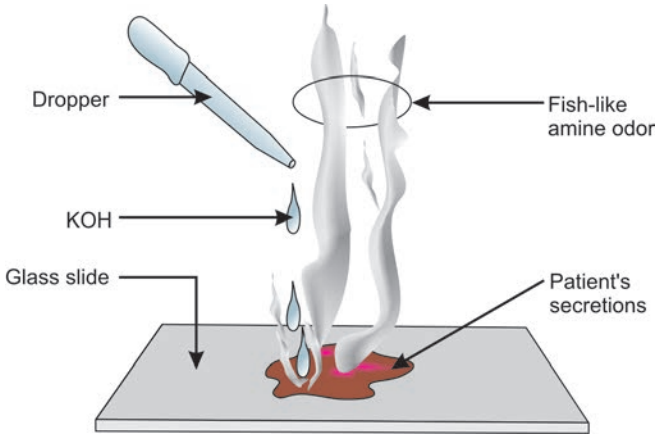


Fig. 20.3: Whiff test

treatment of bacterial vaginosis. A seven-day course of oral metronidazole, 400 mg TDS or vaginal metronidazole gel (metrogel) is an effective treatment. A 7-day course of metronidazole (500 mg TDS) is effective in nearly 85% cases. The oral metronidazole can cause some minor, but unpleasant side effects, such as anorexia, nausea, metallic taste, abdominal cramps, headache, glossitis, dryness of mouth, dizziness, rashes, transient neutropenia, etc. Despite of these side effects, it is believed to be the most effective treatment. The gels do not typically cause any side effects. Tinidazole is an antibiotic that appears to have fewer side effects than metronidazole and is also effective in treating bacterial vaginosis. Ornidazole, 500 mg vaginal tablet daily for seven days is another effective option. Use of vaginal tablets help in avoiding first past metabolism.

Ampicillin: Ampicillin 500 mg TDS or cephalosporins 500 mg BID for seven days is also effective.

Tetracyclines: Tetracycline 500 mg, four times a day or doxycycline 100 mg twice daily for seven days is effective.

Lincosamides: Vaginal clindamycin cream, 2% (cleocin) or oral clindamycin, 300 mg daily for seven days is also effective.

Complications of bacterial vaginosis

Though bacterial vaginosis can resolve completely without any complications following treatment, a variety of complications have also been found to be associated with bacterial vaginosis. Some of these include, pelvic inflammatory disease, an increased frequency of endometritis, abnormal Papanicolaou (Pap) smears, abdominal pain, uterine bleeding and uterine and adnexal tenderness. Performance of an invasive gynecological procedure or surgery in a patient with bacterial vaginosis may result in the development of vaginal cuff cellulitis, pelvic inflammatory disease and endometritis. Bacterial vaginosis during pregnancy can result

in complications like premature labor, preterm birth, chorioamnionitis, postpartum endometritis, ectopic pregnancy and post-cesarean section wound infections.

Vulvovaginal Candidiasis

General features

Vulvovaginal candidiasis (VVC) is the second most common cause of vaginitis in the United States and the most common cause of vulvovaginitis in Europe. In most of the cases, the infecting agent is the yeast *Candida albicans* (figure 20.4). Recently, due to the increasing use of over-the-counter antifungal medications, the frequency of non-albicans species (e.g., *Candida glabrata, Candida tropicalis, etc.*) in causation of candidal vaginitis has greatly increased.

Clinical features

In vulvovaginal candidiasis, the discharge is usually white and thick, with no odor and a normal pH. Pruritis vulva is a cardinal feature. Women with vulvovaginal candidiasis frequently complain of pruritus, vaginal irritation, dysuria, vulvar and vaginal erythema and occasionally, scaling and fissures of vulvar tissue.

Risk factors

Severe factors are thought to be associated with an increased risk for uncomplicated vulvovaginal candidiasis. Some such factors which are associated with an increased risk of this infection include the following:

- Women using oral contraceptive pills or an IUCD for contraception
- Diabetes mellitus
- Antibiotic use
- Immunodeficiency or use of immunosuppressive agents
- Use of tight-fitting synthetic undergarments
- Pregnancy
- Previous episode of vulvovaginal candidiasis

This infection is more likely to occur during pregnancy probably because high levels of estrogen or glycogen in the vaginal secretions during pregnancy are likely to increase a woman's risk of developing VVC. Use of adequate pharmacotherapy and avoidance of risk factors can help in the resolution of symptoms related to VVC over a short period of time.

Diagnosis

Microscopic examination: Microscopic examinations of wet-mount and KOH preparations are positive in 50% to 70% of patients with candidal infections. In patients whose symptoms are strongly suggestive of candidal vaginitis, but the microscopic examination is negative, Gram staining or culture using Nickerson's medium or Sabouraud's dextrose agar may prove to be helpful. In candidal infections, KOH preparation may reveal budding filaments, mycelia, or pseudohyphae. A fungal culture may be used if the diagnosis is uncertain. Microscopy for candidal disease has an estimated sensitivity of 65%.

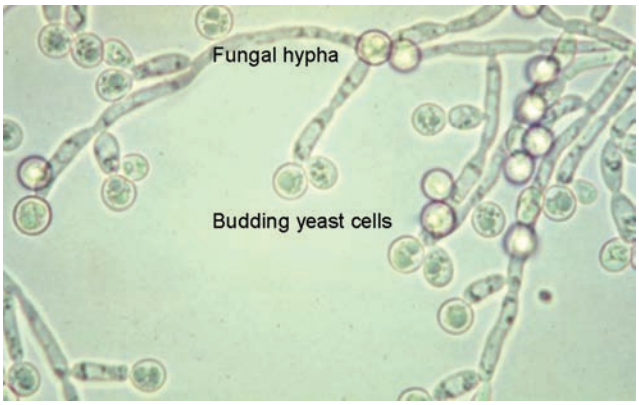


Fig. 20.4: Wet mount preparation of *Candida albicans*

Complications of vulvovaginal candidiasis are rare. Chorioamnionitis in pregnancy and vulvar vestibulitis syndrome have also been reported.

Candidal organisms are not transmitted sexually, and episodes of vulvovaginal candidiasis do not appear to be related to the number of sexual partners. Treating the male partner is unnecessary unless he is uncircumcised or has inflammation of the glans of the penis. Recurrent vulvovaginal candidiasis is defined as four or more episodes in a one-year period. It is not clear whether recurrences are secondary to predisposing and/or precipitating factors, sexual transmission, intestinal reservoir or vaginal persistence.

Treatment

Antifungals: Imidazoles and triazoles are presently the most extensively used antifungal drugs for treatment of VVC. Imidazole antifungal agents which can be used in form of creams and pessaries for treatment of VVC include butoconazole, clotrimazole and miconazole. Some of these agents are freely available over the counter. Trizole agents include systemically acting agents such as fluconazole. A single dose of triazole antifungals (e.g., 150 mg of fluconazole) has also been shown to be effective in most cases. Oral fluconazole in the dosage of 150 mg every 72 hours for 3 doses serves as an effective therapy for recurrent vulvovaginitis. This should be then followed by weekly doses for a few weeks. Ideally, both the partners should be treated and the underlying predisposing factors be corrected to provide long-term relief.

Most clinicians prefer not to use fluconazole during pregnancy due to an increased risk of major congenital

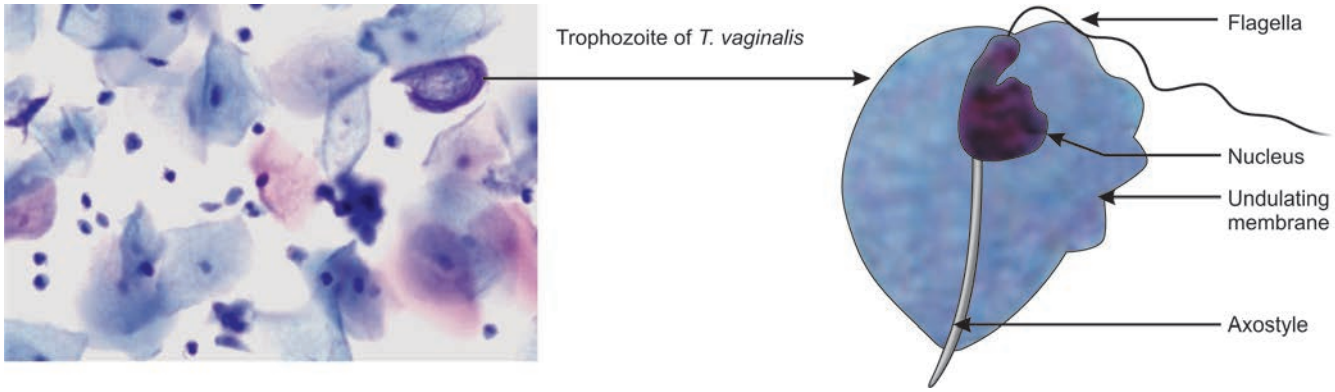


Fig. 20.5: *Trichomonas vaginalis*

malformations. However, the available evidence indicates that fluconazole in a single dosage of 150 mg is usually not teratogenic to the fetus. Most clinicians, however, prefer to use topical formulations of imidazole and triazole antifungals during pregnancy. Systemic absorption of these topical medications is minimal, posing little risk of transfer to the unborn baby. Topical nystatin is another safe alternative to azole antifungals that can be used during the first trimester of pregnancy. Since nystatin has negligible systemic absorption, there are unlikely to be any major malformations associated with the use of this drug. The recommended dose of nystatin during pregnancy is 100,000 units intravaginally once daily for 2 weeks. For symptomatic relief of redness or itching, short-term use of a low-potency topical corticosteroid is also considered as a safe option during pregnancy.

Antiseptics: Boric acid suppositories are often used for the treatment of VVC. Although not commercially available, boric acid serves an alternative to the antifungal agents. The typical dose of boric acid is 600 mg intravaginally per night for 14 consecutive nights. Presently, there is little evidence regarding the safety of boric acid in women at the time of pregnancy. Unless the vaginal epithelium is severely excoriated, only a limited amount of boric acid is systemically absorbed. Therefore, in most of the cases the amount absorbed through the vaginal mucosa is minimal and risk to the unborn fetus is negligible.

Corticosteroids: Topical corticosteroids are commonly prescribed to alleviate symptoms such as itchiness and redness, which may commonly occur in cases of VVC.

Trichomoniasis

General characteristics

This vaginitis is caused by the protozoa *Trichomonas vaginalis* (figure 20.5), a motile organism affecting nearly 180 million women worldwide and currently accounting for 10% to 25% of vaginal infections. Trichomonads are usually transmitted sexually (figure 20.6) and may be identified in 30% to 80% of the male sexual partners of infected women. Trichomoniasis may commonly act as a vector for other sexually transmitted diseases, including, the human immunodeficiency virus.

Clinical features

Classic manifestations of vaginal trichomoniasis include a purulent, frothy, yellow discharge with an abnormal odor, pruritus and dysuria. The typical discharge associated with this infection is profuse, thin, creamy or slightly green in color, irritating and frothy. Since the discharge commonly

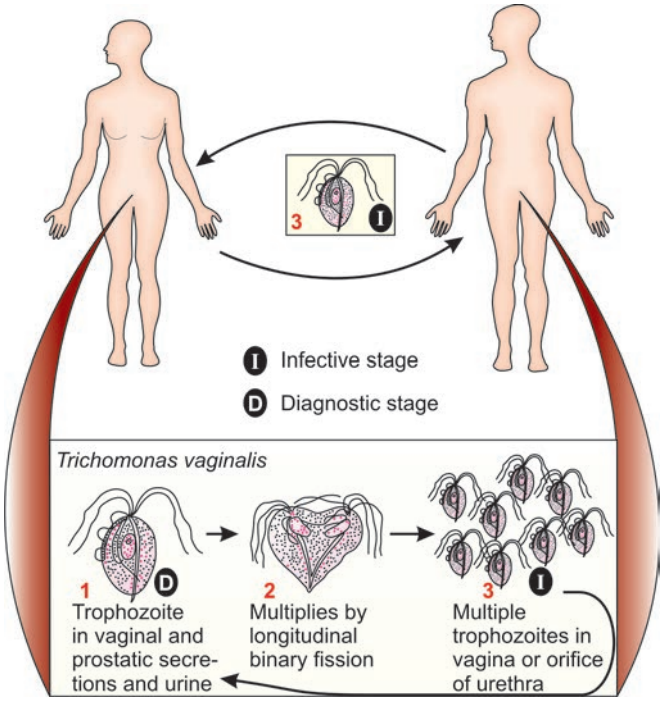


Fig. 20.6: Transmission of *trichomonas vaginalis*

causes pruritis and inflammation of the vulva and vagina, the vaginal walls are often tender and appear angry looking. There may be presence of multiple, small, punctuate, strawberry spots on the vaginal vault and portio vaginalis of the carvix resulting in a "strawberry vagina." The pH of the discharge is often elevated, i.e. >4.5.

Risk factors

Risk factors for trichomoniasis include use of an IUD, cigarette smoking and having multiple sexual partners. Since trichomoniasis is a sexually transmitted disorder, both the sexual partners must be treated and instructed to avoid sexual intercourse until both partners have been cured.

Diagnosis

Microscopic examination: Motile trichomonads are usually observed on microscopic examination of wet mounts. Warming the slide and decreasing the intensity of substage lighting are ways for increasing the detection rate of trichomonads on the microscopic examination. If the index of suspicion for trichomoniasis is high and microscopic examination of the wet mount preparation reveals negative results, the microorganism may be cultured using Diamond's medium. Additionally, tests using DNA probes and polymerase chain reaction tests, which are associated with high rates of sensitivity and specificity, may also be performed. Another test which is highly sensitive and specific for detection of trichomoniasis is the latex agglutination test. In this test, a trichomonas antibody or antigen, attached to latex beads, is mixed with the speculum sample. If the protozoan is present in the discharge sample, it reacts with the latex bead complex, resulting in an agglutination reaction. The results of the test are usually available within 10 minutes to an hour. However, the high cost of this examination has largely limited the widespread use of this test in the urgent care setting.

Treatment

Metronidazole in the dose of 200 mg TDS or 375 mg BID must be prescribed to both the partners for a period of seven days. The Centers for Disease Control and Prevention, however recommends a single dose of 2 g of metronidazole. This single dose regimen has been found to be associated with a greater cure rate varying from 90% to 95% in comparison to the week-long treatment with either 250 mg TID or 375 mg BID of metronidazole. Additionally, the single dose regimen is more convenient to take in comparison to 7-day regimen and is associated with better patient compliance. Since tricomoniasis is largely believed to be a sexually transmitted disease, both the partners should be advised to avoid intercourse or use a condom during the course of therapy. An alternative to metronidazole could be to prescribe tinidazole in the dose of 300 mg BD for seven days or secnidazole in a single dose of 1000 mg daily for two days. The husband should be treated simultaneously, especially if the woman develops recurrent infection. Use of metronidazole is contraindicated during pregnancy and lactation. During early pregnancy, the following may be used: Vinegar douches to lower the vaginal pH, trichofuran suppositories and betadine gel.

Atrophic Vaginitis

Atrophic vaginitis is one of the commonest causes for vaginal discharge in the postmenopausal women. After menopause, vaginal atrophy can result due to falling estrogen levels. Dyspareunia is common complication of atrophic vaginitis. Per speculum examination in women with vaginal atrophy may show loss of vaginal rugosity and thinning of the vaginal epithelium. This condition can be treated using topical formulations of conjugated estrogens (premarin) in the dosage of 2–4 g intravaginally qHS.

Sexually Transmitted Diseases (STDs)

Sexually transmitted diseases (STDs) are infections that can be transferred from one person to another due to any type of sexual contact. Some of the STDs which would be discussed in relation to their propensity to cause vaginal discharge are chlamydial infection, genital herpes and gonorrhea. Though these STDs are most commonly associated with vaginal discharge, other common STDs in women have also been described just for the sake of completion. Many STDs are treatable, but effective cures are lacking for others, such as HIV, HPV and hepatitis B and C. Condoms are commonly thought to protect against STDs. Condoms are useful in decreasing the spread of certain infections, such as chlamydia and gonorrhea; however, they do not fully protect against other infections such as genital herpes, genital warts, syphilis and AIDS. Early diagnosis and treatment of infections is important for prevention of the spread of STDs infections.

Chlamydial Infection

Chlamydia trachomatis is a gram-negative, aerobic, intracellular pathogen which is typically coccoid or rodshaped. However, it is different from other bacteria because it requires growing cells in order to remain viable. *Chlamydia* cannot be grown on an artificial medium because it cannot synthesize its own ATP molecules. *Chlamydia trachomatis* can be considered as one of the most common causes for STD, worldwide in association with blindness and infertility. Chlamydia has a very unique life cycle (figure 20.7), which alternates between a nonreplicating, infectious elementary body (EB) and a replicating, noninfectious reticulate body (RB). The

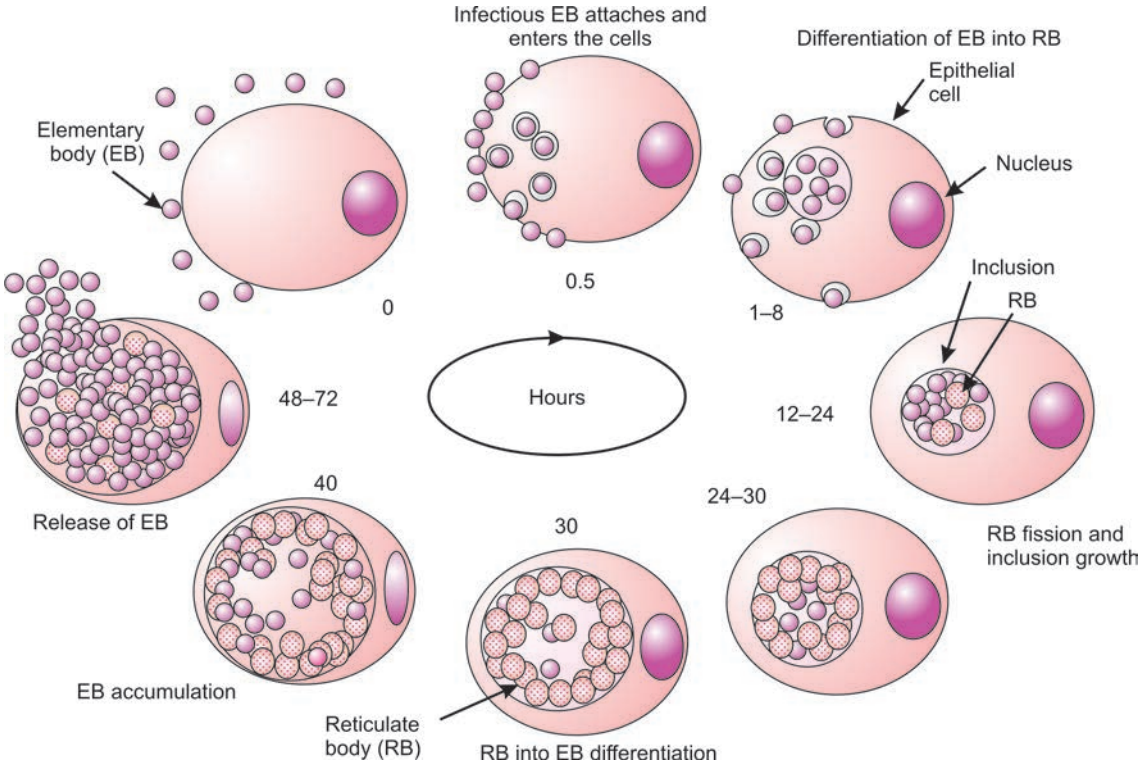


Fig. 20.7: Life cycle of *Chlamydia trachomatis*

20

elementary body, which is metabolically inactive can be considered equivalent to the spore and helps in transmitting the disease. The infectious EB attaches to the host cells. Following the entry into the cell, it gets differentiated into a RB. Once inside a cell, the elementary body germinates as the result of interaction with glycogen and gets converted into its reticulate form. The reticulate form divides by binary fission every 2–3 hours and has an incubation period of about 7–21 days in its host. Within 40–48 hours, the RBs transform back into infective EBs, which are subsequently released from the infected cell through the process of exocytosis and infect the neighboring cells.

Clinical features

The majority of women with chlamydial infection remain asymptomatic. However, some women may develop vaginal discharge, dysuria, abdominal pain, increased urinary frequency, urgency, urethritis and cervicitis. Infection of the urethra is often associated with chlamydial infection of the cervix. Chlamydia is very destructive to the fallopian tubes. If left untreated, nearly 30% of women with chlamydia may develop pelvic inflammatory disease. Pelvic infection often results in symptoms such as fever, pelvic cramping, abdominal pain or dyspareunia. Pelvic infection can often lead to infertility or even absolute sterility. Tubal destruction due to chlamydial infection may also result in an increased incidence of tubal pregnancy.

Chlamydial infection, similar to gonorrhea, is associated with an increased incidence of premature births. Additionally, the organism can infect the infant during passage through the infected birth canal, leading to serious eye damage or pneumonia. Due to this, all newborns born to women infected with *Chlamydia trachomatis* must be treated with eye drops containing a broad spectrum antibiotic (e.g. tetyracycline), which kills chlamydia.

Diagnosis

Direct immunoflorescence test: Fluorescein-conjugated monoclonal antibodies can be used on smears prepared from urethral and cervical swabs for detecting chlamydial antigens.

Enzyme-linked immunosorbent assay (ELISA): Can help in detecting the chlamydial antigen.

Polymerase and ligase chain reactions: For routine diagnostic use, newer and inexpensive diagnostic tests such as polymerase and ligase chain, which depend upon identification and amplification of the genetic material of the organism, have replaced the older, time-consuming culture methods.

Treatment

Treatment of chlamydia involves the use of broad spectrum antibiotics. A convenient single-dose therapy for chlamydia is 1 gm of azithromycin per orally. Alternatively, doxycycline can be used orally in the dosage of 100 mg BID for seven days. The combination of cefoxitin and ceftriaxone with doxycycline or tetracycline also proves to be useful. Erythromycin or amoxicillin in TID or QID dosage may also be given during pregnancy. Use of protective barrier such as condoms often helps prevent the spread of the infection. Gonorrhea and chlamydia are bacterial STDs, which are frequently found together.

Genital Herpes

Genital herpes is a viral infection caused by the herpes simplex virus (most commonly HSV II) which is transmitted through sexual contact. Two types of viruses are commonly associated with Herpes lesions: Herpes simplex virus-I (HSV-I) and herpes simplex virus-II (HSV-II). HSV-I is commonly responsible for causing herpes blisters in the perioral region, while HSV-II is more commonly associated with lesions in the genital or the perianal area. Genital herpes is spread only by direct person-to-person contact. The virus enters through the mucous membrane of the genital tract via microscopic tears. From there the virus travels to the nerve roots near the spinal cord and settles down permanently.

Symptoms of genital herpes

Once exposed to the virus, there is an incubation period which generally lasts from 3 to 7 days before development of lesions begin. Prior to this, there are no symptoms and the virus cannot be transmitted to others. The primary infection may be associated with constitutional symptoms like fever, malaise, vulval paresthesia, itching or tingling sensation on the vulva and vagina followed by redness of the skin. Finally, the formation of blisters and vesicles begins, which eventually develop into shallow and painful ulcers within a period of 2–6 weeks. In women, these lesions may appear on the vulva, vagina, cervix, perianal area, or inner thigh and are frequently accompanied by itching and a mucoid vaginal discharge. When the blisters break, they are usually very painful to touch. These lesions peak in seven days and last for approximately 2 weeks. The outbreak is self-limited and usually heals without scarring. From the beginning of itching, until the time of complete healing of the ulcer, the infection is definitely contagious.

Diagnosis of genital herpes

Diagnosis is usually based on clinical examination. Genital herpes is suspected when multiple painful blisters are present on external genitalia. Immunological or cytological tests are not very sensitive. The blister fluid may be sent to the laboratory for culturing the virus. However, it is associated with a high false negative rate of nearly 50%. Blood tests for detecting antibodies may prove to be useful in some situations. These tests are specific for HSV-1 or HSV-2 and may be able to demonstrate that a person has been infected at some point in time with the virus. Thus, they may be useful for identifying infection with atypical manifestations. However, these tests may be associated with false-positive results and therefore cannot be recommended for routine use in screening low-risk populations for HSV infection. Other diagnostic tests such as polymerase chain reaction (PCR) and rapid fluorescent antibody screening tests are being used to identify HSV in some laboratories.

Biopsy

The Tzanck smear is a rapid, fairly sensitive and inexpensive method for diagnosing HSV infection. Smears are preferably prepared from the base of the lesions and stained with 1% aqueous solution of toluidine blue "O" for 15 seconds. Positive smear is indicated by the presence of multinucleated giant cells with faceted nuclei and homogeneously stained "ground glass" chromatin (Tzanck cells).

Treatment for genital herpes

Treatment of genital herpes helps in shortening the duration of attack, preventing the occurrence of complications and reducing the risk of transmission. Oral antiviral medications, such as acyclovir, (Zovirax), famiciclovir (Famvir) or valacyclovir (Valtrex), which prevent the multiplication of the virus, are commonly used. For the treatment of primary outbreaks, oral acyclovir is prescribed in the dosage of 200 mg five times a day for five days. Local application of acyclovir provides local relief and accelerates the process of healing. In severe cases, acyclovir can be administered intravenously in the dosage of 5 mg/kg body weight every eight hourly for five days. The couple is advised to abstain from intercourse starting right from time of experiencing prodromal symptoms until total re-epithelization of the lesions occurs. Although topical agents do exist, they are generally less effective than oral formulations and therefore are not routinely used. However, it is important for the clinician to remember that there is still no curative medicine available for genital herpes and the above mentioned antiviral drugs only help in reducing the severity of symptoms and duration of outbreaks. Since the initial infection with HSV tends to be the most severe episode, an antiviral medication is usually recommended. Though the use of these medications can significantly help in reducing pain and decreasing the length of time until the sores heal,

treatment of the first infection does not appear to provide protection against the future episodes. In contrast to a new outbreak of genital herpes, recurrent herpes episodes tend to be milder in intensity. In these cases, the benefit of antiviral medication is derived, only if therapy is started immediately prior to the outbreak or within the first 24 hours of the outbreak. Thus, the antiviral drug must be provided to the patient well in advance and the patient is instructed to begin treatment as soon as she experiences the pre-outbreak "tingling" sensation or as soon as the blisters appear.

Herpes can be spread from one part of the body to another during an outbreak. Therefore, it is important to instruct the patient not to touch her eyes or mouth after touching the blisters or ulcers. Thorough hand-washing is a must during outbreaks. Clothing that comes in contact with ulcers should not be shared with others. Couples who want to minimize the risk of transmission should always use condoms if a partner is infected. Such couples must be instructed to avoid all kinds of sexual activity, including kissing, during an outbreak of herpes. Women who have herpes and are pregnant can have a vaginal delivery as long as they are not experiencing symptoms or actually having an active outbreak while in labor. Pregnant women with active herpetic lesion must be preferably delivered by cesarean section.

20

Gonorrhea

Gonorrhea is a sexually transmitted disease, which is derived from the Greek words *gonos* (seed) and *rhoia* (flow) implying "flow of seeds" and is caused by the bacterium *Neisseria gonorrheae*. Gonorrhea is spread through contact with the penis, vagina, mouth or anus. Gonorrhea can also be spread from mother to baby at the time of delivery. The disease is characterized by adhesion of the gonococci to the surface of urethra or other mucosal surfaces. The gonococci penetrate through the intercellular spaces between the columnar epithelial cells and reach the subepithelial connective tissue by the third day of infection. Gonococci usually penetrate the columnar epithelial cells because the stratified squamous epithelium is relatively resistant to infection. Thus infection usually does not occur in adult women; however, severe vulvovaginitis can occur in prepubertal girls. The incubation period is 2–8 days.

The commonest clinical presentation of the disease in men is acute urethritis resulting in dysuria and a purulent penile discharge. The infection may extend along the urethra to the prostate, seminal vesicles and epididymis, resulting in complications such as epididymitis, prostatitis, periurethral abscesses and chronic urethritis. The infection may spread to the periurethral tissues, resulting in formation of abscesses and multiple discharging sinuses ("watercan perineum").

In women, the primary site of infection is the endocervix and the infection commonly extends to the urethra and vagina, giving rise to mucopurulent discharge. Symptomatic patients commonly experience vaginal discharge, dysuria and abdominal pain. The infection may extend to Bartholin's glands, endometrium and fallopian tubes. The gonococci can typically ascend to the fallopian tubes at the time of menstruation or after instrumentation (for MTP) giving rise to acute salpingitis. Acute salpingitis, may be followed by pelvic inflammatory disease. This may be associated with a high probability of sterility if not treated adequately. Peritoneal spread occasionally occurs and may produce a perihepatic inflammation, resulting in Fitz-Hugh-Curtis syndrome.

Granuloma Inguinale (Donovanosis)

Granuloma inguinale, also known as "Donovanosis" or "Granuloma venereum" is a disease caused by the bacteria *Calymmatobacterium granulomatis*. The disease is characterized by occurrence of painless genital ulcers which can be sometimes mistaken for syphilitic ulcers. However, these ulcers are associated with destruction of internal and external tissue, along with leakage of mucus and blood. The disease is highly contagious and is transmitted through repeated sexual or anal intercourse. Very rarely, the infection may spread due to oral sexual activity.

Clinical features

The disease is characterized by presence of small, painless, beefy-red nodules, which usually appear on the genitals or around the anus, after about 10–40 days of the contact with the bacteria. The skin gradually wears away and the nodules soon get converted into raised, beefy-red, velvety, open, fleshy, oozing lesions called granulation tissue. These lesions are usually painless, but bleed easily if injured. The infection often spreads, mutilating the infected tissue and continues to destroy the tissue until it is treated. The lesions occur typically on the labia or the perineum in the women and may spread to inguinal region. Rarely, the vaginal wall or cervix may also be involved.

Diagnosis

Microscopic examination of smears from the lesions shows presence of pathognomonic intracytoplasmic donovan bodies and clusters of bacteria with bipolar (safety-pin) appearance.

Treatment

The standard form of therapy comprises of treatment with erythromycin, streptomycin or tetracycline (500 mg QID) for three weeks, or treatment with ampicillin for twelve weeks.

Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is a sexually transmitted disease, caused by the bacteria *Chlamydia trachomatis* (L1, L2, and L3 serovars) which primarily infects the lymphatic ducts and the lymph nodes. The bacteria gains entrance into the body either through the breaks in the skin or through the epithelial cell layer of mucous membranes. From there, the organism travels via the lymphatic channels into the lymph nodes and multiplies within mononuclear phagocytes of the lymph nodes, while it passes through them.

The clinical picture is termed as inguinal syndrome if the buboes or abscesses typically develop in the inguinal region where draining lymph nodes are located. The rectal syndrome arises if the infection takes place via the rectal mucosa through anal sex. It is mainly characterized by development of symptoms related to proctocolitis. Under rare circumstances, the oral sex may result in the pharyngeal syndrome, which is characterized by development of buboes in the neck region.

The LGV infection occurs in three stages: Primary, secondary and tertiary. In majority of cases, the patients in primary and secondary stages remain undetected. Primary stage is usually characterized by self-limited painless genital ulceration at the site of contact. These signs usually appear by 3 days to a month after exposure. Primary lesion in the urethra may result in the symptoms of nonspecific urethritis. The primary stage normally heals within a few days. Erythema nodosum may occur in approximately 10% of cases.

The most common sites of primary infection in men include the coronal sulcus, frenulum, prepuce, penis, urethra, glans and scrotum. In women, the most common sites of the primary lesion include the posterior vaginal wall, fourchette, posterior lip of the cervix and vulva.

The secondary stage usually occurs after 10–30 days. The secondary stage is characterized by the formation of enlarged, tender regional lymph nodes known as buboes. Patients may experience constitutional symptoms, such as fever, headache, malaise, chills, nausea, vomiting and arthralgias. The infection spreads to the lymph nodes via the lympathic drainage pathways, resulting in lymphadenitis and lymphangitis and tender inguinal and/or femoral lymphadenopathy. Lymphangitis of the dorsal penis may also occur and resembles "string or cord." In women, the infection can result in the development of cervicitis, perimetritis or salpingitis as well as lymphangitis and lymphadenitis in the deeper nodes. With the progression of the disease, the lymph nodes enlarge and are called buboes. The buboes may be painful initially and later become painless. This is often associated with inflammation, thinning and fixation of the overlying skin. Eventually, there occurs development of necrosis, fluctuant and suppurative lymph nodes, abscesses, fistulas, strictures and sinus tracts.

As the infection subsides and healing occurs, fibrosis may develop. This is known as the tertiary stage and can result in the development of lymphatic obstruction, chronic edema and strictures. Tertiary stage is characterized by proctocolitis and may produce symptoms such as anal pruritus, bloody mucopurulent rectal discharge, fever, rectal pain, tenesmus, constipation, weight loss, etc.

Chancroid (Soft Sore)

Chancroid is a sexually transmitted disease caused by the bacteria *Hemophilus ducreyi*, characterized by occurrence of painful sores on the genitalia. The disease is typically more common in the developing countries. Following an incubation period of one day to two weeks, the disease begins with a small nodule. Within a few days, these become filled with pus and eventually rupture, leaving painful, open sores or ulcers in the genital region. These ulcers can range in size from 1–3 centimeters in diameter. Ulcers can bleed or ooze pus and can take weeks to heal without medication. The ulcer may range in size from 3–50 mm across and is painful. The borders of the ulcer may be either sharply defined and undermined or have irregular or ragged edges. The ulcer base is covered with a gray or yellowish-gray material and it bleeds easily on being traumatized or scraped. The patient has one or more painful genital ulcers. The combination of a painful ulcer with tender or suppurative lymphadenopathy is pathognomonic of chancroid.

While the infected men have a single ulcer, infected women frequently have multiple (four or more ulcers), with fewer symptoms. The ulcers typically appear in the fourchette and labia minora in women. "Kissing ulcers" commonly develop over the labia. These are ulcers that occur on opposing surfaces of the labia. The affected women may commonly experience dysuria and dyspareunia. The initial "soft chancre" of chancroid ulcer may sometimes be mistaken as a "hard" chancre, the typical sore of primary syphilis. Approximately one third of the infected individuals will develop enlargement of the inguinal lymph nodes.The most commonly used antibiotics for treatment of chancroid include ciprofloxin, trimethoprim or erythromycin.

Syphilis

Syphilis is a sexually transmitted disease caused by the spirochete *Treponema pallidum*. Though the route of transmission of syphilis is almost always through sexual contact, sometmes congnital syphilis can occur via transmission from mother to child in utero. The disease is typically characterized by three stages: Primary, secondary and tertiary. Primary lesions appear approximately 10–90 days after the initial exposure. Primary lesion, also known as a chancre often

appears at the point of contact, usually the external genitalia. The chancre of syphilis is a firm, painless, relatively avascular, circumscribed, indurated, superficially ulcerated lesion. The chancre of syphilis is often termed as "hard chancre" in order to distinguish it from the "soft sore" caused by *H. ducreyi* (described previously). The "hard chancre" of syphilis usually persists for about 4 to 6 weeks and heals spontaneously. In most patients, a painless regional lymphadenopathy develops within one-two weeks after the appearance of the chancre. As a result, the regional lymph nodes often become swollen, discrete, rubbery and nontender.

Secondary syphilis occurs approximately 1–6 months after the primary infection. This stage is typically characterized by a "flu-like" syndrome, lymphadenopathy and the appearance of symmetrical reddish-pink nonitchy rashes on the trunk and extremities. The rash can involve the palms of the hands and the soles of the feet. In moist areas of the body, such as the anus and vagina, the rash often develops into flat, broad, whitish lesions known as condylomata lata. Mucous patches may also appear on the genitals or in the mouth. All of the lesions of secondary stage are infectious and harbor active treponema organisms and therefore patients in this stage are most contagious. Other common symptoms of this stage include fever, malaise, sore throat, weight loss, headache, meningismus, enlarged lymph nodes, etc.

Following the secondary stage, there often occurs a period of quiescence known as "latent syphilis". No clinical manifestations are evident during this phase and all the lesions of secondary stage have disappeared. The diagnosis during this period is possible only by serological tests. In many cases, this phase is followed by natural cure. However, in some other cases manifestations of tertiary syphilis may appear after several years.

Tertiary syphilis usually occurs 1–10 years after the initial infection and is characterized by the formation of gummas, which are soft, tumor-like balls of granulomatous inflammation. Other characteristic features of untreated tertiary syphilis include neuropathic joint disease, (characterized by degeneration of joint surfaces resulting in loss of proprioception), neurosyphilis and cardiovascular syphilis.

The disease is usually diagnosed on the basis of serological tests such as Kahn test, VDRL (veneral disease research laboratory) test, rapid plasma reagin test, etc. Syphilis can generally be treated with intramuscular injections of benzathine penicillin.

History

The various specific symptoms on history, per speculum and per vaginal examination related to different types of vaginitis have been described previously in the text. This section provides a basic overview of clinical approach in a patient presenting with vaginal discharge.

History of Presenting Complaints

For most patients with vaginal discharge, laboratory evaluation and investigations do not lead to an etiologic diagnosis; thus, lengthy evaluations are not indicated. The first step in the gynecological evaluation of patients with vaginal discharge is to obtain a directed history. A complete history and physical examination are all that are required in most cases. Questions regarding the type of vaginal discharge that need to be asked include the following:

- The amount of discharge
- Color of vaginal discharge
- Duration of symptoms
- Presence of any odor with the discharge
- Association of the discharge with menstrual cycles
- *History of constitutional symptoms:* History of constitutional symptoms such as fever, pelvic or abdominal pain and malaise may be associated with pelvic inflammatory disease.
- *History of vulvar/vaginal irritation and itching:* History of any vaginal pruritus or discomfort in association with the vaginal discharge needs to be asked. While there is usually no vulvar/vaginal irritation in cases of bacterial vaginosis, vaginal irritation or pruritis is characteristically present in cases of trichomoniasis or vulvovaginal candidiasis. Asking the time when the patient experiences discomfort is also important. History of pruritis especially at night is typically suggestive of pinworm infection.
- *History of urinary symptoms:* History of urinary symptoms such as increased frequency of urination, urgency and dysuria needs to be enquired. This is important because such symptoms may be frequently associated with vaginitis.
- *Hygiene practices:* It is important to ask the patient about certain hygiene practices which may have an important role in the etiopathogenesis of her problem. Some of these habits include:
  - Habits such as vaginal douching at least once a week are associated with an increased risk of bacterial vaginosis, suggesting that daily habits may play an important role in the development of bacterial vaginosis.
  - Regular use of irritants such as soaps, baths, spermicides, perfumes, douches and creams can also cause vulvovaginitis.
  - Tightfitting, synthetic, nylon undergarments can increase moisture, exacerbating the condition. The patient should be asked to wear loose fitting cotton undergarments.

Table 20.5: Interpretation for the various causes of vaginal discharge based on the history and examination

Clinical elements		*Bacterial vaginosis*	*Trichomoniasis*	*Vulvovaginal candidiasis*
Symptoms	Color of vaginal discharge	Thin, grayish, homogeneous	Green-yellow	White, curd-like
	Consistency	Frothy	Frothy	Curdy
	Amount of discharge	Abundant	Varies	Varies
	Vaginal malodor	Present	May be present or absent	Absent
	Vulvar irritation and itching	May be present or absent	Present	Present
	Dyspareunia	Absent	Present	Absent
Signs	Vulvar erythema and strawberry cervix	Absent: Vaginal lining usually appears pink	May be present or absent: Vaginal lining is tender and red	May be present or absent: Vaginal lining is dry and red
	Bubbles in the vaginal fluid	May be present or absent	Present	Absent
Saline wet mount/KOH	Clue cells	Present	Absent	Absent
	Motile protozoa	Absent	Present	Absent
	Hypha/pseudohyphae	Absent	Absent	Present
	Whiff test	Positive	May be positive or negative	Negative
pH with Nitrazine paper		>4.5	>4.5	<4.5

– Wiping the anus from posterior to anterior while using the toilet paper is likely to increase the risk for developing vaginitis.

Interpretation of the various causes of vaginal discharge based on the history is shown in table 20.5.

History of symptoms suggestive of malignancy: In women belonging to perimenopausal and postmenopausal age groups, malignancy (vulval, vaginal, endometrial or cervical) is a common cause of vaginal discharge. Thus, in these women, it is important to enquire about vaginal bleeding or spotting, watery discharge and postmenopausal or postcoital bleeding. Detailed history of symptoms related to cervical and endometrial malignancy have been described in chapter 21 and chapter 17 respectively.

Dysuria and dyspareunia: History of dysuria and dyspareunia may be commonly associated with vulvovaginitis. However, both these conditions could be related to numerous other causes, which need to be ruled out. For example, the exact time of dysuria in relation to the flow of urine needs to be asked. Dysuria related to vaginitis is usually external and produces pain and burning sensation when urine touches the vulva. On the other hand, internal dysuria, defined as pain inside the urethra, is usually a sign of cystitis.

Sexual History

Previous history of any sexually transmitted diseases needs to be enquired. The other questions which need to be asked include the following:

- Current and previous sexual partners
- History of having protected or unprotected intercourse
- Frequent change of sexual partner in past 3 months
- History of having multiple sexual contacts
- Similar symptoms (e.g. dysuria, dyspareunia, etc) in the partner
- Use of any oral contraceptives, or IUCDs in the past
- Presence of positive pregnancy test in the patient

Past Medical History

- Any history of experiencing similar symptoms in the past
- Use of any antibiotics in recent past

General Physical Examination

No specific findings are present on general physical examination.

Specific Systemic Examination

PELVIC EXAMINATION

Per speculum Examination

On per speculum examination, the following features need to be observed:

Identification of the site of discharge: A per speculum examination can help to identify the anatomic site of involvement (vulva, vagina or cervix).

Thickness of vaginal mucosa: Vaginal mucosa may be thin and friable with loss of folds in cases of atrophic vaginitis.

Signs of vaginal mucosal inflammation: Presence of erythema, petechial spots or ecchymoses on vaginal mucosal surface, could be related to vulvovaginal candidiasis or trichomoniasis (table 20.5).

Type of vaginal discharge: The pooled vaginal discharge should be assessed for color, consistency, volume, odor and adherence to the vaginal walls. While bacterial vaginosis is typically characterized by absence of inflammation, both trichomonal and candidial infection may be associated with vulvar and vaginal erythema, edema and excoriation. Punctate hemorrhages may be visible on the vagina and cervix. The characteristic features of different types of vaginal discharge as observed on per speculum examination are described in table 20.5.

Presence of any lesions: The external genitalia must be examined for the presence of inflammation, lesions or masses.

Bimanual Pelvic Examination

The gynecologist must assess the patient for presence of uterine or tubo-ovarian tenderness on vaginal examination. Cervical tenderness could be indicative of PID. The technique of bimanual examination has been explained in chapter 16.

Differential Diagnosis

The diagnosis of vaginitis is based on the patient's symptoms, the physical examination, the findings of microscopic examination of the wet-mount and KOH preparations, and the results of the pH litmus test. The various causes of vaginal discharge based on patient's age group are listed in table 20.6.

Sexually Transmitted Diseases

Presence of sexually transmitted diseases (table 20.7) is an important cause for vaginal discharge.

Infections Involving the Lower and Upper Genital Tract - PID

Pelvic inflammatory disease (PID) is characterized by the presence of following clinical features: Pelvic pain, adenxal tenderness, fever and vaginal discharge. The infection could be caused by sexually transmitted diseases such as gonococci, chlamydia, etc. It can also occur as a sequale following spontaneous or induced abortions or delivery. In these cases the infection is commonly polymicrobial, involving organisms such as *Staphylococci*, *Streptococci*, *Coliform bacteria*, *Clostridium perfringens*, etc.

Management

Management of a patient with vaginal discharge has been shown in flow chart 20.1.

Investigations

In a patient presenting with vaginal discharge, the following investigations need to be carried out:

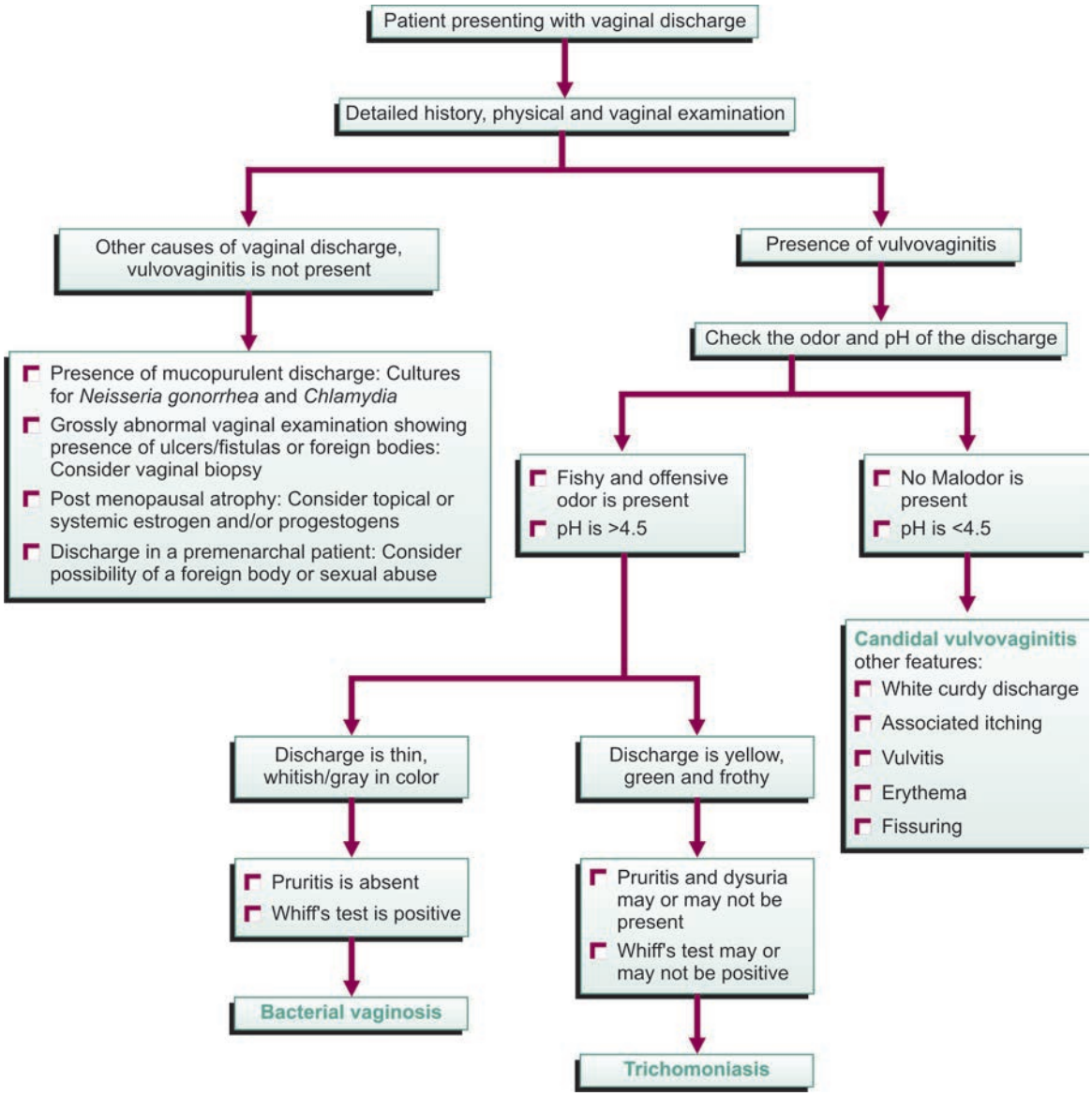
Table 20.6: Different causes of vaginal discharge

Premenarchal	*Childbearing age*	*Postmenarchal*
Poor perineal hygiene (wiping the anus from posterior to anterior)	Sexually transmitted diseases (Chlamydial infection, genital warts (HPV), gonorrheal infection)	Atrophic vaginitis
Chemical irritants (e.g., bubble baths, lotions)	Bacterial vaginosis, *Trichomonas* species, *Candida* species and gonorrhea (many of these are associated with sexual abuse)	Cervicitis, cervical cancer, vulvar, vaginal, or sometimes even endometrial cancer
Vaginal foreign bodies	Chemical irritants	
Pinworm infection		
Skin conditions - Eczema, psoriasis, seborrhea		

Table 20.7: Sexually transmitted diseases of the lower genital tract

Organism	*Vulva*	*Vagina*	*Cervix corpus*	*Adnexa*
HSV	Ulcers			
Molluscum contagiosum	Molluscum lesions			
HPV	Genital warts		Intraepithelial neoplasia, cancer	
Chlamydia trachomatis			Cervicitis, endometritis	Salpingoophoritis
Neisseria gonorrheae	Skene gland adenitis		Cervicitis, endometritis	Salpingitis
Trichomonas		Cervicovaginitis		

Flow chart 20.1: Management plan for a patient presenting with vaginal discharge



Pregnancy Test

Pregnancy test must be done to rule out pregnancy because certain treatment medicines might be contraindicated during pregnancy.

Microscopic Examination

If the findings of the history and/or physical examination suggest that the patient has vaginitis, a sample of the vaginal discharge should be obtained for gross and microscopic examination.

Wet mount preparation

The wet smear is an easy, reliable method of screening for sexually transmitted diseases. The necessary equipment for performing a wet smear include normal saline, slides, cover slips, and a microscope. The procedure of wet mount preparation involves the following steps (figure 20.8):

- A specimen of the discharge is collected from the cervix or posterior fornix of vagina with a cotton-tipped applicator at the time of per speculum examination.
- The sample is placed on the slide with a drop of saline. The slide is covered with a cover slip and then examined microscopically using low power (for white blood cells, red blood cells and epithelial cells) and then under high power of microscope to look for trichomonads, clue cells, pseudohyphae, lactobacillus and white blood cells.

The saline should be at room temperature, and microscopy should be performed within 10–20 minutes to reduce

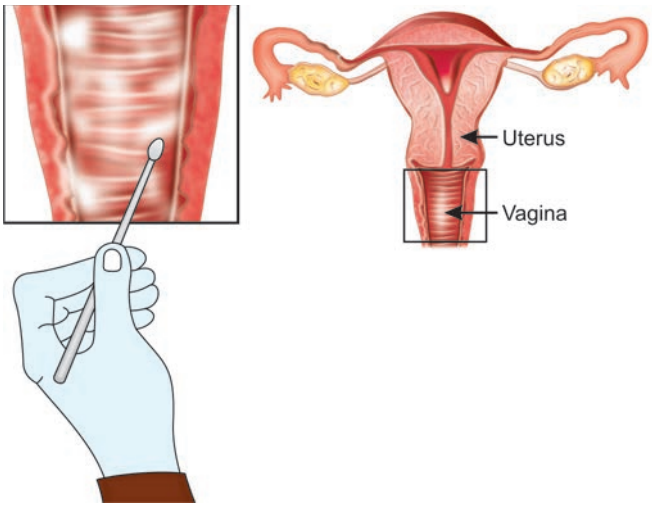


Fig. 20.8: Preparing a wet mount: A sample of vaginal discharge is taken and slide made for microscopic examination

the possibility of loss of any trichomonads. Viewing the specimen should not be delayed, since drying could change the result. For example, trichomonads may lose their motility, if the wet smear dries.

- Following the wet mount preparation, the slide must be examined using 10% KOH solution.

KOH preparation

The slide is prepared by placing a drop of vaginal secretion on a slide with a drop of 10% to 20% KOH and using a coverslip to protect the microscope lens. A coverslip is placed on the slide and air or flame dried before examination is carried out under the microscope. KOH by dissolving the nonfungal elements is useful for detection of candidal hyphae, mycelial tangles and spores. The test is positive in 50% to 70% of women with candidal infection. This is particularly useful in diagnosis of candidal vaginitis. Following the examination of the slide, the KOH whiff test is performed.

KOH Whiff Test

Smelling ("whiffing") the slide immediately after applying KOH is useful for detecting the fishy (amine) odor of bacterial vaginosis. The odor results from the liberation of amines and organic acids produced from the alkalization of anaerobic bacteria. A positive whiff test is suggestive of bacterial vaginosis.

Nitrazine pH Paper

Nitrazine pH paper is used to evaluate the pH of vaginal discharge sample, which is collected at the time of per speculum examination. The normal vaginal pH ranges between 3.8 and 4.2. The gynecologist must remember that both blood and cervical mucus are alkaline in nature and their presence may alter the pH of a vaginal sample. The pH level is also high in cases with atrophic vaginitis. A pH > 4.5 is found in 80% to 90% of patients with bacterial vaginosis and frequently in patients with trichomoniasis. Vulvovaginal candidiasis is normally associated with a pH of < 4.5.

Obtaining a Vaginal Culture

Vaginal culture may help to diagnose the exact etiology in case of a bacterial or fungal infection. Cultures are not useful for *Trichomonas* species infections and bacterial vaginosis.

Rx Treatment/Gynecological Management

Normal physiological discharge usually requires no treatment. Discharge associated with infections should respond to the specific treatment. If infections like gonorrhea, chlamydia or trichomoniasis, are suspected, the woman's sexual partner/s must also be tested and treated.

Patient Education

Both the women belonging to premenarchal and the child bearing age groups must be given the following advice:

- Patient must be advised to wipe thoroughly and anteriorly to posteriorly while using toilet paper.
- The importance of wearing loose-fitting, cotton undergarments must be particularly stressed.
- The patient must be advised to avoid using vaginal irritants such as bubble baths and creams. A sitz bath with baking soda may also be helpful.
- The patient must be advised to thoroughly dry up her perineum and avoid unnecessary prolonged exposure to moisture (e.g. wearing a wet bathing suit for prolonged periods of time).

Therapeutic Options

Treatment should be specifically aimed at treatment of specific bacterial, parasitic or fungal infection. Treatment of various causes of vaginal discharge has been described in detail previously in the chapter and is summarized in table 20.8.

Alcohol use should be avoided during oral metronidazole therapy and for 24 hours after treatment. Topical antifungal therapy for vaginitis has been described in table 20.9.

Complications

- Pelvic inflammatory disease
- Intrauterine infections

Table 20.8: Treatment summary of various causes of vaginal discharge

Treatment regimens	*Bacterial vaginosis*	*Vulvovaginal candidiasis*	*Trichomoniasis*
Acute regimens	Metronidazole (Flagyl), 500 mg orally twice daily for seven days, forms the first line treatment. Clindamycin phosphate vaginal cream (2%): Application of one full applicator (5 g) intravaginally each night for 7 days or metronidazole gel 0.75% (Metrogel-vaginal): Application of one full applicator (5 g) intravaginally twice daily for 5 days.	Topical antifungal agents (see table 20.9) or Fluconazole 150 mg orally, single dose.	Metronidazole, 2 g orally in a single dose
Alternative regimens	Metronidazole, 2 g orally in a single dose or Clindamycin (Cleocin), 300 mg orally twice daily for 7 days or metronidazole 375 mg TID, orally for 7 days	Boric acid powder in size-0 gelatin capsules intravaginally once or twice daily for 2 weeks.	Metronidazole, 500 mg orally twice daily for 7 days
Pregnancy	Metronidazole, 250 mg orally three times daily for 7 days (recommended regimen)	Only topical azole agents such as clotrimazole, miconazole, terconazole, and tioconazole intravaginally for 7 to 10 days.	Metronidazole, 2 g orally in a single dose (usually not recommended in first trimester)
Recurrence	Retreat with an alternative regimen.	For four or more episodes of symptomatic vulvovaginal candidiasis annually: Initial acute intravaginal regimen for 10 to 14 days followed immediately by maintenance regimen for at least 6 months (e.g., ketoconazole, 100 mg orally once daily).	Metronidazole, 2 g orally once daily for 3 to 5 days (Note that treatment of sexual partners increases cure rate)

Table 20.9: Topical antifungal therapy for vaginitis

Antifungal drug	*Intravaginal cream preparation*
Butoconazole	2% cream: Application of 5 g per day intravaginally for 3 days
Clotrimazole	1% cream: Application of 5 g per day intravaginally for 7 to 14 days
Miconazole	2% cream: Application of 5 g per day intravaginally for 7 days
Tioconazole	5% ointment: Application of 5 g intravaginally in a single application
Terconazole	0.4% cream: Application of 5 g per day intravaginally for 7 days 0.8% cream: Application of 5 g per day intravaginally for 3 days
Antifungal drug	*Intravaginal suppository*
Clotrimazole	100-mg vaginal tablet, one tablet per day intravaginally for 7 days 500-mg vaginal tablet, one tablet administered intravaginally in a single dose application Clotrimazole 100-mg vaginal tablet, two tablets per day intravaginally for 3 days
Miconazole	200-mg vaginal suppository per day for 3 days or 100-mg vaginal suppository per day for 7 days
Nystatin	100,000-unit vaginal tablet (Mycostatin), one tablet per day intravaginally for 14 days
Terconazole	80-mg vaginal suppository, one suppository per day for 3 days

- Chorioamnionitis
- Postpartum endometritis
- Vaginitis emphysematous
- Preterm labor
- Premature rupture of membranes
- Newborn infections
- Low-birth weight babies

Important Questions and Answers

Q.1. What is the likely diagnosis in the above mentioned case study?

Ans. The patient's symptomatic history is typically indicative of candidal vulvovaginitis. The predisposing factor which led to the development of vaginitis in this case is most likely to be exposure to antibiotics.

Q.2. What are the likely medicolegal pitfalls associated with the case of vaginal discharge?

Ans. The possible medicolegal pitfalls associated with the case of vaginal discharge are as follows:

- Failure to consider child sexual abuse in the correct clinical context.
- Failure to appreciate that endometrial and/or endocervical lesions also may be etiologies of vaginal spotting after menopause.

Q.3. What should be offered for severe pruritis to a woman with vulvovaginal candidiasis?

Ans. A mildly sedating antihistamine at bedtime may help in relieving the nocturnal irritation and scratching (chlorpheniramine 4 mg orally).

Q.4. What are the likely risk factors for presence of STIs?

Ans. The following risk factors could be associated with STI's:

- Age under 25 years
- No condom use
- Frequent change of sexual partner in past 3 months
- History of having multiple sexual contacts
- Similar symptoms (e.g. dysuria, dyspareunia, etc) in the partner
- Previous history of sexually transmitted infection

Q.5. What are the most common causes for vaginal discharge in premenarchal women?

Ans. The most common cause for itching, soreness, bleeding and foul smelling vaginal discharge in premenarchal women has been suggested to be presence of a vaginal foreign body. Vulvovaginitis may also be secondary to sexual abuse of the premenarchal children.

Bibliography

1. 1998 guidelines for treatment of sexually transmitted diseases. Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep. 1998;47:1-111.
2. ACOG technical bulletin. Vaginitis. Number 226—July. 1996 (replaces no. 221, March. 1996). Committee on Technical Bulletins of the American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet. 1996;54:293-302.
3. Amsel R, Totten PA, Spiegel CA, Chen KC, Eschenbach D, Holmes KK. Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. Am J Med. 1983;74:14-22.
4. Barbone F, Austin H, Louv WC, Alexander WJ. A followup study of methods of contraception, sexual activity, and rates of trichomoniasis, candidiasis, and bacterial vaginosis. Am J Obstet Gynecol. 1990; 163:510-14.
5. Bump RC, Buesching WJ. Bacterial vaginosis in virginal and sexually active adolescent females: Evidence against exclusive sexual transmission. Am J Obstet Gynecol. 1988;158:935-39.
6. Carr PL, Felsenstein D, Friedman RH. Evaluation and management of vaginitis. J Gen Intern Med. 1998;13:335-46.
7. CDC 2002 guidelines for treating STDS: Part I: Diseases characterized by vaginal discharge and PID. Am Fam Physician. 2002;66 (9):1777-78.
8. Chiaffarino E, Parazzini F, DeBesi P, et al. Risk factors for bacterial vaginosis. Eur J Obstet Gynecol Reprod Biol. 2004; 117(2):222-26.
9. Cotch MF, Hillier SL, Gibbs RS, Eschenbach DA. Epidemiology and outcomes associated with moderate to heavy Candida colonization during pregnancy. Vaginal infections and prematurity study group. Am J Obstet Gynecol. 1998;178:374-80.
10. Cotch MF, Pastorek JG 2d, Nugent RP, Yerg DE, Martin DH, Eschenbach DA. Demographic and behavioral predictors of Trichomonas vaginalis infection among pregnant women. The vaginal infections and prematurity study group. Obstet Gynecol. 1991;78:1087-92.
11. DeMeo LR, Draper DL, McGregor JA, Moore DF, Peter CR, Kapernick PS, et al. Evaluation of a deoxyribonucleic acid probe for the detection of Trichomonas vaginalis in vaginal secretions. Am J Obstet Gynecol. 1996;174:1339-42.
12. Eckert LO, Hawes SE, Stevens CE, Koutsky LA, Eschenbach DA, Holmes KK. Vulvovaginal candidiasis: Clinical manifestations, risk factors, management algorithm. Obstet Gynecol. 1998;92:757-65.
13. Eltabbakh GH, Eltabbakh GD, Broekhuizen FF, Griner BT. Value of wet mount and cervical cultures at the time of cervical cytology in asymptomatic women. Obstet Gynecol. 1995;85:499-503.
14. Eschenbach DA, Hillier SL. Advances in diagnostic testing for vaginitis and cervicitis. J Reprod Med. 1989;34:555-64.
15. Forna F, Gulmezoglu AM. Interventions for treating trichomoniasis in women. Cochrane Database Syst Rev. 2005;(2):CD000218.
16. Guaschino S, De Seta F, Sartore A, et al. Efficacy of maintenance therapy with topical boric acid in comparison with oral itraconazole in the treatment of recurrent vulvovaginal candidiasis. Am J Obstet Gynecol. 2001; 184; 4:598-602.
17. Haefner HK. Current evaluation and management of vulvovaginitis. Clin Obstet Gynecol. 1999;42:184-95.
18. Hager WD, Brown ST, Kraus SJ. Metronidazole for vaginal trichomoniasis. Sevenday vs single-dose regimens. JAMA. 980; 244(11):1219-20.
19. Hammill HA. Trichomonas vaginalis. Obstet Gynecol Clin North Am. 1989;16:531-40.
20. Handsfield HH, Jasman LL, Roberts PL, Hanson VW, Kothenbeutel RL, Stamm WE. Criteria for selective screening for Chlamydia trachomatis infection in women attending family planning clinics. JAMA. 1986;255:1730-34.
21. Hanson JM, McGregor JA, Hillier SL, et al. Metronidazole for bacterial vaginosis. A comparison of vaginal gel vs. oral therapy. J Reprod Med. 2000;45(11): 889-96.
22. Haukkamaa M, Stranden P, Jousimies-Somer H, Siitonen A. Bacterial flora of the cervix in women using different methods of contraception. Am J Obstet Gynecol. 1986;154:520-24.
23. Hauth JC, Goldenberg RL, Andrews WW, DuBard MB, Cooper RL. Reduced incidence of preterm delivery with metronidazole

and erythromycin in women with bacterial vaginosis. N Engl J Med. 1995;333:1732-36.
24. Hay PE. Recurrent bacterial vaginosis. Dermatol Clin. 1998;16:769-73.
25. Hill GB. The microbiology of bacterial vaginosis. Am J Obstet Gynecol. 1993;169:450-54.
26. Hillier SL, Nugent RP, Eschenbach DA, Krohn MA, Gibbs RS, Martin DH, et al. Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. The Vaginal Infections and Prematurity Study Group. N Engl J Med. 1995;333:1737-42.
27. Hill LH, Ruparelia H, Embil JA. Nonspecific vaginitis and other genital infections in three clinic populations. Sex Transm Dis. 1983;10:114-18.
28. Holzman C, Leventhal JM, Qiu H, et al. Factors linked to bacterial vaginosis in nonpregnant women. Am J Public Health. 2001; 91(10):1664-70.
29. Hooton TM, Roberts PL, Stamm WE. Effects of recent sexual activity and use of a diaphragm on the vaginal microflora. Clin Infect Dis. 1994;19:274-78.
30. Horowitz BJ, Giaquinta D, Ito S. Evolving pathogens in vulvovaginal candidiasis: Implications for patient care. J Clin Pharmacol. 1992;32:248-55.
31. Joesoef MR, Schmid GP, Hillier SL. Bacterial vaginosis: Review of treatment options and potential clinical indications for therapy. Clin Infect Dis. 1999;28 (suppl 1):S57-65.
32. Jovanovic R, Congema E, Nguyen HT. Antifungal agents vs. boric acid for treating chronic mycotic vulvovaginitis. J Reprod Med. 1991;36:593-97.
33. Kent HL. Epidemiology of vaginitis. Am J Obstet Gynecol. 1991;165:1168-76.
34. Korn AP, Bolan G, Padian N, Ohm-Smith M, Schachter J, Landers DV. Plasma cell endometritis in women with symptomatic bacterial vaginosis. Obstet Gynecol. 1995;85:387-90.
35. Krieger JN, Tam MR, Stevens CE, Nielsen IO, Hale J, Kiviat NB, et al. Diagnosis of trichomoniasis. Comparison of conventional wet-mount examination with cytologic studies, cultures, and monoclonal antibody staining of direct specimens. JAMA. 1988;259:1223-27.
36. Krohn MA, Hillier SL, Eschenbach DA. Comparison of methods for diagnosing bacterial vaginosis among pregnant women. J Clin Microbiol. 1989;27: 1266-71.
37. Laga M, Manoka AT, Kivuvu M, Malele B, Tuliza M, Nzila N, et al. Nonulcerative sexually transmitted diseases as risk factors for HIV-1 transmission in women: Results from a cohort study. AIDS. 1993;7:95-102.
38. Landers DV, Wiesenfeld HC, Heine RP, et al. Predictive value of the clinical diagnosis of lower genital tract infection in women. Am J Obstet Gynecol. 2004; 190(4):1004-10.
39. Lossick JG, Kent HL. Trichomoniasis: Trends in diagnosis and management. Am J Obstet Gynecol. 1991;165:1217-22.
40. McCue JD. Evaluation and management of vaginitis. An update for primary care practitioners. Arch Intern Med. 1989;149: 565-68.
41. Monif GR. Classification and pathogenesis of vulvovaginal candidiasis. Am J Obstet Gynecol. 1985;152: 935-39.
42. Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of Gram stain interpretation. J Clin Microbiol. 1991;29: 297-301.
43. Okun N, Gronau KA, Hanna ME. Antibiotics for bacterial vaginosis or Trichomonas vaginalis in pregnancy: A systematic review. Obstet Gynecol. 2005; 105(4):857-68.
44. Omar AA. Gram stain versus culture in the diagnosis of vulvovaginal candidiasis. East Mediterr Health J. 2001;7;6:925-34.
45. Pagano R. Vulvar vestibulitis syndrome: An often unrecognized cause of dyspareunia. Aust N Z J Obstet Gynaecol. 1999;39:79-83.
46. Pappas PG, Rex JH, Sobel JD, et al. Guidelines for treatment of candidiasis. Clin Infect Dis. 2004; 38: 161-89.
47. Petrin D, Delgaty K, Bhatt R, Garber G. Clinical and microbiological aspects of Trichomonas vaginalis. Clin Microbiol Rev. 1998;11:300-17.
48. Reilly BM. Practical strategies in outpatient medicine. (2d Ed.) Philadelphia: Saunders,. 1991:1016-46.
49. Schaaf VM, Perez-Stable EJ, Borchardt K. The limited value of symptoms and signs in the diagnosis of vaginal infections. Arch Intern Med. 1990;150:1929-33.
50. Skinner CJ, Stokes J, Kirlew Y, Kavanagh J, Forster GE. A case-controlled study of the sexual health needs of lesbians. Genitourin Med. 1996;72:277-80.
51. Sobel J. Bacterial vaginosis. Br J Clin Pract Infect. 1990;71(suppl):65-69.
52. Sobel JD, Faro S, Force RW, Foxman B, Ledger WJ, Nyirjesy PR, et al. Vulvovaginal candidiasis: Epidemiologic, diagnostic and therapeutic considerations. Am J Obstet Gynecol. 1998;178:203-11.
53. Sobel JD. Candidal vulvovaginitis. Clin Obstet Gynecol. 1993;36:153-65.
54. Sobel JD. Pathogenesis and treatment of recurrent vulvovaginal candidiasis. Clin Infect Dis. 1992;14 (suppl 1):S148-53.
55. Sobel JD. Pathophysiology of vulvovaginal candidiasis. J Reprod Med. 1989;34:572-79.
56. Sobel JD. Vaginitis. N Engl J Med. 1997;337:1896-903.
57. Sobel JD. Vulvovaginitis in healthy women. Compr Ther. 1999;25:335-46.
58. Soper DE, Brockwell MJ, Dalton HP, Johnson D. Observations concerning the microbial etiology of acute salpingitis. Am J Obstet Gynecol. 1994;170: 1008-14.
59. Spiegel CA, Amsel R, Holmes KK. Diagnosis of bacterial vaginosis by direct Gram stain of vaginal fluid. J Clin Microbiol. 1983;18:170-77.
60. Spinillo A, Capuzzo E, Acciano S, De Santolo A, Zara F. Effect of antibiotic use on the prevalence of symptomatic vulvovaginal candidiasis. Am J Obstet Gynecol. 1999;180:14-17.
61. Thomason JL, Gelbart SM, Anderson RJ, Walt AK, Osypowski PJ, Broekhuizen FF. Statistical evaluation of diagnostic criteria for bacterial vaginosis. Am J Obstet Gynecol. 1990;162:155-60.
62. Van Der Pol B, Williams JA, Orr DP, et al. Prevalence, incidence, natural history, and response to treatment of Trichomonas vaginalis infection among adolescent women. J Infect Dis. 2005;192(12):2039-44.
63. Watson MC, Grimshaw JM, Bond CM, et al. Oral versus intravaginal imidazole and triazole antifungal treatment of uncomplicated vulvovaginal candidiasis. Cochrane Database Syst Rev. 2002;(4):CD002845.

Chapter

21

Cancer Cervix (Postcoital Bleeding)

Case Study

A 62-year-old para 4 woman has presented with the complaints of postcoital bleeding since past 2 months. She had been getting regular Pap smear examinations done in the past. The last smear done one year back had shown normal pathology.

Introduction

Cervical cancer is the second most common type of cancer in women worldwide, after breast cancer. Cancer of the cervix involves the squamous epithelium of cervix (figures 21.1A and B), and typically begins at the transformation zone between the ectocervix and endocervix (figure 21.2). The cervix is the lower, narrow lower-most portion of the uterus which is joined with the upper portion of the vagina. It is anatomically composed of two parts: Ectocervix and endocervix. The part of the cervix projecting into the vagina is known as the portio vaginalis or ectocervix, whereas the region of the cervix opening into the uterine cavity is known as the endocervix. The opening of ectocervix inside the vagina is known as the external cervical os, while the opening of the cervix inside the uterine cavity is known as the internal cervical os. The endocervical canal extends between the internal and the external cervical os. The ectocervix is lined by squamous cells, while endocervical cells are mainly of the columnar type. The transformation zone lies at the junction of ectocervix and endocervix. Columnar cells are constantly changing into squamous cells in the transformation zone. Since the cells in the transformation zone are constantly changing, this is the most common place for cervical malignancy to develop.

In 2006, the annual incidence rate of cervical cancer in the UK was 8.5 per 100,000 women. Of all the cancers diagnosed in women, nearly one in every ten women is diagnosed with cancer of the cervix. It has become the most commonly diagnosed cancer among women in Southern Africa and Central America. Mortality due to cervical cancer generally increases with the woman's age, with the highest number of deaths occurring in women in their late seventies. Women who are infected with high-risk human papillomavirus genital subtypes are associated with an increased risk of malignant transformation. Widespread use of the Papanicolaou (Pap)

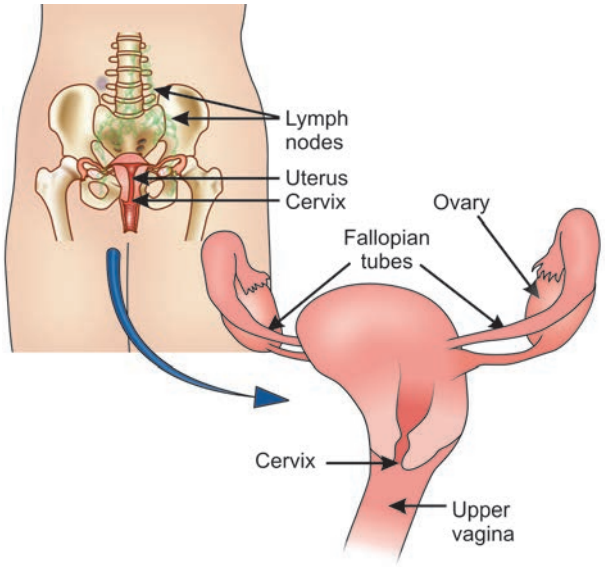


Fig. 21.1A: Anatomical location of cervix

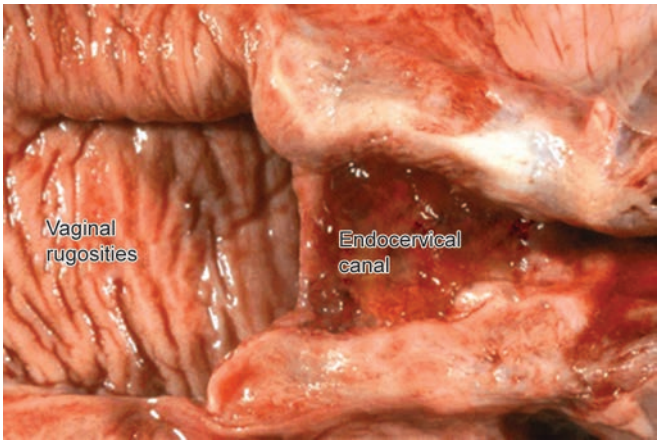


Fig. 21.1B: Cervical morphology at the region of external cervical os

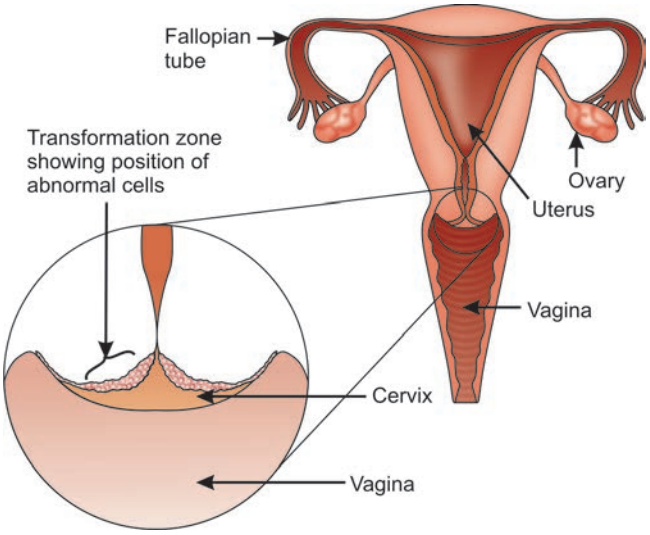


Fig. 21.2: Transformation zone

smear has dramatically reduced the incidence of cervical cancer in developed countries. As a result, cervical cancer has become relatively uncommon in developed countries having intensive cytologic screening programs. Since the advent and widespread use of Pap smears, which helps in early detection of preinvasive cervical lesions at an early stage, the incidence of cervical cancer has dramatically decreased from 32 cases per 100,000 women in the 1940s to 8.3 cases per 100,000 women in the 1980s. However, in many parts of the developing world, cervical cancer continues to cause significant morbidity and mortality. The various types of malignant tumors in the cervix are enlisted in table 21.1. Out of these, the most common types of cancer in the cervix is squamous cell carcinoma, which is responsible for nearly 80% cases of cancer.

Table 21.1: Malignant tumors of the cervix

Tumors of the epithelium	*Non-epithelial cell tumors*
Squamous cell carcinoma	*Tumors of mesenchymal tissue*
• Large cell nonkeratinizing	• Endocervical stromal sarcoma
• Large cell keratinizing	• Carcinosarcoma
• Small cell	• Adenosarcoma
• Verrucous carcinoma	• Leiomyosarcoma
	• Embryonal rhabdomyosarcoma
Adenocarcinoma	*Others*
• Common pattern	• Metastatic
• Adenoma malignum	• Lymphoma
• Mucinous	• Melanoma
• Papillary	• Carcinoid
• Adenoid cystic	
• Adenosquamous carcinoma	
Endometroid cancer	
Clear cell	
Stem cell carcinoma	

History

The factors which are associated with an increased risk of cervical cancer and need to be elicited at the time of taking history include the following:

RISK FACTORS

Age

Cancer of the cervix can occur at any age. It is found most often in women older than 40 years, but can occur in younger women. However, it rarely occurs in women younger than 21 years. The average age for occurrence of carcinoma cervix is 35–45 years.

Obstetric history

Women who give birth to babies at young age, particularly the women who have their first delivery before the age of 20 years are at an increased risk. Multiparous women with poor spacing between pregnancies are also at an increased risk.

Sexual history

The factors which are associated with an increased risk of cervical cancer and need to be elicited at the time of taking sexual history include the following:

- Promiscuity or history of having multiple sexual partners.
- History of having a male sexual partner who has had sex with more than 1 person (the more partners the person has, the greater is the risk).
- Young age (less than 18) at the time of first sexual intercourse.
- Having a male sexual partner who has had a sexual partner with cervical cancer.
  These factors can increase the woman's risk for developing cancer of the cervix, because they increase the chances of acquiring HPV infection, which can lead to dysplasia.
- Women who have had sexually transmitted diseases in the past including the diseases like HIV infection, herpes simplex virus 2 infection, human papilloma virus infection (16, 18, 31, 33) are also at an increased risk of developing cancer of the cervix.

Personal history

- Smoking is associated with an increased risk for development of cancer cervix.
- Women who do not come for regular health check-ups and Pap tests are at an increased risk.

Reduced immunity

Women with reduced immunity are at an increased risk of developing cervical cancer. Some of the conditions associated with reduced immunity include the following:

- Human immunodeficiency virus (HIV) infection
- Organ (especially kidney) transplant
- Hodgkin's disease

Previous history of cancerous lesions in the cervix

The woman is at a high risk of developing cancer cervix if she has a previous history of HSIL; history of cancer of the cervix, vagina, or vulva or has not been getting routine Pap tests done in the past.

Socioeconomic status

Individuals belonging to low socioeconomic classes or low income groups have been found to be at a high risk of developing cancer cervix. This could be probably due to the fact that poor women may not be able to afford good health care, such having regular Pap tests.

Treatment history

It is important to elicit the history of intake of medicines like DES (diethylstilbestrol), OCP's, etc.

The daughters of women who consumed DES at the time of their pregnancy are at a slightly higher risk of developing cancer of the vagina and cervix. Long-term use of the contraceptive pills for more than 10 years can slightly increase the woman's risk of developing cervical cancer.

Dietary history

Diets low in fruits and vegetables are linked to an increased risk of cervical and other cancers. Also, women who are overweight are at an increased risk of developing cervical cancer in the future.

Family history

Cervical cancer may run in some families. If the woman's mother or sister had cervical cancer, her chances of getting the disease in future are increased.

Symptoms of Cervical Cancer

There may be no symptoms in the early stages of cancer and the woman may be completely asymptomatic. The cervical lesion may be detected at the time of routine Pap smear. The most common symptoms indicative of cervical cancer, which need to be elicited, include the following:

- History of abnormal bleeding, spotting or watery discharge in-between periods or after intercourse. A history of post-coital bleeding must specifically raise the suspicion of cervical cancer.
- Often there is also a foul smelling vaginal discharge and discomfort during intercourse.
- The presentation could be in the form of post-menopausal bleeding.
- In advanced stages of cancer there may be symptoms like pelvic pain, loss of appetite, weight loss, fatigue, back pain, leg pain, leg swelling, bleeding from the vagina, leaking of urine or feces from the vagina and bone fractures.

General Physical Examination

No specific finding may be detected on the general physical examination. Chronic bleeding may be associated with anemia. Advanced stages of cancer may be associated with cancer cachexia, lymphadenopathy or pedal edema.

Specific Systemic Examination

PER SPECULUM EXAMINATION

Squamous cell cancers of the ectocervix may appear as proliferative or cauliflower like, vascular, friable growth, which bleeds on touch; ulcerative lesions or as flat indurated areas. The growth may undergo ulceration and necrosis, which may result in an offensive foul smelling vaginal discharge.

Detailed description about conducting a pelvic examination has been done in chapter 16. A per speculum examination may be helpful in detection of abnormal lesions over the cervix. A per speculum examination also enables the gynecologist to simultaneously take the punch biopsy of the suspected lesion. On vaginal examination, both fungating and ulcerative cervical lesions may be identified. Uterus may appear bulky due to occurrence of pyometra in advanced stage when the cervix gets blocked by growth.

A rectovaginal examination is also essential in cases of suspected cervical malignancy. This examination may help the examiner to identify nodules or masses which indicate the possibility of locally invasive disease. The rectal examination may reveal thickening and induration of uterosacral ligaments.

Differential Diagnosis

The diagnosis of malignancy is confirmed on biopsy. The biopsy results can help in diagnosing other conditions such as the ulcers of the cervix (tubercular and syphilitic) and polyps (mucus, cervical, and fibroid polyps).

Management

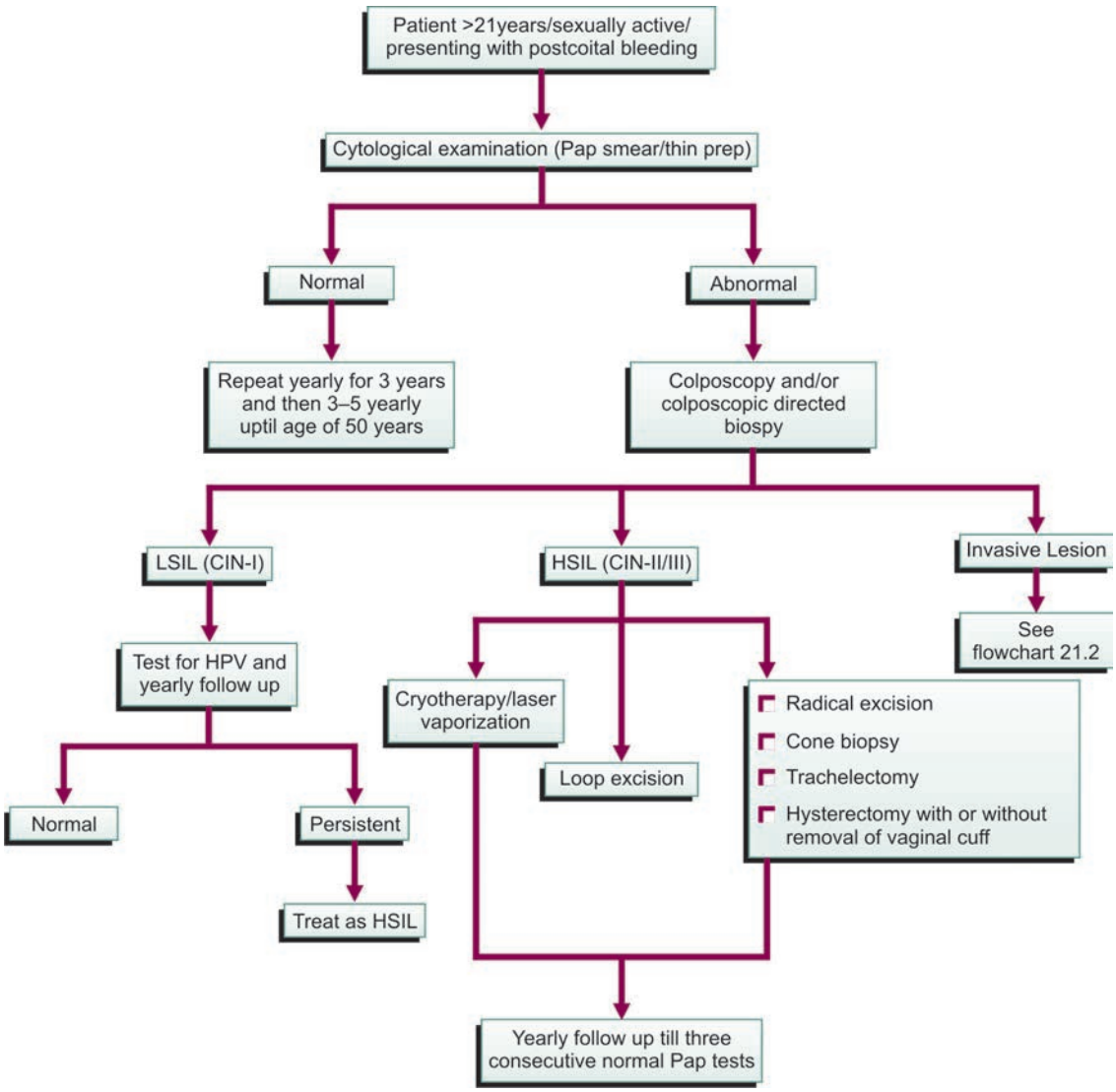
MANAGEMENT OF PREINVASIVE CANCER

Management of a patient presenting with postcoital bleeding would be described in two parts: Those diagnosed to have a preinvasive lesion and those diagnosed to have invasive lesions on cytological screening and colposcopy. Management of patients with preinasive lesions has been described in flow chart 21.1, whereas those with invasive lesions has been described in flow chart 21.2. A Pap smear must be done at the time, when the patient is not actively bleeding. If any locally visible lesion on the cervix is seen, a cervical punch biopsy must be immediately performed. If the Pap smear shows severe dysplasia (HSIL) the next step is to perform a colposcopic directed biopsy and endocervical curettage. Once the diagnosis of cervical cancer is confirmed on histopathology, staging and grading of the disease is performed. Further management is based on the cancer grade and stage.

Investigations

The most important investigation which helps in detection of cervical cancer in its preinvasive stage is the Pap smear. Pap smear involves cytological analysis of the cells from the squamocolumnar junction (SCJ), which is an area of rapid cell turnover, squamous metaplasia and the site of oncogenic transformation. In young women of childbearing age, the SCJ is usually readily visible on the ectocervix. With age as the

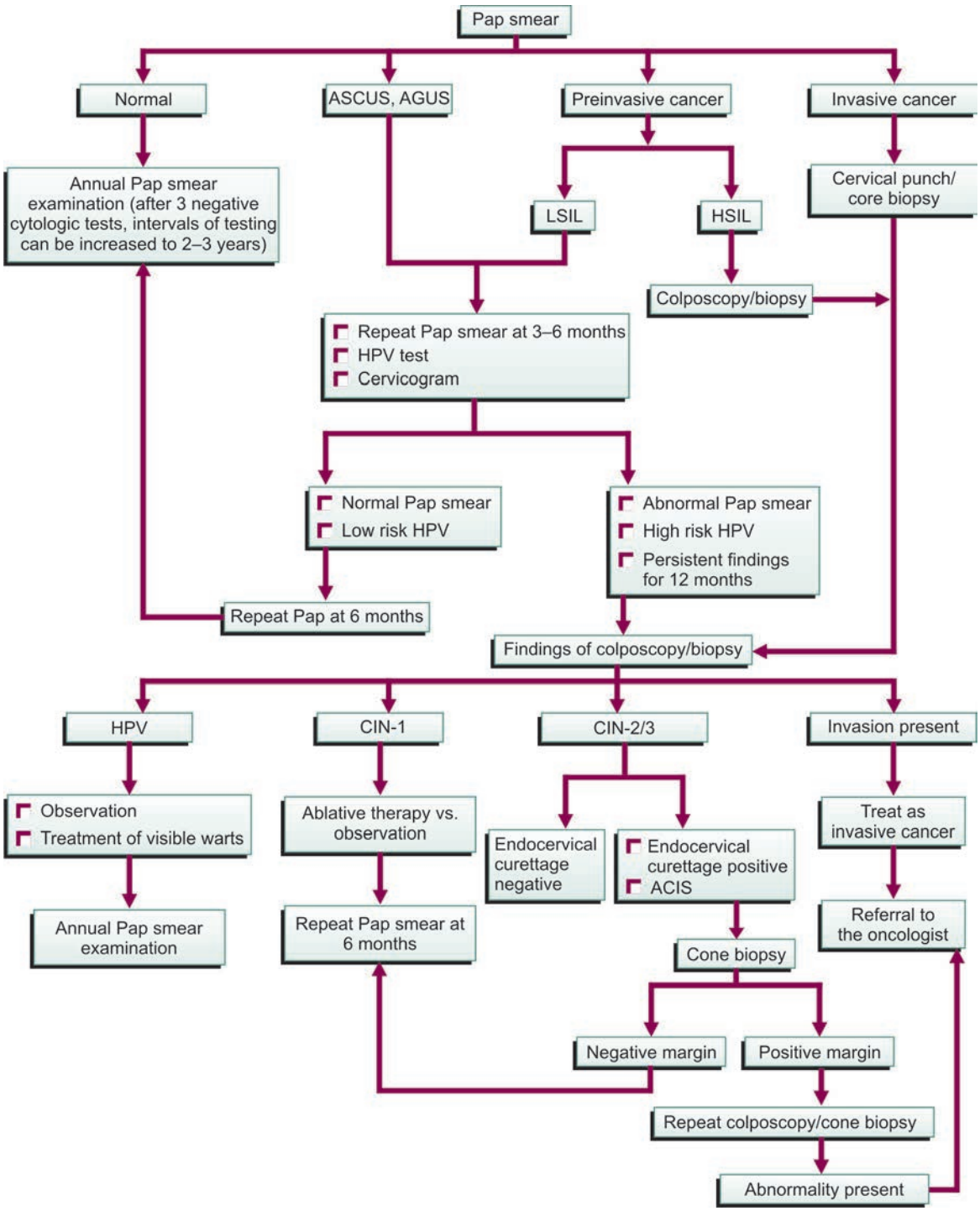
Flow chart 21.1: Management of patients with preinvasive lesions



cervical epithelium matures, the SCJ may recede within the endocervical canal. As a result, the SCJ may be difficult to visualize and to be adequately sampled.

Cancer of cervix usually is the end stage of the spectrum of disorders progressing from mild through moderate to severe dysplasia and carcinoma in situ. Diagnosis of cervical dysplasia is mainly based on cytological screening (Pap smear) of the population. The peak incidence of occurrence of dysplasias appears to be 10 years earlier than that of frank invasive cancer. Presence of dysplasia may be associated with minimal clinical findings on clinical examination. On inspection, the cervix often appears normal, or there may

Flow chart 21.2: Algorithm for management of abnormal Pap smears



be cervicitis or erosion which bleeds on touch. The changes like cervical metaplasia, dysplasia, and cervical intraepithelial neoplasia would be discussed before Pap smear is described.

Metaplasia

Metaplasia is a pathological change which refers to the reversible replacement of one type of differentiated cells with another type of mature differentiated cells. As previously described, the squamocolumnar junction represents the transformation zone of the cervix where columnar endocervical epithelium meets the squamous epithelium of the ectocervix. The reserve cells lying beneath the columnar epithelium at this junction, sometimes, transform into mature squamous cells. This process is known as metaplasia. However, metaplastic cells are the normal cells without nuclear atypia and do not act as precursors of malignancy. Atypical metaplasia with abnormal nuclear changes act as precursors of dysplasia and malignancy.

Dysplasia

Dysplasia is the process which refers to an abnormal maturation of cells within a tissue. This process differs from metaplasia in the sense that normal differentiated cells are replaced by abnormal undifferentiated cells unlike metaplasia in which one type of differentiated epithelial cells are replaced by another type of normal differentiated epithelial cells. Dysplasia is often indicative of an early neoplastic process and is characterized by presence of nuclear changes such as anisocytosis (abnormality in size), poikilocytosis (abnormality in shape), hyperchromatism and presence of mitotic figures. Dysplasias can be graded as follows:

Mild dysplasia or CIN-I: The undifferentiated cells are confined to the lower one-third of the epithelium. The cells are more differentiated towards the surface. According to Bethesda classification, CIN-1 has been lately described as low grade squamous intraepithelial lesion (LSIL).

Moderate dysplasia (CIN-II): Undifferentiated cells occupy the lower 50% to 75% of the epithelial thickness. The cells show mild-moderate nuclear changes such as moderate nuclear enlargement, hyperchromasia, irregular chromatin and multiple nucleation.

Severe dysplasia and carcinoma in situ (CIN-III): In this grade of dysplasia, the entire thickness of epithelium is replaced by abnormal cells. There is no cornification and stratification is lost. The basement membrane, however, remains intact and there is no stromal infiltration.

According to latest Bethesda classification CIN-II and CIN-III are described as high grade squamous intraepithelial lesions (HSIL). The presence of HSIL is significant because these lesions have a high degree potential to progress to invasive cancer that needs to be treated. Sensitivity of Pap smear for detection of HSIL is 70% to 80% and specificity is 95% to 98%.

Cervical Intraepithelial Neoplasia (CIN) or Preinvasive Cervical Cancer (Stage 0)

Histopathological progression of cervical dysplasia is shown in figure 21.3, while the morphological progression of invasive cancer is shown in figure 21.4. The term, cervical intraepithelial neoplasia can be considered as a precancerous lesion (dysplasia) in which a part or the full thickness of the stratified squamous cervical epithelium is replaced by cells showing varying degrees of dysplasia. Cervical intraepithelial neoplasia represents a spectrum of disease that most

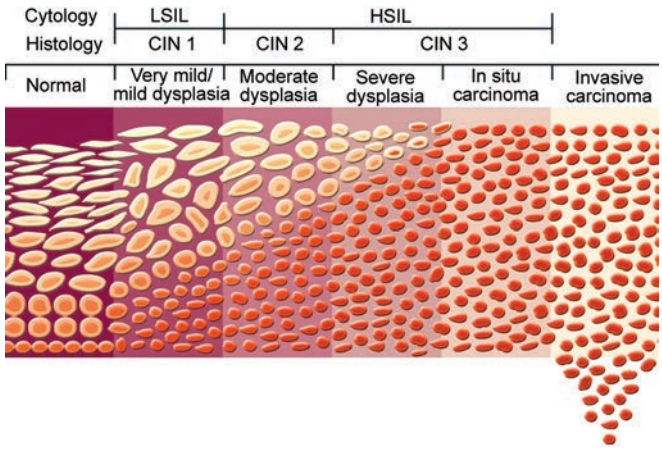


Fig. 21.3: Progression of cervical dysplasia

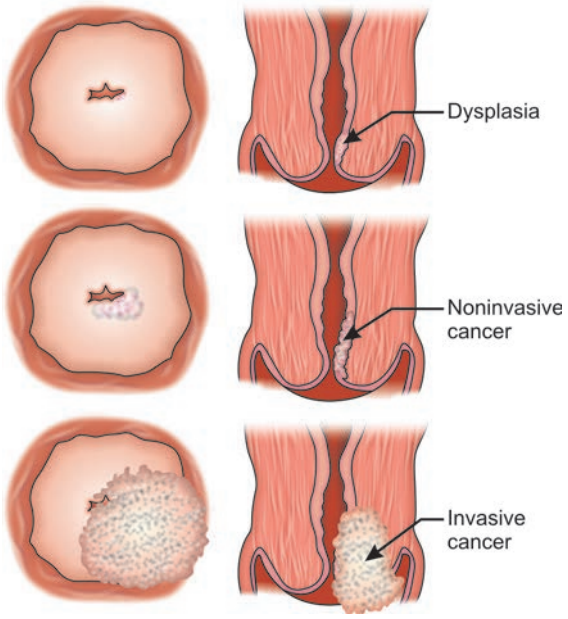


Fig. 21.4: Morphological progression of cervical cancer

commonly affects women during their 40s and 50s. This is different from the invasive cancer as in this case the basement membrane remains intact. The intraepithelial neoplasia can be classified as mild, moderate or severe depending upon the thickness of cervical epithelium involved. Mild degrees of dysplasia may occur with inflammatory conditions like trichomoniasis and HPV and is reversible following treatment; whereas the severer varieties of dysplasias may progress to invasive cancer in about 10–30% of cases in 5 to 10 years' time. As the severe degree CIN can progress into an invasive cancer, the neoplastic cells penetrate the underlying basement membrane and invade the stroma with the potential for widespread dissemination. Figure 21.5A shows histopathology of normal cervical epithelium, while figure 21.5B shows transformation zone of the normal cervical squamous epithelium at the left hand side, which gets transformed into dysplastic changes at the right hand side. Figure 21.5C shows histopathology of invasive squamous cell carcinoma showing nests of squamous cancer which has invaded the underlying stroma towards the center and left hand side of the slide.

DIAGNOSIS OF CERVICAL DYSPLASIA

Cytologic Screening: Pap Smear

Since its introduction in the 1940s, cytological screening in form of Pap smear has become the investigation of choice for detection of precancerous lesions of the cervix. The widespread introduction of the Papanicolaou test for cervical cancer screening has resulted in significantly reducing the incidence and mortality of cervical cancer in developed countries. Presence of abnormal results on Pap test or symptoms of cervical cancer, may mandate further testing in form of colposcopy, colposcopic directed biopsy and endocervical curettage, which can help in confirming if abnormal cells are dysplastic or cancerous.

Since Pap smear is associated with a negative reporting rate of 30%, it is important to repeat Pap smear annually for 3 consecutive years. If still, the Pap smear continues to remain negative, it should be repeated at 3–5 yearly intervals up to the age of 50 years. After the age of 50 years Pap smear is not required, because the incidence of CIN drops to 1%.

Prerequisites before taking a Pap smear

- No vaginal douching should be done 48 hours prior to the test.
- Vaginal creams should not be used for 1 week before the test.
- There should be abstinence from sexual intercourse 24 hours prior to the test.

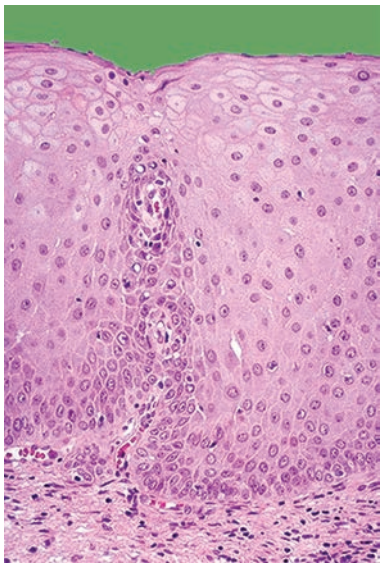


Fig. 21.5A: Histopathology of normal cervical epithelium

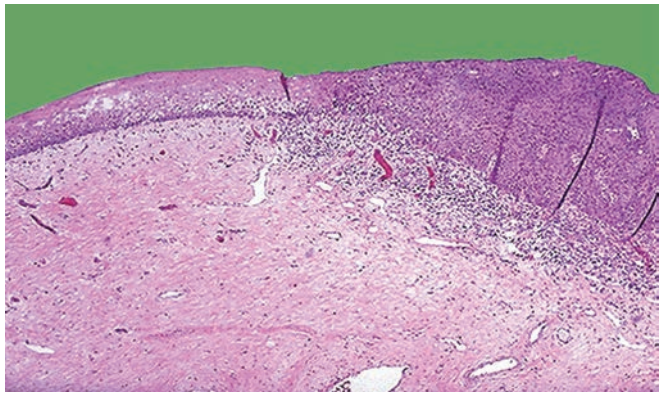


Fig. 21.5B: Transformation of the normal cervical squamous epithelium (at the left) into dysplasia (at the right)

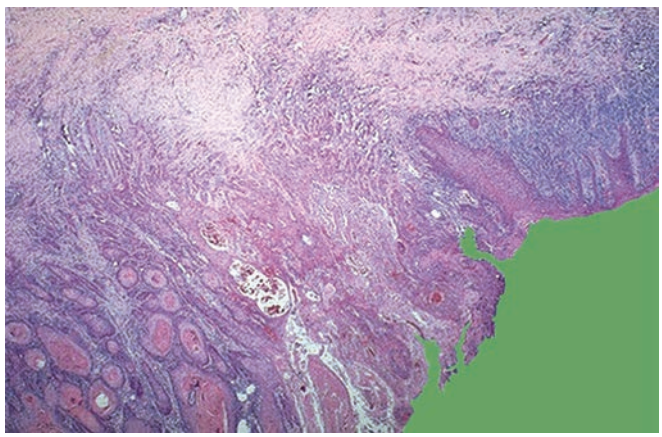


Fig. 21.5C: Histopathology of invasive squamous cell carcinoma showing nests of squamous cancer which has invaded the underlying stroma in the center and left

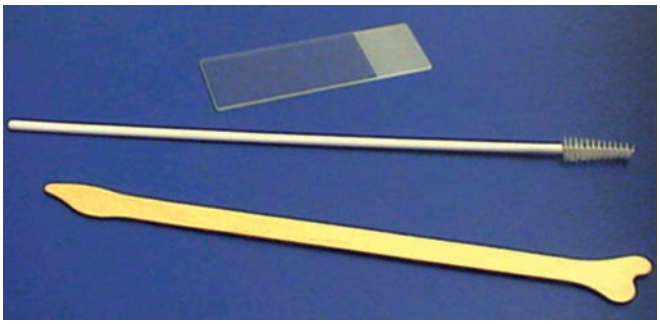


Fig. 21.6: Pap smear kit

Procedure

- Figure 21.6 shows the Pap smear kit, while figures 21.7A and B demonstrate the procedure for taking a Pap smear. The patient is made to lie in a dorsal position and adequate light must be used to visualize the cervix and vagina properly.
- A Cusko's speculum must be used to expose the cervix.
- No lubricant should be used on the Cusko's speculum.
- After exposing the cervix, an endocervical brush or a cotton tipped swab must be placed inside the endocervix and rotated firmly against the canal in order to take an endocervical sample, which is then placed on the glass slide.
- Next the Ayre's spatula must be placed against the cervix with the longer protrusion in the cervical canal.
- The spatula must be rotated clock-wise for 360° against the cervix. This would help in scraping the entire transformation zone.
- If it appears that the entire transformation zone has not been adequately sampled, the spatula must be rotated several times.
- The sample from the spatula is placed onto the glass slide by rotating the spatula against the slide in a clock-wise manner.
- The slide must be immediately fixed with the help of a spray fixative which is held at a distance of about 9–12 inches.

Qualities of a good smear

The smear should be thick enough, but not transparent. Too thin smear may result in formation of artifacts upon drying. Also a thin smear might contain too few cells which might not allow adequate sampling. On the other hand, if the smear is too thick, the papanicolaou stain will not penetrate.

Visual Inspection of Cervix

In areas where facilities for Pap smear screening do not exist, visual inspection with 5% acetic acid (VIA) or

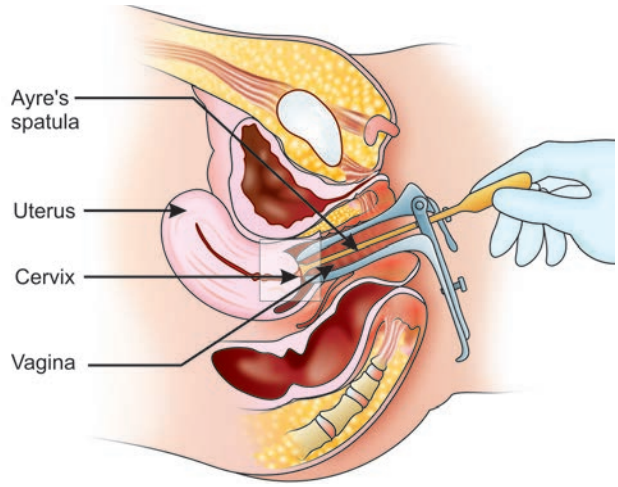


Fig. 21.7A: Placing the Cusko's speculum in the cervix

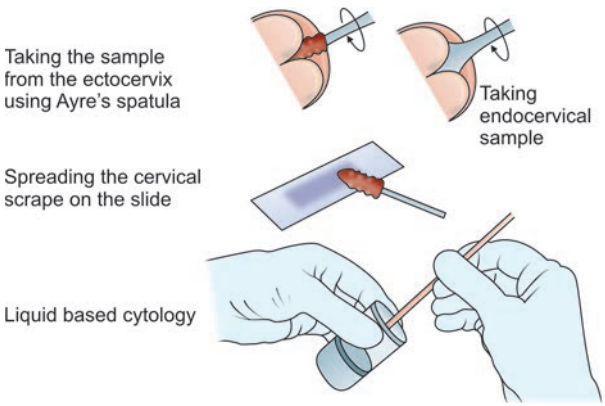


Fig. 21.7B: Taking a Pap smear

visual inspection with Lugols iodine (VILI) can be done. Application of 5% acetic acid causes dehydration and coagulation of the abnormal areas containing increased nuclear material and protein, which turns acetowhite (opaque and white in appearance). The areas of abnormalities can then be biopsied. The dull white plaques with faint borders can be considered as LSIL, while those with sharp borders and thick plaque are suggestive of HSIL. The acetic acid does not affect the mature glycogen producing epithelium.

Sometimes instead of acetic acid, Schiller's iodine can be employed. The normal cervical cells contain glycogen, which takes up iodine and turns mahogany brown, while the abnormal area remains unstained.

Frequency of doing Pap smear

The American College of Obstetricians and Gynecologists (ACOG, 2003), the American Academy of Family Physicians and the US Preventive Services Task Force (USPSTF)

recommend that all women must receive screening Pap smears by approximately 3 years after onset of vaginal sexual intercourse, but no later than age 21. Screening should be done at least once every 2 or 3 years starting within 3 years after a woman begins to have sexual intercourse. Once three normal annual Pap smears have been documented, the interval for continued surveillance with screening Pap smears may be increased at the discretion of the physician and the patient. Cervical cancer screening may be stopped in women 65 (USPSTF) years to 70 years (ACS) of age who have had at least three normal Pap tests and no abnormal Pap tests in the last 10 years. The decision to stop screening is taken in consultation with the health care provider. Women who have had a total hysterectomy do not need to undergo cervical cancer screening, unless the surgery was done as a treatment for cervical preinvasive or invasive cancer. In all women with abnormal Pap tests showing mild dysplasias, it is important to treat any accompanying inflammatory pathology and repeat the Pap test. Recommendations for Pap smear testing are summarized in table 21.2.

Types of Cell Changes in Pap Smear

According to the World Health Organisation, cervical dysplasia has been categorized into mild, moderate, or severe dysplasia and a separate category called carcinoma in situ (CIS). The term "Cervical intraepithelial Neoplasia" (CIN) was introduced by Richart (1968). CIN1 represents mild to moderate dysplasia; CIN2 is an intermediate grade and CIN 3, severe dysplasia or CIS. However according to the most recent classification that is the Bethesda System (table 21.3), all cervical epithelial presursor lesions have been divided into 2 groups: Low grade squamous intraepithelial lesion (LSIL) and high grade Squamous intraepithelial lesion (HSIL). LSIL corresponds to CIN1 and HSIL includes CIN2 and CIN3. The epithelial cell abnormalities on Pap smear can be classified as follows:

- *Squamous cell abnormalities*
  - Atypical squamous cells (ASC)
  - ASC of undetermined significance (ASCUS)
  - ASC, cannot exclude HSIL (ASC-H)
  - Low grade squamous intraepithelial lesion (LSIL), encompassing: Human papillomavirus infection/mild dysplasia/cervical intraepithelial neoplasia (CIN 1)
  - High grade squamous intraepithelial lesion (HSIL), encompassing moderate and severe dysplasia, carcinoma in situ, CIN 2, and CIN 3
  - Squamous cell carcinoma
- *Glandular cell abnormalities*
  - Atypical glandular cells (AGC) (specify endocervical, endometrial, or not otherwise specified)

21

Table 21.2: Recommendations for Pap smear testing

	American Cancer Society (2002)	*US Preventive Services Task Force (USPSTF, Jan 2003)*	*American College of Obsterics and Gynecology (ACOG, Jan 2004)*
Time for starting	Approximately three years after the onset of sexual intercourse but no later than age of 21 years	Within 3 years of onset of sexual activity or age 21, whichever comes first	Approximately 3 years after onset of sexual intercourse, but no later than age 21
Intervals for conventional Pap testing	Annually, every 2-3 years in a woman ≥30 with 3 negative cytology tests	At least every 3 years	Annually; every 2-3 years for women ≥30 with 3 negative cytology tests
Intervals for liquid-based cytology	Every 2 years; every 2-3 years for women ≥30 with 3 negative cytology tests	Insufficient evidence	Annually; every 2-3 years for women ≥30 with 3 negative cytology tests
Intervals for pap smear testing if HPV testing is also used	Every 3 years if HPV negative, cytology negative	Insufficient evidence	Every 3 years if HPV negative, cytology negative
Time for stopping pap smear test	Women ≥70 years with ≥3 recent, consecutive negative tests and no abnormal tests in prior 10 years	Women >65 years with negative tests, who are not otherwise at high risk for cervical cancer	Inconclusive evidence to establish upper age limit
Pap smear testing post-hysterectomy	Discontinue if for benign reasons and no prior history of high-grade CIN	Discontinue if for benign reasons	Discontinue if for benign reasons and no prior history of high-grade CIN

Source: Saslow D, Runowicz CD, Solomon D, et al. American Cancer Society Guideline for the Early Detection of Cervical Neoplasia and Cancer. *CA Cancer J Clin* 2002*; 52*: 342-62. Available from http://caonline.amcancersoc.org/cgi/content/full/52/6/342 [Accessed August, 2009]

US Preventive Services Task Force. Screening for cervical cancer January 2003. Available from http://www.ahcpr.gov/clinic/uspstf/uspscerv.htm [Accessed August, 2009].

American College of Obsterics & Gynecology. Cervical Cytology Screening. ACOG Practice Bulletin No. 45. *ACOG* 2003;102:417-27. Available from http://www.acog.org/from_home/publications/press_releases/nr07-31-03-1.cfm [Accessed August, 2009].

Table 21.3: The Bethesda System (2001) for reporting cervical cytologic diagnoses

Specimen adequacy

This may be the single most important quality assurance component of the system

- Satisfactory for evaluation (note presence/absence of endocervical/transformation zone component)
- Unsatisfactory for evaluation (specify reason)
- Specimen rejected/not processed (specify reason)
- Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of specific reason

General categorization (optional)

- Negative for intraepithelial lesion or malignancy
- Epithelial cell abnormality
- Other

Interpretation/result

- Negative for intraepithelial lesion or malignancy
- Observed organisms, such as *Trichomonas, Candida*, bacteria or cellular changes consistent with *herpes simplex virus*, are reported.
- Reporting other nonneoplastic findings is optional (i.e., inflammation, atrophy)

Epithelial cell abnormalities

Squamous cell abnormalities

- Atypical squamous cells (ASC)
- ASC of undetermined significance (ASCUS)
- ASC, cannot exclude HSIL (ASC-H)
- Low grade squamous intraepithelial lesion (LSIL), encompassing: Human papillomavirus/mild dysplasia/cervical intraepithelial neoplasia (CIN) 1
- High grade squamous intraepithelial lesion (HSIL), encompassing: Moderate and severe dysplasia, carcinoma in situ, CIN 2 and CIN 3
- Squamous cell carcinoma

Glandular cell abnormalities

- Atypical glandular cells (AGC) (specify endocervical, endometrial, or not otherwise specified)
- AGC, favor neoplastic (specify endocervical or not otherwise specified)
- Endocervical adenocarcinoma in situ (AIS)
- Adenocarcinoma

Others

- List not comprehensive

Endometrial cells in a woman aged 40 years or older

Automated review and ancillary testing (include as appropriate)

Educational notes and suggestions (optional)

  - AGC, favor neoplastic (specify endocervical or not otherwise specified)
  - Endocervical adenocarcinoma in situ (AIS)
  - Adenocarcinoma
- *Others:* List is not comprehensive
- Endometrial cells in a woman aged 40 years or older

Risks associated with Pap smear

The risks of cervical cancer screening include the occurrence of false-negative as well as false-positive test results. False-negative test results imply that screening test results may appear to be normal even though cervical cancer is present. This may delay the patient from seeking medical care even if she has symptoms suggestive of cancer. False-positive test results occur when screening test results appear to be abnormal even though no cancer is present. This can cause unnecessary patient anxiety. A false-positive test may be followed by more invasive tests and procedures such as colposcopy, cryotherpy or LEEP, which are associated with their own risks. Also, the long-term effects of these procedures on fertility and pregnancy are not known.

Liquid-based Cytology in Cervical Screening: A Rapid and Systematic Review

Liquid-based cytology is a new way of sampling and preparing cervical cells (figure 21.8). While the conventional "Pap smear" involves direct preparation of the slide from the cervical scrape obtained, the procedure of "thinprep" involves

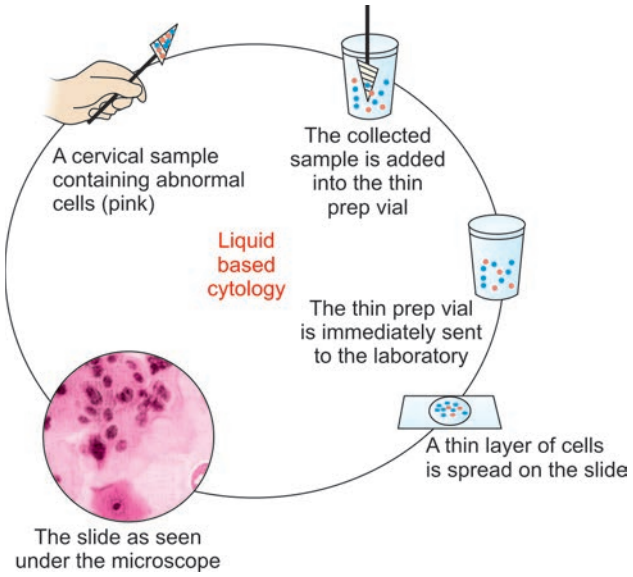


Fig. 21.8: Liquid-based cytology

making a suspension of cells from the sample, which is then used to produce a thin layer of cells on a slide. Using this technique, the cells collected from the cervix are placed in a preservative fluid, which is then sent to the laboratory rather than being directly spread onto a slide. At the laboratory, the sample is mixed and treated to remove unwanted material (blood, mucus and inflammatory material) and then a thin layer of the cell suspension is placed on the slide for inspection.

Until recently, the Pap smear had remained the principal technology for preventing cervical cancer. However, following a review of the present published literature, liquid based cytology has become now been incorporated within the UK national screening program. Two systems are presently available, but only one called "the thinprep" has been approved by the FDA.

There is some evidence that liquid-based cytological methods offer the following advantages over traditional smear techniques:

- A reduction in the proportion of inadequate specimens.
- An improvement in sensitivity rates: During clinical trials, use of thinPrep was associated with a reduction in the number of ambiguous interpretations and increased the detection rate of dysplasias by nearly 13%. The use of liquid-based cytology has mainly helped in reducing the number of inadequate smears from around 9% to around 1%. This has reduced the need to recall women for a repeat smear.
- A possible reduction in specimen interpretation times.
- Reduction in the number of false-negative test results by optimizing the collection and preparation of cervical cells.

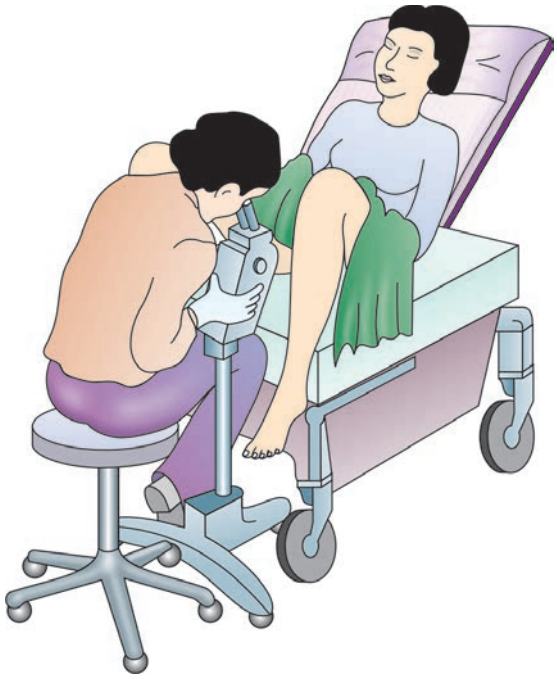


Fig. 21.9: Colposcopic examination

According to the ACOG Committee Opinion, though the quality of smear obtained using the "thinprep" was better than that obtained using the conventional smear and contained less mucus and debris, it also contained fewer cervical cell clumps, which could compromise the diagnosis. Therefore, presently due to lack of good evidence based literature, this method should not be considered as a standard of care.

Colposcopy

If abnormal cells are found in a smear test or liquid-based cytology, the patient may be referred for a colposcopic examination and/or a colposcopic directed biopsy. While the Pap smear detects abnormal cells, colposcopy helps in locating the abnormal lesions. A colposcope is like a small microscope with a light and enables the gynecologist to perform a thorough examination of the cervix (figure 21.9). Colposcopy is an office-based procedure during which the cervix is examined under illumination and magnification before and after application of dilute acetic acid and Lugol's iodine. The characteristic features of malignancy and premalignancy on colposcopic include changes such as acetowhite areas, abnormal vascular patterns, mosaic pattern, punctuation and failure to uptake iodine stain. Endocervical sampling may accompany colposcopy, particularly in nonpregnant women where the cytology shows atypical glandular cells or adenocarcinoma in situ. Satisfactory colposcopy requires visualization of the entire squamocolumnar junction and transformation zone for the presence of any visible lesions. Both a regular white

light and a green light are used during colposcopy. The green filter enhances visualization of blood vessels by making them appear darker in contrast to the surrounding epithelium.

The colposcopic examination helps in the following:

- When abnormal cells have been detected on the Pap smear, location and extent of abnormal lesions on the cervix can be assessed with the help of colposcopy.
- Biopsy can be taken from the areas of abnormality.
- Conservative surgery (e.g. conization) can be performed under colposcopic guidance.
- Colposcopic examination can also be performed during follow up examination of cases who have undergone conservative therapy.

Procedure

- The patient is placed in the lithotomy position.
- Under all aseptic precautions, a speculum is inserted into the vagina.
- The colopscope is brought into the position. The perineum, vulva, vagina and cervix must be examined for presence of lesions using the colposcope's white light and then green light.
- The entire cervix must be viewed both under the low and high power magnification. Higher-power magnification helps in visualization of small details and features.
- Cervix is visualized after the application of both dilute 5% acetic acid and Lugol's iodine in order to enhance any abnormal epithelial findings. Both acetic acid and Lugol's iodine are applied onto the cervix with the help of a cotton swab and allowed to remain there for at least thirty seconds.
- Under white light, the cervix is visualized for acetowhite changes. The location of the squamo-columnar junction, transformation zone, abnormal and atypical vessels and areas of acetowhite changes are recorded. On application of Lugol's iodine, the areas of abnormalities such as those with squamous metaplasia, leukoplakia as well as neoplastic tissue do not take up iodine stain and become yellowish in appearance, whereas the normal glycogen containing cervical cells turn deep brown. A scoring system such as "the Reid Colposcopic Index" may be used to help the colposcopist in classifying the colposcopic appearance.
- The cervix is reexamined under the green light, which helps in accentuating the margins of the acetowhite areas and in identifying the abnormal blood vessels.

Colposcopic directed punch biopsy (figure 21.10)

Following the identification of the biopsy site, the cervical punch biopsy forceps are used to obtain the specimen under colposcopic visualization. Specimens are firstly obtained from the most inferior aspect of the cervix first to avoid bleeding from the biopsy site and obscuring other biopsy sites. Monsel's paste or silver nitrate can be used to achieve hemostasis after cervical punch biopsy.

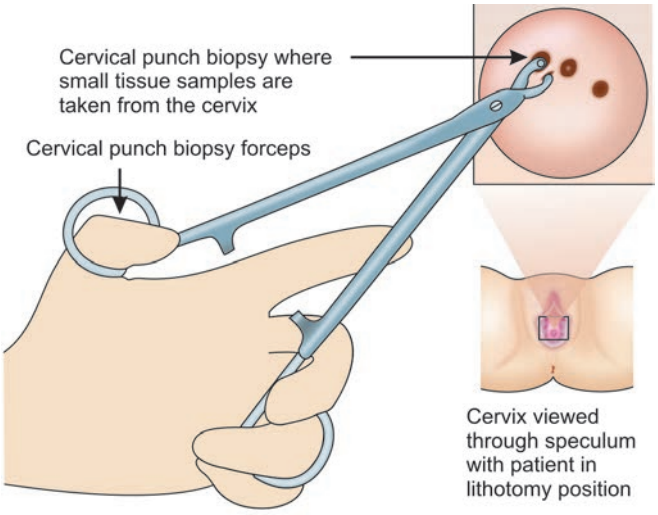


Fig. 21.10: Cervical punch biopsy

The majority of CIN grade I and II lesions regress and aggressive treatment of an adolescent is usually not warranted, because excisional procedures increase the risk of developing cervical stenosis and preterm labor in subsequent pregnancies.

Cervicography

This investigation may be useful when either the procedure of colposcopy or colposcopists are not available for immediate evaluation of the cervix. This procedure involves taking the photograph of the enire cervical os with a 35 mm camera after application of 5% acetic acid. The photographs are then sent to the colposcopist for evaluation in order to select areas for biopsy. Although the sensitivity of colposcopy and cervicography are similar, the specificity of cervicography is much greater than that of colposcopy.

Rx *Treatment/Gynecological Management*

The management of abnormal Pap smear has been described in the flow chart 21.2. In case the Pap smear shows LSIL or ASCUS or AGUS, the Pap smear must be repeated at intervals of 3–6 months. This can be later converted to yearly Pap testing if the result of the 2-3 consecutive tests is negative. While about 60% of LSIL lesions regress, 15% may progress to HSIL or invasive cancer in the future.

In case abnormal results persist or a high risk HPV type is detected, colposcopy and/or directed biopsy may be required.

If the woman has a colposcopically identifiable abnormal transformation zone or CIN 1 on biopsy, ablative therapy for destruction of that abnormal zone must be used. The patient must be followed with a repeat Pap smear after 6 months. If the cytology specimen is suggestive of HSIL in any women, she must undergo coloscopy and directed biopsy or conization. Following colposcopically directed biopsy and determination of the distribution of the lesion, ablative therapy aimed at the destruction or removal of the entire transformation zone must be performed. Since all therapeutic modalities could be associated with an inherent recurrence rate of 10%, cytological follow up at approximately 3 monthly intervals for one year is necessary. Flow chart 21.2 presents the algorithm for evaluation of abnormal Pap smear.

TREATMENT OF DYPLASTIC CHANGES

If the smear results are positive, the patient must be followed up with a colposcopy and/or a colposcopic directed biopsy. In case a preinvasive cervical lesion is detected on colposcopy, the various treatment options, which are available, are as follows:

- Local destructive methods such as cryosurgery, fulguration/electrocoagulation and laser ablation.
- Excision of the abnormal tissue with cold knife conization, laser conization, LLETZ, LEEP (Loop electrosurgical excision procedure) and NETZ (Needle excision of transformation zone).
- Surgical options such as therapeutic conization, hysterectomy or hysterectomy with removal of vaginal cuff if carcinoma in situ extends to the vaginal vault.

HSIL changes have the greatest risk of turning cancerous in the future, thus these need to be definitively treated. The other types of changes also may require further testing, but may not need treatment.

Mild dysplasia (LSIL) is usually due to infection which should be treated and cytology follow-up done every 3–6 months. Indications for treatment of LSIL are listed in table 21.4.

Table 21.4: Indications for treatment of LSIL

Persistent LSIL (CIN 1) over one year
Patient showing poor compliance for follow up
Associated HPV and HIV viral infection

Locally Destructive Methods

Cryosurgery

Cryosurgery is a locally destructive OPD procedure in which the dysplastic cells are destroyed using freezing agents [CO_2 (–60°C) and nitrous oxide (–80°C)]. A cryoprobe is used, usually without any anesthesia or analgesia and causes destruction of the cells by crystallization of intercellular fluid. It uses the "freeze-thaw-freeze" technique in which an ice ball is achieved 5 mm beyond the edge of the probe. The cryoprobe is applied over the area of abnormality for over 9 minutes and destroys the tissue up to the depth of about 4–5 mm. The time required for the procedure is related to the pressure of gas. Overall, cryosurgery is a relatively safe procedure with fewer complications.

Electrocoagulation

Electrocoagulation is a locally destructive procedure in which the dysplastic cells are destroyed using temperature over 700°C. The procedure is quite painful and is therefore usually performed under general anesthesia. The abnormal tissues are destroyed upto the depth of about 8–10 mm. This procedure can be associated with numerous complications including recurrence of the lesions, bleeding, sepsis, cervical stenosis and indrawing of the squamocolumnar junction within the cervical canal.

Laser ablation

Laser ablation is a locally destructive OPD procedure, usually done under local anesthesia, which uses laser energy to destroy the dysplastic cells by boiling, steaming and exploding the cells. The extensive heat energy liberated causes incineration of the protein and mineral content of the tissues, resulting in a charred appearance at the base of exposed area. The main advantage of this method is that the tissue can be ablated up to the depth of about 7 mm, which is the location of the deepest endocervical gland. Thus laser ablation can be used in lesions with extensive glandular involvement. The other advantages of laser ablation are that it is associated with minimal bleeding, no infection, minimal post-laser scar formation and does not cause in-drawing of the squamocolumnar junction. It is also associated with a rapid post treatment healing phase.

Excision of the Abnormal Tissue

The advantage of various excisional methods over the locally destructive methods is that the piece of cervical tissue that is removed can be sent for histopathological examination.

Cone biopsy

Cone Biopsy serves as both a diagnostic and therapeutic procedure. The procedure involves the removal of entire area of abnormality (figure 21.11). It is capable of providing tissue for histopathological examination. The cone biopsy may be

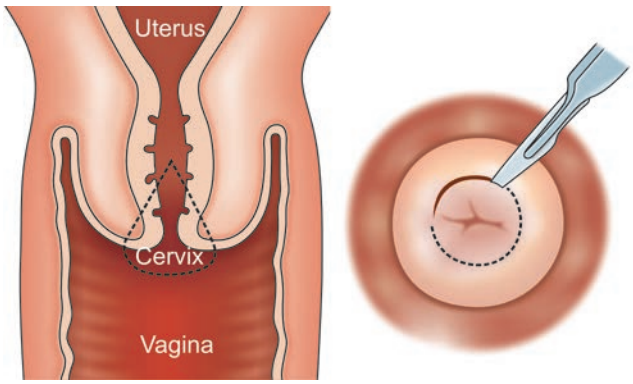


Fig. 21.11: Cone biopsy

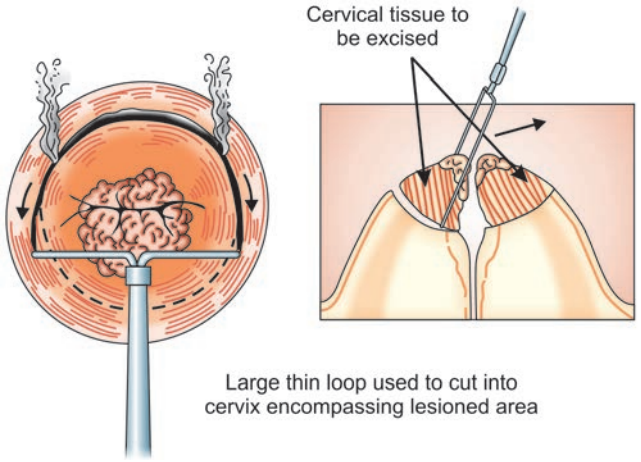


Fig. 21.12: Large loop excision of the transformation zone

performed under general or local anesthesia. This method involves obtaining a wide cone of excision including the entire outer margin of the lesion and the entire endocervical lining. Indications for cone biopsy are as follows:

- The area of the abnormality is large, or its inner margin has receded into the cervical canal
- The squamo-columnar junction is not completely visible on colposcopy
- There is discrepancy between the findings of cytology and colposcopy.
- There is a suspicion of microinvasion based on the results of biopsy, colposcopy or cytology.
- The findings of endocervical curettage are positive for CIN 2 or CIN 3.

Laser excision

In this method laser beams are adjusted to a width of 0.2–0.5 mm in diameter. The power of the beam is set at 20–30 Watts and the margins of the cone are outlined. The incision is deepened circumferentially by passing the laser beam progressively across the tissues. This is associated with less bleeding, infection and faster healing, without scar formation.

LLETZ

LLETZ stands for "large loop excision of the transformation zone". In the USA, this procedure is called LEEP – loop electrosurgical excision procedure. This method basically uses low voltage diathermy and may be given at the same time as colposcopy. In this procedure, the loop of wire is advanced into the cervix lateral to the lesion until the required depth is reached. The loop is then taken across to the opposite side and a cone of tissue is removed. The area of abnormal cells is removed completely using a loop of wire and electrosurgey (figure 21.12). It is an out-patient treatment and is usually performed under local anesthesia. If a large area of tissue needs to be removed, or if the patient is very anxious about the treatment, the surgery may also be performed under general anesthesia.

Loop electrosurgical excision procedure (LEEP)

In this procedure, a thin wire loop that carries an electric current is used to remove abnormal areas of the cervix (figures 21.13A and B). The excised area of the cervix removed is sent to the laboratory for histopathological examination. This electric energy is also used to coagulate the blood vessels on the surface of the cervix. LEEP is even simpler than LLETZ and is applicable anywhere in the lower genital tract whereas LLETZ is applicable only to the cervix.

Surgical Options

These include therapeutic conization, hysterectomy or hysterectomy with removal of vaginal cuff.

Therapeutic conization

The procedure of conization, not only provides tissue for histopathological study, but can also serve as a therapeutic procedure. Conization includes the entire outer margin of the cervix and endocervical lining, short of internal os. A smaller cone may be desirable in young women as it helps in avoiding complications such as abortion or preterm labor. Complications associated with the procedure include bleeding, sepsis, cervical stenosis, abortion and preterm labor. Conization may also be done in cases of endocervical dysplasia, when transformation zone cannot be completely visualized or when there is discrepancy in findings between the findings of cytology, colposcopy and biopsy.

Hysterectomy

Hysterectomy may serve as an appropriate option in older and parous women who have attained menopause or those who

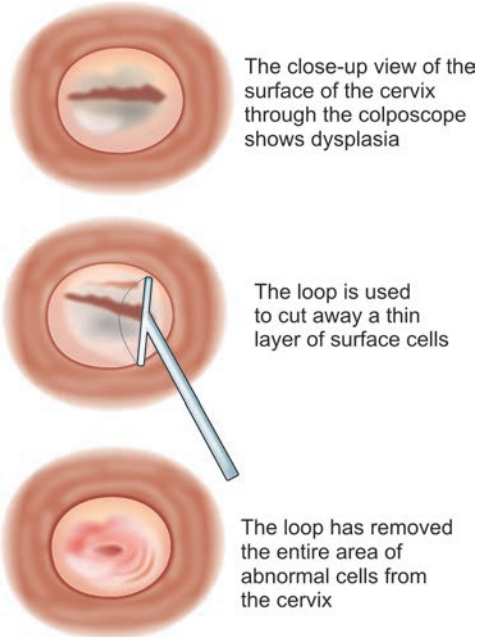


Fig. 21.13A: Procedure of LEEP

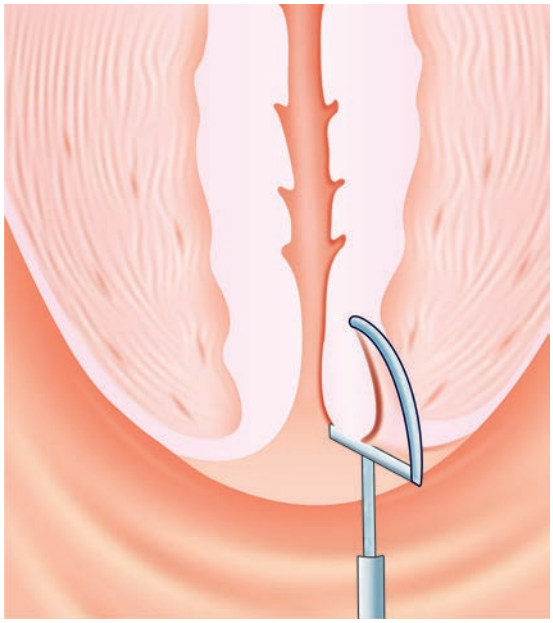


Fig. 21.13B: Procedure of LEEP (magnified view)

have completed their families. Hysterectomy can also be performed when it appears that the woman would not be able to comply with the follow up, recurrence occurs following conservative therapy, if microinvasion exists or if the dysplastic changes are associated with the presence of other pathologies such as fibroids, DUB or uterine prolapse.

Follow up after Therapy

An abnormal smear must be followed with a repeat smear about 6 months after treatment and then a further smear after about 12 months. Following this, a repeat smear is performed one year later, in case of CIN 1. In case of CIN 2 or 3, yearly smears are carried out for 9 more years. After that the frequency is changed to 3 or 5 yearly smears (depending on the patient's age). If the patient has undergone hysterectomy for cervical dysplasia, vault smears are required at six months and one year after hysterectomy. If these smears are normal, there would be no future requirement for smears.

Management: Invasive Cancer

Management of invasive cancer primarily depends on the stage of malignancy, which is essentially based on clinical findings and results of various investigations such as chest radiography, IVP, cystoscopy, proctoscopy, CT, MRI and FDG-PET. MRI examination helps in detecting lymph node enlargement of more than 1 cm in diameter. FDG-PET is Positron Emission Tomography based on the use of radiolabelled compound flurodeoxyglucose. This investigation is also useful in the determination of lymph node metastasis and has presently become the gold standard investigation. This test is based on the fact that malignant tissue exhibits greater glycolysis in comparison to normal tissue. As a result, FDG accumulates in the malignant tissue resulting in increased tumor contrast.

Management of cervical cancer changes based on lymph node involvement. Lymph node involvement increases with increasing staging of the disease. Pelvic lymph nodes are involved in 5% cases in Stage I, 15% cases in Stage II and 25% in Stage III.

Investigations

Pretreatment Investigations

Pretreatment investigations in a woman with histologic diagnosis of cervical cancer are enumerated in table 21.5. These investigations are useful in assessing the spread of metastatic disease. Assessment of renal function is important for staging of cervical cancer. The presence of unilateral or bilateral ureteral obstruction with azotemia often indicates metastatic disease and is associated with poor prognosis.

Examination Under Anesthesia (EUA)

This is an examination of the vagina and cervix after the patient has been administered general anesthesia. This allows

Table 21.5: Pretreatment investigations in a woman with histologic diagnosis of cervical cancer

Physical examination
Complete blood count, LFT, KFT
Chest radiography
Pelvic ultrasound
Magnetic resonance imaging (MRI)
Computed tomography (CT) scans
Laparoscopy
Intravenous pyelography or imaging of abdomen with intravenous contrast
Barium enema, cystoscopy, rectosigmoidoscopy
Cystoscopy: For visualization of the interior of the urethra and bladder
Proctoscopy: For visualization of the interior of the rectum

the clinician to examine the patient thoroughly without it being uncomfortable for her. The abdomen (especially large bowel, bladder and rectum) and pelvis are carefully assessed for the spread of metastatic disease. An endometrial biopsy may also be taken to assess the endometrial status.

Staging of Cervical Cancer

Once the diagnosis of invasive cervical cancer has been established confidently by histological examination, the disease is clinically staged which involves assessment of the degree of cancer dissemination. The results of bimanual pelvic palpation and cervical inspection and various above mentioned investigations like colposcopy, endocervical curretage, hysteroscopy, cystoscopy, proctoscopy, intravenous pyelography, X-ray examination of the lungs and skeleton and cervical conization/biopsy help in staging the cervical cancer. The most commonly used system for staging of cervical cancer is the staging system devised by Federation International of Gynecology and Obstetrics (FIGO), which is based on clinical examination, rather than surgical findings (table 21.6). Another staging system in use is the TNM staging system (table 21.7), which incorporates lymph node staging unlike the FIGO staging system which does not incorporate lymph node involvement. The TNM staging system for cervical cancer is analogous to the FIGO stage.

Cancer Grading

Cancer grading gives an idea about the degree of malignancy. It is based on the results of the histopathological examination and can be classified as grade 1 (low grade malignancy); grade 2 (moderate grade malignancy) and grade 3 (higher grade malignancy). The more undifferentiated the malignancy, the higher would be its grading.

Table 21.6: International federation of gynecologists and obstetricians staging system for cervical cancer

Stage	*Characteristics*
0	Carcinoma in situ, intraepithelial neoplasia.
I	Carcinoma strictly confined to the cervix.
IA	Invasive cancer identified only microscopically. All gross lesions, even with superficial invasion, are stage IB cancers. Invasion is limited to measured invasion of stroma ≤5 mm in depth and ≤7 mm in width.
IA1	Measured invasion of stroma ≤3 mm in depth and ≤7 mm in width.
IA2	Measured invasion of stroma >3 mm and ≤5 mm in depth and ≤7mm in width.
IB	Clinical lesions confined to the cervix or preclinical lesions greater than IA.
IB1	Clinical lesions ≤4 cm in size.
IB2	Clinical lesions > 4 cm in size.
II	Carcinoma extends beyond the cervix, but not to the pelvic wall; carcinoma involves the vagina but not as far as the lower one third.
IIA	No obvious parametrial involvement.
IIB	Obvious parametrial involvement.
III	Carcinoma has extended to the pelvic wall; on rectal examination no cancer-free space is found between the tumor and the pelvic wall; the tumor involves the lower one-third of the vagina; all cases with a hydronephrosis or nonfunctioning kidney should be included, unless they are known to be related to another cause.
IIIA	No extension to the pelvic wall, but involvement of the lower one-third of the vagina.
IIIB	Extension to the pelvic wall and hydronephrosis or nonfunctioning kidney, or both.
IV	Carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum.
IVA	Spread to adjacent organs.

Lymph nodes
Regional lymph nodes (N), include paracervical, parametrial, hypogastric (obturator), common, internal and external iliac, presacral and sacral group of lymph nodes.
NX: Regional lymph nodes cannot be assessed.
N0: No regional lymph nodes metastasis.
N1: Regional lymph nodes metastasis.

Cervical malignancy is unique because it can be detected at an early preinvasive stage. Recently, there has been a trend towards prevention of invasive cancer. Therefore, management of invasive carcinoma cervix would be discussed under two headings: Prevention of cervical cancer and treatment of invasive cancer.

Table 21.7: TNM cervical cancer staging

TNM Stage	*FIGO Stage*	*Stage description*
Tx	-	Primary tumor cannot be assessed
T0	-	No evidence of primary tumor
Tis	0	Carcinoma in situ
T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
T1a	IA	Invasive carcinoma diagnosed only by microscopy. All macroscopically visible lesions—even with superficial invasion—are T1b/IB. Stromal invasion with a maximal depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification.
T1a1	IA1	Measured stromal invasion 3 mm or less in depth and 7 mm or less in lateral spread
T1a2	IA2	Measured stromal invasion more than 3 mm but not more than 5 mm with a horizontal spread 7 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than IA2
T1b1	IB1	Clinically visible lesion 4 cm or less in greatest dimension
	IB2	Clinically visible lesion more than 4 cm
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to the lower third of vagina
T2a	IIA	Tumor without parametrial invasion
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extends to the pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis or nonfunctioning kidney
T3a	IIIA	Tumor involves lower third of vagina; no extension to pelvic wall
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
-	IV	Cervical carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the bladder mucosa or rectal mucosa. Bullous edema does not qualify as a criteria for stage IV disease.
T4	IVA	Spread to adjacent organs (bladder, rectum, or both)
M1	IVB	Distant metastasis

Table 21.8: HPV types and their association with cancer

Association with cancer	*HPV sub-type*
High risk HPV sub-types	HPV types 16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59, 68, 69, 73 and 82
Probable high-risk	HPV types 26, 53, and 66
Intermediate risk	HPV types 30, 31, 33, 35, 39, 51, 52, 58, 66
Low risk HPV sub-types	HPV types 6 and 11 (mainly cause genital warts), 40, 42, 43, 44, 54, 61, 70, 72, 81 and CP6108

Rx Treatment/Gynecological Management

PREVENTION

Human papilloma viruses

Of the 10 million cases of cancer that develop annually throughout the world, more than 15% have been attributed to infectious agents, especially infection with HPV. Human papilloma viruses (HPVs) are a group of viruses which contain more than 100 viruses. HPVs infect the stratified squamous epithelium of skin and mucous membranes, where they cause benign lesions, some of which have the potential to progress to invasive cancer. While some of these viruses belong to low-risk group and produce wart like, benign growths or papillomas, some types of high-risk HPV have been found to be associated with certain types of cancers, particularly cervical cancer. The presence of the virus may cause morphological abnormalities in the epithelium, including papillomatosis, parakeratosis and koilocytosis.

HPVs are usually transmitted sexually and nearly 40 types of HPV can be sexually transmitted and infect the genital area, including the cervix, vagina, vulva, anus and penis. Different HPV types and their association with cancer are shown in table 21.8. HPV infections are usually asymptomatic and therefore the majority of infections remain unnoticed. Most genital warts are caused by HPV types 6 and 11. The high risk types (e.g. HPV 16 and 18) may cause flat, abnormal growths in the genital area and on the cervix. While infection with low-risk HPV viruses is benign, subclinical, self-limited and usually regresses spontaneously, persistent cervical infection (infection that lasts for an interval of 6 months or longer) with a high-risk HPV type, especially HPV16 and HPV18, is the most important risk factor for progression to high-grade dysplasia. The interval between the acquisition of HPV infection and malignant progression usually takes at least 10 years and is frequently longer. Cervical cancer is, therefore, very uncommon in women under 25; the incidence rises progressively for women over 25 and is highest for women over 40.

Prevention of HPV infection

Thus one way to prevent the occurrence of cervical cancer is to eliminate risk for genital HPV infection by refraining from any genital contact with another individual. For those who want to remain sexually active, a long-term, mutually monogamous relationship with an uninfected partner is the

strategy, which is most likely to prevent genital HPV infection. Presently, it is not known whether condoms can provide any protection against HPV infection, because areas not covered by a condom can be infected by HPV.

HPV vaccination

Identification of a viral agent such as HPV as a cause of disease(s) implies that successful prophylactic or therapeutic intervention against the viral agent would be able to prevent the disease(s) it causes. Presently there are two vaccines available for preventing HPV infection. The first is a quadrivalent vaccine, which is effective against four strains of HPV (6, 11, 16 and 18), called Gradasil, which was developed by Merck & Co. Together, HPV types 16 and 18 currently cause about 70% of cervical cancer cases. HPV types 6 and 11 cause about 90% of genital wart cases. This vaccine has gained approval from the US Food and Drug Administration and has been made available in the market since June 2006. Gardasil has also been approved in the European Union. Gardasil is given through a series of three intramuscular injections over a period of 6-months. The second vaccine called Cervarix is a bivalent vaccine that has been developed by GlaxoSmithKline and has yet not gained FDA approval. This vaccine is also given in three doses over a 6-month period. For both the vaccines, three separate doses are needed. The second and third doses are given two months and six months after the first dose. The high cost of both these vaccine has been a cause for concern.

Since both the vaccines only work if they are administered before HPV infection actually occurs, this vaccine is specifically targeted at girls and women between the age of 9 to 26 year, before they become sexually active. However, neither of these HPV vaccines have been proven to provide complete protection against persistent infection with other HPV types, some of which may cause cervical cancer. Despite this fact, widespread vaccination has the potential to reduce cervical cancer deaths around the world by nearly 70%, if all women were to be given this vaccine. The duration of immunity provided by these vaccines is not yet known. Research is still being conducted to find out how long the protection will last. Studies conducted so far have shown that Gardasil can provide protection against HPV 16 for 4 years, while Cervarix can provide protection from infection with both HPV 16 and 18 for more than 4 years. Further studies in future are required to determine if booster vaccinations would be necessary. There are no major side effects associated with HPV vaccination except for redness, pain and swelling at the injection site and raised temperature. Despite of receiving HPV vaccination, women who are over the age of 21 years are advised to have a cervical smear test before they are immunized with the vaccine. They would still require attending their routine cervical smear test, because there are other types of HPV linked with cervical cancer which the vaccines are not active against. Since September 2008, all 12-13 year-old girls in the UK are being routinely offered HPV vaccination.

The HPV test

The HPV test is a newer technique which helps in detecting the presence of human papilloma virus infection in the cervix. The HPV test checks directly for genetic material (DNA) of HPV and may be used to determine which women with an ambiguous Pap test result (e.g. ASCUS) are most likely to have underlying precancerous or cancerous changes on their cervix. HPV infection may precede nearly 80% cases of ASCUS and LSIL positive smears in young women. While nearly 80% of such cases are transitory and self-limited and disappear over a year or so, approximately 20% cases may persist and transform to HSIL beyond 30 years of age. Therefore, integration of HPV testing along with cytology screening, helps in improving the predictive value of Pap smear and reducing unnecessary colposcopy referrals. Combined HPV testing and Pap smear yields 96% sensitivity as compared to only 60 to 70% with Pap smear alone. The HPV testing is done either by study of cells in liquid based cytology or endocervical secretion and self-obtained vaginal swab. Though, this test is more sensitive (less likely to produce false negative results), but less specific (more likely to produce false positive results) in comparison to the conventional Pap smear, its role in routine screening is still evolving. Since more than 99% of invasive cervical cancers worldwide contain HPV, some researchers recommend that HPV testing be done together with routine cervical screening. The routine HPV testing is likely to cause undue alarm to carriers because the prevalence of HPV infection can be as high as 80% among the sexually active population due to high rates of asymptomatic carriers of the infection.

There currently is only one FDA-approved, commercially available test for HPV, the Hybrid Capture, produced by Digene Corporation. The HPV test specifically aims at detecting certain high-risk HPV types which are known to be associated with cervical cancer. A positive test implies that one of the types of HPV being tested is present and the amount is enough to cause an infection.

Use of condoms

Though the use of condoms is unlikely to reduce the rates of HPV infection, its use has been found to be useful in preventing potentially precancerous changes in the cervix. Exposure to semen has been found to be associated with an increased

risk of precancerous changes, especially CIN 3. Therefore, use of condoms does help in providing some protection.

Nutrition

Fruits, vegetables and antioxidants

Consumption of high amounts of fruits and vegetables (at least five portions) has been found to be associated with a reduced risk of persistent HPV infection. Consumption of high levels of antioxidants, particularly vitamin A, E and C have also been found to exert a protective role. Higher circulating levels of carotenoids have been found to be associated with a significant decrease in the clearance time of type specific HPV infection, particularly during the early stages of infection (≤120 days). Another food stuff which has been observed to exert a protective role in the development of cancer cervix is folic acid. High levels of folic acid have been found to be inversely related with the risk of developing HPV. Some studies have shown that lower levels of antioxidants coexisting with low levels of folic acid increases the risk of CIN development. Improving folate status in subjects at risk of getting infected or already infected with high-risk HPV may have a beneficial impact in the prevention of cancer. However, presently, the role of various antioxidants and other foodstuffs in cancer prevention is not yet clear as the present evidence regarding the role of folic acid and carotenoids in prevention of cervical carcinoma has largely presented with conflicting results.

DEFINITIVE TREATMENT FOR INVASIVE CANCER

The treatment of cervical cancer varies with the stage of the disease. For early invasive cancer, surgery is the treatment of choice. In more advanced cases, radiation combined with chemotherapy is the current standard of care. In patients with disseminated disease, chemotherapy or radiation provides symptom palliation. Palliative radiotherapy is often useful for controlling bleeding, pelvic pain and urinary or partial large bowel obstructions resulting from pelvic disease. Depending on the staging and grading of the cervical cancer, various treatment options are summarized in table 21.9 and are described below in details:

Table 21.9: Summary of treatment of invasive cervical carcinoma

Cervical cancer stage	*Therapeutic option*
Stage 0	Loop electrosurgical excision procedure (LEEP), laser therapy, conization and cryotherapy.
Stage Ia	Simple hysterectomy without pelvic node dissection or careful observation following adequate cone biopsy.
Stage Ib or IIa	Radical hysterectomy with pelvic lymph node dissection or external beam and intracavitary radiotherapy.
Stage II b, III, IVa	Pelvic radiotherapy with concurrent chemotherapy.
Stage IV b	Chemotherapy with or without radiotherapy.

Stage IA Tumors

As described before, stage IA tumors are mainly diagnosed by microscopic examination. The risk of nodal metastasis in the early invasive tumors (Stage IA1) is quite low, only about 0.5%; therefore the prognosis in these cases is quite good. Five-year survival rate exceeds 95% with appropriate treatment. The recommended therapy for stage IA1 tumors is simple hysterectomy with or without pelvic lymph node dissection. Conization with clear margins may be considered adequate in young patients with stage IA disease who want to conserve their uterus. However, these patients require close follow up, including cytology, colposcopy and endocervical curettage. Lymph node dissection is not required if the depth of invasion is less than 3 mm and no lymphovascular invasion is noted on microscopic examination. Patients with lymphatic or the vascular channel infiltration require treatment as in stage IB.

Extended hysterectomy and lymph node sampling may be recommended in cases with Stage IA2 disease. Postoperative radiotherapy may be administered in cases where the nodes are positive. In young women desirous of child bearing, conservative treatment comprising of laparoscopic lymphadenectomy followed by vaginal trachelectomy can be done. The procedure of trachelectomy involves the removal of whole or at least 80% of the cervix, upper vagina and lymph nodes in the pelvis and cutting the Mackenrodts ligament on either side. A radical trachelectomy can be performed abdominally or vaginally. Although, complications associated with the procedure are uncommon, women who are able to conceive after surgery are likely to develop preterm labor or late miscarriages.

Stage IB and IIA Tumors

The treatment options for stage IB and IIA are surgical treatment or radiotherapy or both combined surgery and radiotherapy. Radiotherapy can be either in the form of external beam and intracavitary radiotherapy. Both the treatment options, surgery and radiotherapy produce similar results, with a five-year survival rate of 80 to 90%. Surgery includes a radical hysterectomy, (Wertheims hysterectomy

or Schauta vaginal hysterectomy, known as Mitra operation in India). Wertheims hysterectomy involves removal of the entire uterus, both adnexa, medial one-third of parametrium, uterosacral ligaments, upper 2 to 3 cm cuff of the vagina and dissection of pelvic lymph nodes. Oophorectomy is usually not necessary in premenopausal women. Recently it has been shown that patients with parametrial involvement, positive pelvic nodes, or positive surgical margins may benefit from a postoperative combination of cisplatin containing chemotherapy and pelvic radiation.

Schautas operation is an extended vaginal hysterectomy consisting of removal of the entire uterus, adnexa, most of the vagina and medial portion of the parametrium. This may be preceded by laparoscopic pelvic lymphadenectomy or followed later by extraperitoneal (Taussigs) lymphadenectomy. Alternately, postoperative pelvic radiotherapy may also be given.

Stage IIB, III and IV Tumors

In stage IIB, III and IV cancer as the tumor invades local organs, radiation therapy has become the mainstay of treatment. However, in some cases combination chemotherapy and radiotherapy is employed. Patients with distant metastases (Stage IVB) also require chemotherapy with or without radiotherapy to control systemic disease. Recently, the combination of cisplatin and topotecan is being preferred rather than use of single-agent cisplatin. Adult dose of cisplatin is 50–100 mg/m^2 IV q3wk. Cisplatin can result in side effects such as hypersensitivity; renal failure; peripheral neuropathy and bone marrow suppression. Adult dose of topotecan is 1.5 mg/m^2/d IV for 5 d q4wk.

In advanced cases of cervical cancer, the most extreme surgery, called pelvic exenteration in which all of the organs of the pelvis, including the bladder and rectum are removed, may be employed.

Radiation Therapy

Radiation may be used to treat cancer that has spread beyond the pelvis, or cancer that has returned. Radiation therapy can be either external or internal.

Internal radiation therapy

Internal radiation therapy also known as brachytherapy involves placing the selectron tubes inside the patient's vagina. This method helps in delivering radiation directly to the cervix and the surrounding areas. The radioactive balls in the selectron tube can be withdrawn into the machine when other people come into the patient's room. This helps in keeping the dose of radioactivity to visitors and nurses as low as possible.

External radiation therapy

External radiation therapy involves administration of radiation beams from a large machine onto the body where the cancer is located. External radiotherapy is normally administered on an outpatient basis. The treatments are usually given from Monday to Friday, with a rest at the weekend.

Chemotherapy

The most commonly employed chemotherapy regimens use Cisplatin, 5-flourouracil, carboplatin, ifosfamide, paclitaxel, cyclophosphamide, etc. Chemotherapy is sometimes used in form of neoadjuvant chemotherapy. This method involves use of chemotherapy before surgery or radiotherapy, to shrink the cancer and to make these treatments more effective.

Pelvic Exenteration

If the cancer recurs in the pelvis after radiation therapy, the gynecologist may need to resort to surgery for removing all pelvic organs. This procedure cures up to 50% of women. This is a major operation that involves removing all of the structures in the pelvic area, including the uterus, cervix, vagina, ovaries, bladder and the rectum. This operation may involve creating two stomas: a colostomy and a urostomy. The operation also involves reconstructing a new vagina.

Complications

Therapeutic modalities like surgery, radiotherapy and chemotherapy can result in numerous complications.

Complications Due to Radiotherapy

During the acute phase of pelvic radiation, the surrounding normal tissues such as the intestines, the bladder and the perineum skin are often affected. As a result, radiotherapy to the pelvic area can cause side effects such as tiredness, diarrhea and dysuria. These side effects can vary in severity depending on the strength of the radiotherapy dose and the length of treatment. Some of these complications are described below:

Cystourethritis

Inflammation of bladder and urethra can result in complications like dysuria, increased urinary frequency, and nocturia. Antispasmodics medicines are often helpful in providing symptomatic relief. Urine should be examined for possible infection. If urinary tract infection is diagnosed, therapy should be instituted without delay.

Gastrointestinal effects

Gastrointestinal side effects due to radiotherapy include diarrhea, abdominal cramping, rectal discomfort, bleeding,

etc. Diarrhea can be either controlled by loperamide (imodium) or diphenoxylate (lomotil). Small, steroid containing enemas are prescribed to alleviate symptoms resulting from proctitis.

Sore skin

Radiotherapy can result in erythema and desquamation of skin.

Tiredness

Radiotherapy can result in extreme tiredness. Therefore, the patient must be advised to take as much rest as possible.

Bowel complaints

In a small number of cases, the bowel may be permanently affected by the radiotherapy resulting in continued diarrhea. The blood vessels in the bowel can become more fragile after radiotherapy treatment, resulting in hematochezia.

Vaginal stenosis

Radiotherapy to the pelvis can cause narrowing and shortening of the vaginal orifice, thereby making the sexual intercourse difficult or uncomfortable. This problem can be overcome by prescribing estrogen creams to the patient. Using vaginal dilators or having regular penetrative sex often helps in maintaining the suppleness of the vaginal orifice.

Lymphedema

Side Effects Due to Chemotherapy

Chemotherapy can cause side effects, which may be slightly worse if it is given alongside radiotherapy. Chemotherapy can temporarily reduce the number of normal blood cells, resulting in development of symptoms including increased susceptibility to infection, easy fatigability, anemia, etc. Other side effects, which the chemotherapy drugs can cause, may include oral ulcerations (stomatitis), nausea, vomiting and alopecia. Nausea and vomiting can be well-controlled with effective antiemetic drugs. Regular use of mouthwashes is important in treating the mouth ulcerations.

Complications from Surgery

Premature menopause

Removal of ovaries in young patients can result in symptoms related to premature menopause.

Urinary dysfunction

The most frequent complication of radical hysterectomy is urinary dysfunction as a result of partial denervation of the detrusor muscle.

Other complications

Other complications resulting from surgery may include shortened vagina, ureterovaginal and rectovaginal fistulas, hemorrhage, infection, bowel obstruction, stricture and fibrosis of the intestine or rectosigmoid colon and bladder.

Important Questions and Answers

Q.1. What is the significance of postcoital bleeding?

Ans. Postcoital bleeding usually indicates a structural lesion of the cervix or vagina. Various causes of postcoital/post-menopausal bleeding are enumerated in table 21.10. Infectious etiologies such as chlamydia and gonorrhea are common causes of postcoital bleeding which must must be excluded and treated if required. Uterine or cervical polyps may also be a source of bleeding. Dysplastic or malignant lesion of the cervical or vaginal epithelium may cause irregular or postcoital bleeding.

Table 21.10: Causes of postcoital bleeding

Vulva	Vulval trauma, vaginitis and benign or malignant lesions of vulva
Vagina	Senile vaginitis, vaginal tumors
Cervix	Cervical erosions, cervicitis, polyps, decubitus ulcers, malignancy
Uterus	Senile endometritis, tubercular endometritis, endometrial hyperplasia, polyps, endometrial cancer, DUB, metropathia hemorrhagica,
Fallopian tube	Malignancy
Ovaries	Benign ovarian tumor, granulosa or theca cell tumors
Systemic diseases	Hypertension, blood dyscrasias
Medicines	Unopposed estrogen, cyclical HRT

Q.2. What is the prognosis in the above mentioned case study?

Ans. Prognosis depends on the stage of the cancer. If the earliest stage of invasive cervical cancer is treated, the 5-year relative survival rate is nearly 90-95%.With treatment, 80 to 90% of women with stage I cancer and 50 to 65% of those with stage II cancer remain alive 5 years after diagnosis. Only 25 to 35% of women with stage III cancer and 15% or fewer of those with stage IV cancer remain alive after 5 years. With metastasis of cancer to other parts of the body, prognosis progressively worsens.

Q.3. What is the relationship between pregnancy and cervical cancer?

Ans. Pregnancy does not change the course of cervical cancer. The rate of cervical cancer in pregnant patients is similar to that in nonpregnant patients of the same age. In patients with concurrent cervical malignancy and pregnancy, the major

dilemma is regarding diagnosis and treatment. Diagnosis usually requires the performance of a cone biopsy, which carries increased risks of hemorrhage and poor perinatal outcome. Radiotherapy during pregnancy is a matter of concern to many clinicians due to increased risk of the exposure of the fetus to ionizing radiations. However, presently there is no evidence indicating the risk to the fetus if the dose of radiation is less than 5 rads. Thus, the recommended treatments for pregnant and nonpregnant patients are the same.

Before 20 weeks of gestation, radical hysterectomy should be performed with the fetus in situ; beyond 20 weeks, evacuation of the fetus before surgery is recommended. In patients diagnosed with stage I disease and a previable fetus, therapy may be delayed until fetal survival (i.e. pulmonary matuity) has been assured. However, delaying therapy is not recommended in patients with more advanced disease. Delivery should be performed as soon as pulmonary maturity of the fetus is demonstrated, although the route of delivery is highly controversial. Most clinicians advocate cesarean delivery in cases with cervical cancer, because of the possibility of the recurrence of the disease at the site of episiotomy. Furthermore, vaginal delivery through a cervix with advanced cervical cancer is associated with an increased risk for hemorrhage, obstructed labor and infection.

Q.4. What do you know about the adenocarcinoma of the cervix? What is the prognosis of adenocarcinoma in comparison to the squamous cell cancer of the cervix?

Ans. Nearly 80% cases of invasive cancer of cervix are of squamous cell type and arise from the stratified squamous epithelium of the cervix. The second variety of less common type of cancer cervix arises from the mucous membrane of the endocervical canal and accounts for nearly 20% cases of cervical cancer. Adenocarcinoma of cervix is associated with poorer prognosis at every stage when compared with squamous cancer. This is mainly because adenocarcinomas tend to grow endophytically and, therefore, often remain undetected until the tumor volume increases significantly. Furthermore, the colposcopic and cytological findings for glandular disease are not as distinct as those for squamous lesions. When atypical glandular cells of undetermined significance (AGUS) are diagnosed on Pap smear, the presence or absence of squamous intraepithelial lesion, adenocarcinoma in situ or adenocarcinoma needs to be confirmed.

Q.5. When should a woman be advised to contact a medical Professional regarding Pap smear examinations?

Ans. The women should be advised to contact a medical professional under the following circumstances:

- A sexually active woman who has not had a Pap smear in the past year.
- Any women, at least 21 years of age, who has never had a pelvic examination and Pap smear.
- The women whose mother was prescribed DES when she was pregnant with her.
- Any women who did not have regular Pap smears in the past.

Q.6. How may the treatment for cervical cancer affect the patient's sexual life?

Ans. Removal of ovaries at the time of hysterectomy can result in an early menopause. The symptoms of the menopause can include hot flushes, dryness of skin and vagina, anxiety and loss of interest in sexual activity. Radiotherapy can cause cervical stenosis which can result in pain and discomfort at the time of sexual intercourse.

Bibliography

1. Abu J, Davies Q. Endocervical curettage at the time of colposcopic assessment of the uterine cervix. Obstet Gynecol Surv. 2005;60:315-20.
2. ACOG. Cervical Cytology Screening. ACOG Practice Bulletin No. 45. ACOG 2003;102:417-27.
3. ACOG Committee Opinion. Evaluation and management of abnormal cervical cytology and histology in the adolescent. Obstet Gynecol. 2006;107:963-68.
4. Adami, HO, D Hunter and D Trichopoulos, eds. Textbook of cancer epidemiology. 2002, Oxford University Press: New York.
5. Allard JE, Rodriguez M, Rocca M, Parker MF. Biopsy site selection during colposcopy and distribution of cervical intraepithelial neoplasia. J Low Genit Tract Dis. 2005;9:36-9.
6. American Academy of Family Physicians Summary of Policy Recommendations for Periodic Health Examination. AAFP Policy Action. 1997:1-14.
7. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin number 66, September 2005 (Management of abnormal cervical cytology and histology). Obstet Gynecol. 2005;106:645-64.
8. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologists. Number 61, April 2005. Human papillomavirus. Obstet Gynecol. 2005;105(4):905-18.
9. American College of Obstetricians and Gynecologists. New Pap test screening techniques. ACOG committee opinion no. 206. Washington, DC: ACOG, 1998.
10. American College of Obstetricians and Gynecologists. Recommendations on frequency of Pap test screening. ACOG committee opinion no. 152. Int J Gynaecol Obstet. 1995;49: 210-1.
11. Apgar BS, Rubin MM, Brotzman GL. Principles and techniques of the colposcopic examination. In: Apgar BS editors. Colposcopy principles and practice: An integrated textbook and atlas. Philadelphia: WB Saunders; 2002;p. 115-32.
12. Bosch FX et al. The causal relation between human papillomavirus and cervical cancer. Journal of Clinical Pathology. 2002;55(4):244-65.
13. Bosch FX, et al. The causal relation between human papillomavirus and cervical cancer. Journal of clinical pathology. 2002;55(4):244-65.

14. Bosch FX, Schiffman M, Solomon D. editors. Future directions in epidemiologic and preventive research on human papillomaviruses and cancer. J Natl Cancer. Inst Monogr. 2003;31:131.
15. Brown D, Berran P, Kaplan KJ, Winter WE, Zahn CM. Special situations: Abnormal cervical cytology during pregnancy. Clin Obstet Gynecol. 2005;48:178-85.
16. Cannistra SA, Niloff JM. Cancer of the uterine cervix. N Engl J Med. 1996;334:1030-8.
17. Castle PE, Wacholder S, Lorincz AT, Scott DR, Sherman ME, Glass AG, et al. A prospective study of high-grade cervical neoplasia risk among HPV infected women. J Natl Cancer Inst. 2002;94:1406-14.
18. CDC. 1998 guidelines for treatment of sexually transmitted diseases. MMWR Morb Mortal Wkly Rep. 1998;47:1-111.
19. Cox JT. AGUS Pap smears: a follow-up strategy. OBG Management. 1998:74-87.
20. De Villiers EM, Fauquet C, Broker TR, Bernard HU, zur Hausen H. Classification of papillomaviruses. Virology. 2004;324:17-27.
21. Diaz ML. Human Papilloma Virus - Prevention and Treatment. Obstet Gynecol Clin North Am. 2008;35(2);199-217.
22. DiSaia PJ, Creasman WT. Clinical gynecologic oncology. 5th ed. St. Louis: Mosby, 1997.
23. Duggan MA, Brasher P, Nation J. The Pap test at follow-up colposcopy examinations: Usefulness in the enhanced detection of cervical neoplasia. J Low Genit Tract Dis. 2004;8:118-24.
24. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. New England Journal of Medicine. 2007;356:1944-56.
25. Eddy GL, Wojtowycz MA, Piraino PS, Mazur MT. Papanicolaou smears by the Bethesda system in endometrial malignancy: Utility and prognostic importance. Obstet Gynecol. 1997;90: 999-1003.
26. Elkas J, Farias-Eisner R. Cancer of the uterine cervix. Curr Opin Obstet Gynecol. 1998;10:47-50.
27. Ferris DG, Cox JT, O'Connor DM, Wright VC, Foerster J. The colposcopic examination. In: Modern colposcopy textbook and atlas. Dubuque, IA: Kendall/Hunt; 2004;p. 144-172American Society of Colposcopy and Cervical Pathology (ASCCP).
28. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. New England Journal of Medicine. 2007; 356(19):1928-43.
29. Greimel ER, Gappamayer-Locker E, Girardi FL, Huber HP. Increasing women's knowledge and satisfaction with cervical cancer screening. J Psychosom Obstet Gynecol. 1997;18: 273-79.
30. Hines JF, Ghim SJ, Jenson AB. Prospects for human papillomavirus vaccine development. Curr Opin Obstet Gynecol 1998;10: 15-9.
31. Hogewoning CJA, Bleeker MCG, Van Den Brule AJC, Voorhorst FJ, Snijders PJF, Berkhof J, et al. Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papilloma virus: A randomized clinical trial. Int J Cancer. 2003;107:811-16.
32. Irvin W, Taylor P. Biopsy of lesions of the female genital tract in the ambulatory setting. J Long Term Eff Med Implants. 2004; 14:185-99.
33. Keys HM, Bundy BN, Stehman FB. Cisplatin, radiation and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med. 1999;340(15):1154-61.
34. Klam S, Arseneau J, Mansour N, Franco E, Ferenczy A. Comparison of endocervical curettage and endocervical brushing. Obstet Gynecol. 2000;96:90-94.
35. Kolstad P. Followup study of 232 patients with stage Ia1 and 411 patients with stage Ia2 squamous cell carcinoma of the cervix (microinvasive carcinoma). Gynecol Oncol. 1989;33:265-72.
36. Koutsky LA, Ault KA, Wheeler CM, et al. A controlled trial of a human papillomavirus type 16 vaccine. New England Journal of Medicine 2002; 347(21):1645-51.
37. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1998. CA Cancer J Clin. 1998;48:6-29.
38. Lombard I, Vincent-Salomon A, Validire P, Zafrani B, de la Rochefordiere A, Clough K, et al. Human papillomavirus genotype as a major determinant of the course of cervical cancer. J Clin Oncol. 1998;16:2613-9.
39. Long HJ 3rd, Bundy BN, Grendys EC Jr, Benda JA, McMeekin DS, Sorosky J. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. J Clin Oncol. 2005; 23(21):4626-33.
40. Lorincz AT, Reid R, Jenson AB, Greenberg MD, Lancaster W, Kurman RJ. Human papillomavirus infection of the cervix. Obstet Gynecol. 1992;79:328-37.
41. Maiman M, Fruchter RG, Guy L, Cuthill S, Levine P, Serur E. Human immunodeficiency virus infection and invasive cervical carcinoma. Cancer. 1993;71:402-6.
42. Mao C, Balasubramanian A, Koutsky LA. Should liquid-based cytology be repeated at the time of colposcopy?. J Low Genit Tract Dis. 2005;9:82-88.
43. Massad SL, Wright TC, Cox TJ, Twiggs LB, Wilkinson E. Managing abnormal cytology results in pregnancy. J Low Genit Tract Dis. 2005;9:146-48.
44. Miranda AD, Rodriguez R, Novoa DM, Rojas A, Pachon A, DiazGranados CA. The use of endocervical curettage in women with low grade squamous intraepithelial lesions or atypical squamous cells of unknown significance on Pap smear. J Low Genit Tract Dis. 2006;10:146-50.
45. Morris M, Tortolero-Luna G, Malpica A, Baker VV, Cook E, Johnson E, et al. Cervical intraepithelial neoplasia and cervical cancer. Obstet Gynecol Clin North Am. 1996;23:347-410.
46. Nuovo J, et al. Treatment outcomes for squamous intraepithelial lesions. International Journal of Gynecology and Obstetrics. 2000;68(1):25-33.
47. Office for National Statistics. Cancer statistics registrations: Registrations of cancers diagnosed in 2006, England. Series MB1 no.37. 2009
48. Omura GA, Blessing JA, Vaccarello L. Randomized trial of cisplatin versus cisplatin plus mitolactol versus cisplatin plus ifosfamide in advanced squamous carcinoma of the cervix: A Gynecologic Oncology Group study. J Clin Oncol. 1997;15(1): 165-71.
49. Parazzini F, Chatenoud L, La Vecchia C, Negri E, Franceschi S, Bolis G. Determinants of risk of invasive cervical cancer in young women. Br J Cancer. 1998;77:838-41.

50. Park TW, Fujiwara H, Wright TC. Molecular biology of cervical cancer and its precursors. Cancer. 1995;76(10 Suppl): 1902-13.
51. Payne N, Chilcott J, McGoogan E. Liquid-based cytology in cervical screening: A rapid and systematic review. Health Technol Assess 2000;4(18).
52. Pretorius RG, Zhang X, Belinson JL, Zhang WH, Ren SD, Bao YP, et al.Distribution of cervical intraepithelial neoplasia 2, 3 and cancer on the uterine cervix. J Low Genit Tract Dis. 2006;10:45-50.
53. Roden RB, Ling M, Wu TC. Vaccination to prevent and treat cervical cancer. Hum Pathol. 2004;35:971-82.
54. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med. 1999;340:1144-53.
55. Rubin P. and Williams JP, (Eds): Clinical Oncology: A Multidisciplinary Approach for Physicians and Students 8th ed. (2001). W.B. Saunders Company, Philadelphia, Pennsylvania.
56. Saslow D, Castle PE, Cox JT, Davey DD, Einstein MH, Ferris DG, et al. American Cancer Society Guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. CA Cancer J Clin. 2007;57(1):7-28.
57. Sawaya GF et al. Clinical practice. Current approaches to cervical-cancer screening. New England Journal of Medicine. 2001;344(21):1603-7.
58. Schiffman MH, Bauer HM, Hoover RN. Epidemiologic evidence showing that human papillomavirus infection causes most cervical intraepithelial neoplasia. J Natl Cancer Inst. 1993; 85(12):958-64.
59. Snijders PJ, Steenbergen RD, Heideman DA, Meijer CJ. HPV-mediated cervical carcinogenesis: concepts and clinical implications. J Pathol. 2006;208:152-64.
60. Spitzer M. Cervical screening adjuncts: recent advances. Am J Obstet Gynecol. 1998;179:544-56.
61. Steinbrook R. The potential of human papillomavirus vaccines. New England Journal of Medicine. 2006; 354(11):1109-12.
62. Stoler MH. Human papillomavirus biology and cervical neoplasia: implications for diagnostic criteria and testing. Arch Pathol Lab Med. 2003;127:935-39.
63. Sun XW, Kuhn L, Ellerbrock TV, Chiasson MA, Bush TJ, Wright TC. Human papillomavirus infection in women infected with the human immunodeficiency virus. N Engl J Med. 1997;337:1343-49.
64. Suzich JA, et al. Systemic immunization with papillomavirus L1 protein completely prevents the development of viral mucosal papillomas. Proc Natl Acad Sci USA. 1995;92:11553-57.
65. Szentirmay Z, et al. Human papillomavirus in head and neck cancer: molecular biology and clinicopathological correlations. Cancer Metastasis Rev. 2005;24:19-34.
66. Tewari K, Cappuccini F, Freeman RK, DiSaia PJ. Managing cervical cancer in pregnancy. Contemp Obstet Gynecol. 1999; 44:134-45.
67. Thigpen JT, Vance R, Puneky L. Chemotherapy as a palliative treatment in carcinoma of the uterine cervix. Semin Oncol. 1995;22(2 Suppl 3):16-24.
68. Thoms WW, Unger ER, Johnson PR, Spann CO, Hunter SH, Smith R, et al. Cervical cancer survival in a high risk urban population. Cancer. 1995;76:2518-23.
69. US National Library of Medicine, National Institutes of Health Web site. Colposcopy. www.nlm.nih.gov/medlineplus/tutorials/colposcopy/htm/index.htm[Accessed July, 2009].
70. Vetter KM and Geller SE. Moving forward: human papillomavirus vaccination and the prevention of cervical cancer. Journal of Women's Health. 2007;16(9):1258-68.
71. Wilbur DC, Cibas ES, Merritt S, James LP, Berger BM, Bonfiglio TA. ThinPrep Processor. Clinical trials demonstrate an increased detection rate of abnormal cervical cytologic specimens. Am J Clin Pathol. 1994;101:209-14.
72. Woolf SH. Screening for cervical cancer. U.S. Preventive Services Task Force. Guide to clinical preventive services: Report of the U.S. Preventive Services Task Force. 2d ed. Baltimore: Williams & Wilkins. 1996;105-17.
73. Wright, TC Jr. et al. ASCCP Sponsored Consensus Conference. Consensus Guidelines for the management of women with cervical cytological abnormalities. JAMA. 2002;287:2120-9.
74. Wright TC, Cox JT, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, et al.2006 consensus guidelines for the management of women with abnormal cervical screening tests. J Low Genit Tract Dis. 2007;11:201-22.
75. Wright TC, Cox JT, Massad LS, et al. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. JAMA. 2002;287(16):2120-9.
76. Wright TC, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ. 2001 consensus guidelines for the management of women with cervical cytological abnormalities. JAMA. 2002;287:2120-9.
77. Zur Hausen H. Papillomaviruses and cancer: from basic studies to clinical application. Nat Rev Cancer. 2002;2:342-50.

Section 6

Uterine, Ovarian and Tubal Pathology

- Prolapse Uterus
- Pelvic Pain
- Abdominal Lump (Ovarian Cancer)
- Ectopic Pregnancy

Chapter

22

Prolapse Uterus

Case Study

A 40-year-old G5P5 lady presented with the complaints of something descending out of vaginal introitus since past 1 year. According to the patient the feeling worsens while coughing or standing. On a per speculum examination, a grade II cystocele and a grade I rectocele were noticed. There was no enterocele. Both the cystocele and rectcele were observed to increase in size when the patient strained. On bimanual examination, uterus was normal sized, anteverted and mobile. There has been no history of urinary incontinence. Her previous menstrual history has also been normal. She has completed her family and has five children. All her children were delivered at home by an untrained dai. She works on the farm with her husband. Due to lack of social support, she had to resume her activities immediately following each delivery.

Introduction

Uterine prolapse is a descent or herniation of the uterus into or beyond the vagina. Uterine prolapse is best considered under the broader heading of "pelvic organ prolapse," which also includes cystocele, urethrocele, enterocele and rectocele. Anatomically, the vaginal vault has 3 compartments: An anterior compartment (consisting of the anterior vaginal wall), a middle compartment (cervix) and a posterior compartment (posterior vaginal wall). Weakness of the anterior compartment results in cystocele and urethrocele, whereas that of the middle compartment in the descent of uterine vault and enterocele. The weakness of the posterior compartment results in rectocele.

Uterine prolapse involves the middle compartment. Uterine prolapse usually occurs in postmenopausal and multiparous women in whom the pelvic floor muscles and the ligaments that support the female genital tract have become slack and atonic. Injury to the pelvic floor muscles during repeated childbirths causing excessive stretching of the pelvic floor muscles and ligaments acts as a major risk factor for causing reduced tone of pelvic floor muscles. Reduced estrogen levels following menopause is another important cause for atonicity and reduced elasticity of the muscles of pelvic floor. Uterine prolapse can be classified into four stages based on Baden-Walker Halfway system as described in table 22.1.

Pelvis consists of three compartments: Anterior, middle and posterior (figure 22.1). The normal female pelvic anatomy is shown in figure 22.2A. Descent of the anterior compartment results in cystocele (figure 22.2B) and urethrocele (figure 22.2C) that of the middle compartment in the descent of uterine vault (figure 22.2D) and enterocele (figure 22.2E) and that of the posterior compartment in rectocele (figure 22.2F).

Table 22.1: Baden-Walker Halfway system for evaluation of pelvic organ prolapse

Stage	*Definition*
Stage 0	Normal position for each respective site
Stage I	Descent of the uterus to any point in the vagina above the hymen
Stage II	Descent of the uterus uptil the hymen
Stage III	Descent of the uterus halfway past the hymen
Stage IV	Total eversion or procidentia

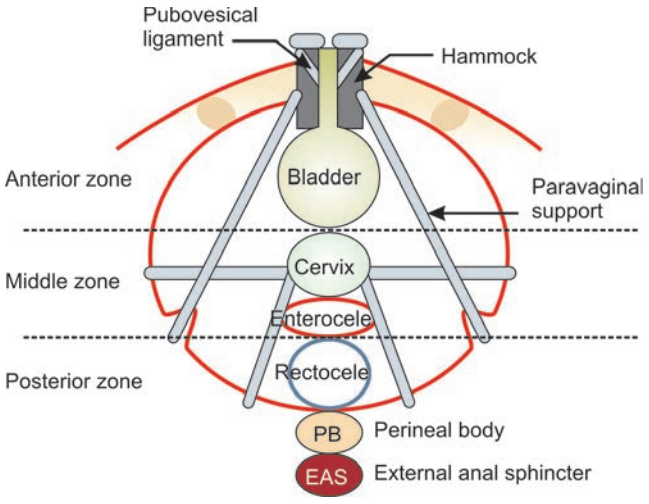


Fig. 22.1: Different pelvic compartments

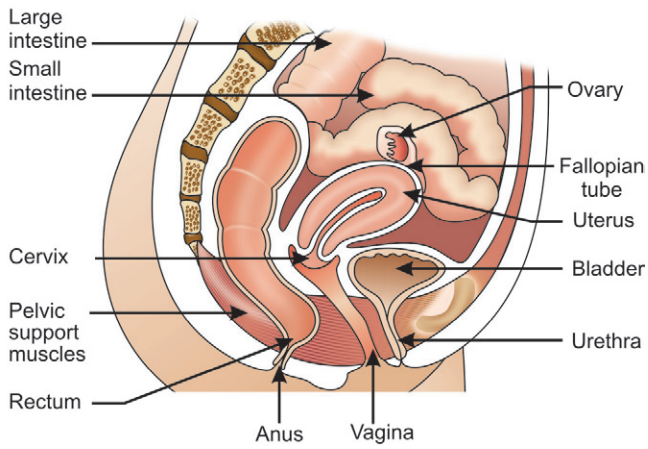


Fig. 22.2A: Normal female pelvic anatomy

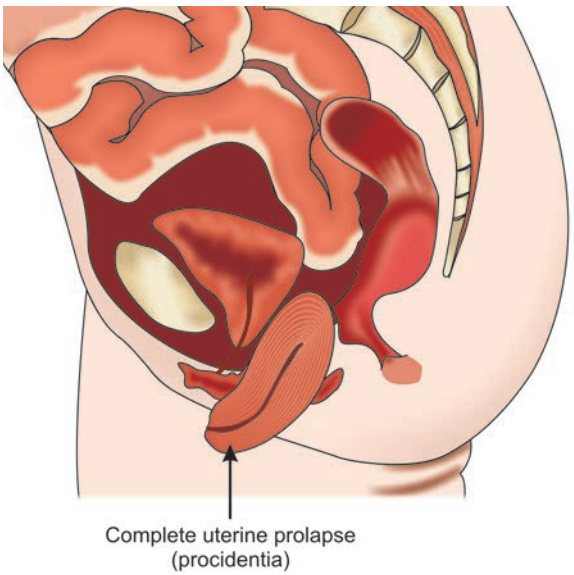


Fig. 22.2D: Uterine prolapse

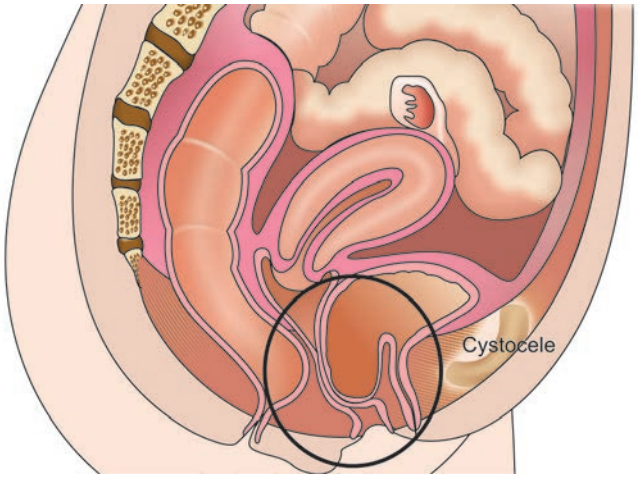


Fig. 22.2B: Cystocele

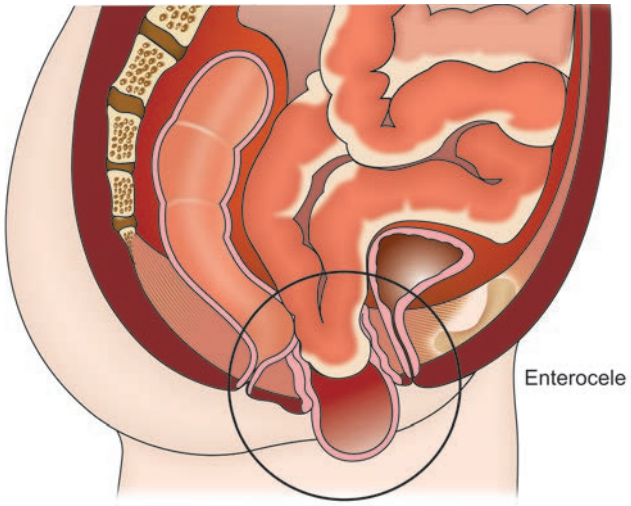


Fig. 22.2E: Enterocele

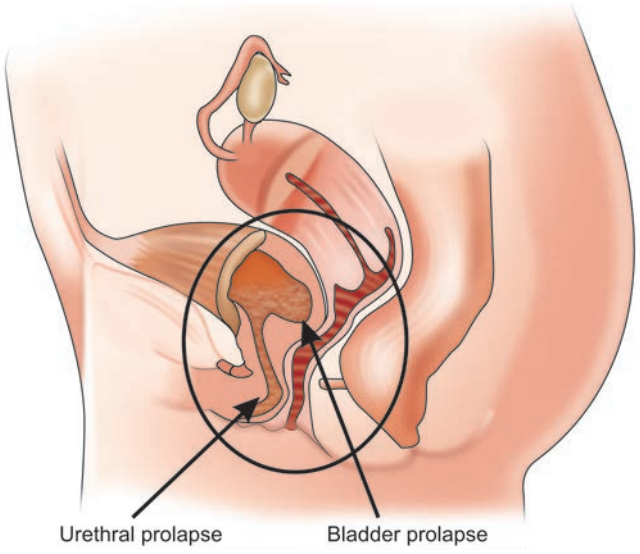


Fig. 22.2C: Urethrocele with moderate cystocele

Supports of the Uterus

A basic knowledge of pelvic anatomy and uterine supports is essential for the gynecologist in order to understand the mechanism of prolapse and the methods of correcting it. Thus the various pelvic supports would be discussed now.

The various support structures of the pelvis are attached to the bony pelvis, which is formed by the pelvic bones (comprising of the pubic bone, ilium, and ischium) anteriorly and on either side and posteriorly by sacrum and coccyx. Various pelvic structures including urinary structures (bladder, urethra), genital structures (vagina, cervix, uterus, fallopian tubes, ovaries), and the rectum are present within this "supporting structure." The failure of the pelvic support system

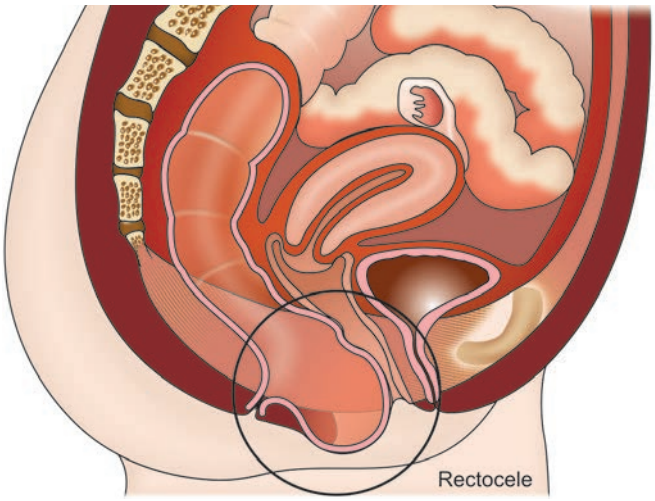


Fig. 22.2F: Rectocele

allows for descent of one or more of the pelvic organs into the potential space of the vagina, and at its most severe degree, outside the vaginal opening.

The vagina can be divided into proximal (deep), middle, and distal (superficial) thirds. Depending upon the anatomical location of different parts of vagina, three levels of support for vaginal tissues can be defined. Level I support suspends the upper vagina and mainly comprises of the cardinal and the uterosacral ligaments. Level II support attaches the mid-vagina along its length to the arcus tendineus fascia of the pelvis. Level III support on the other hand, results from the fusion of the distal vagina to the adjacent structures and mainly comprises of levator ani and perineal muscles. The supports for different parts of vagina have been summarized in table 22.2.

In the supine position, the upper vagina lies almost horizontal and superior to the levator plate. The uterus and vagina have two main support systems. Active support is provided by the levator ani (level III support). On the other hand, passive support is provided by the condensations of the endopelvic fascia (i.e. the uterosacral-cardinal ligament complex, the pubocervical fascia, and the rectovaginal septum) and their attachments to the pelvis and pelvic sidewalls through the arcus tendineus fascia pelvis (level I and level II support). The contraction of the levator plate creates a flap-valve effect in which the upper vagina is compressed against it during the periods of increased intraabdominal pressure. When the tone of levator ani muscles decreases, the vagina drops from a horizontal to a semi-vertical position. This causes the widening of the genital hiatus thereby predisposing the prolapse of pelvic viscera.

Table 22.2: Different levels of support for vaginal tissue

Different levels of support of vagina	*Support elements*
Level I (for proximal 1/3rd of vagina)	Cardinal and the uterosacral ligaments
Level II (for middle 1/3rd of vagina)	Paravaginal fascia
Level III (for distal 1/3rd of vagina and the introitus)	Levator ani and perineal muscles

Level I Support

Level I support comprises of the attachments of the cardinal (transverse cervical ligaments) and uterosacral ligament to the cervix and upper vagina (figure 22.3). Cardinal ligaments fan out laterally and attach to the anterior border of the greater sciatic foramen and ischial spines and the parietal fascia of the obturator internus and piriformis muscles. The cardinal ligaments contain the uterine arteries and provide attachment of uterus to the pelvic side walls. The uterosacral ligaments provide attachment of the cervix to the bony sacrum at the level of S2 to S4. Together, this dense visceral connective tissue complex helps in maintaining vaginal length and horizontal axis. It allows the vagina to be supported by the levator plate and positions the cervix just superior to the level of ischial spines.

Some other important ligament supports which help maintain the relationships between the urethra, bladder, vagina, and uterus within the bony pelvis include the pubourethral ligaments, the urethropelvic ligaments and the vesicopelvic ligaments. The pubourethral ligaments provide support to the middle portion of the urethra by anchoring it to the undersurface of the pubic bone. The urethropelvic ligaments are composed of the levator fascia. This ligament provides support to the urethra by helping in its attachment to the tendinous arc. On the other hand, the vesicopelvic ligament provides support to the bladder by facilitating its attachment to the tendinous arc.

Level II Support

This consists of paravaginal attachments that are contiguous with the cardinal/uterosacral ligament complex at the ischial spine. These comprise of the connective tissue attachments of the lateral vagina anteriorly to the arcus tendinous fascia of the pelvis and posteriorly to the arcus tendinous rectovaginalis. Detachment of this connective tissue from arcus tendinous leads to lateral or paravaginal anterior vaginal wall prolapse.

Level III Support

The perineal body along with superficial and deep perineal muscles of the pelvic floor comprises the level III support

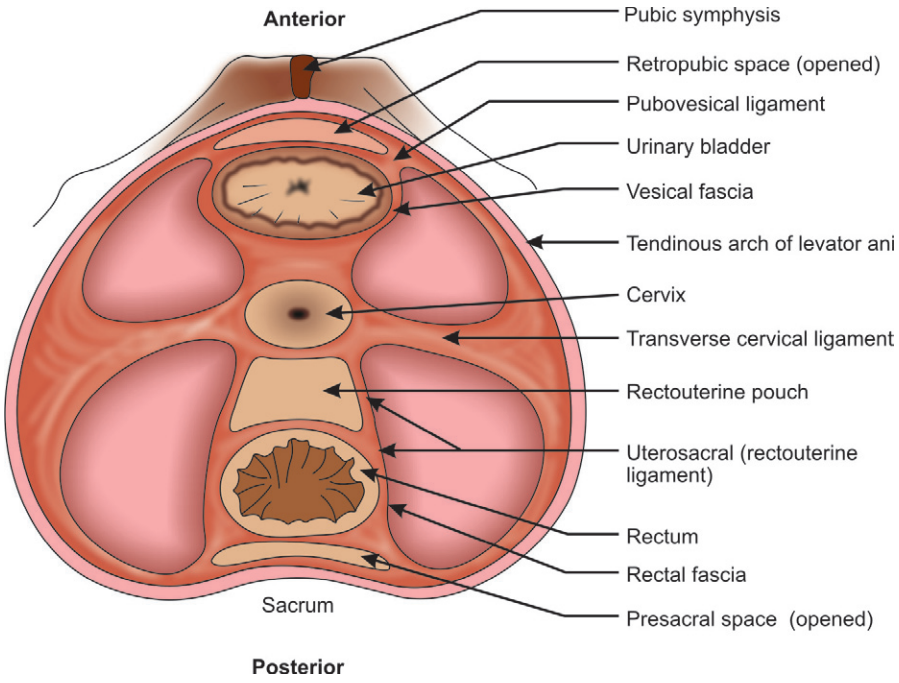


Fig. 22.3: Different ligamentous supports of the uterus

structures. Together, these structures support the distal 1/3rd of the vagina and the introitus. The perineal body is not only essential for providing support to the distal vagina, it is also required for the proper functioning of the anal canal. Damage to level III support structures results in anterior/posterior vaginal wall prolapse, gaping introitus and perineal descent.

22

Muscles of the Pelvic Floor (Figures 22.4A and B)

These can be grouped into three layers:

- Muscles of the pelvic diaphragm (levator ani muscle).
- Muscles of the urogenital diaphragm (deep transverse perineal muscle).
- Superficial muscles of the pelvic floor (superficial transverse perineal muscle, external anal sphincter and bulbospongiosus).

Levator Ani Muscle

The levator ani muscle constitute the pelvic diaphragm and supports the pelvic viscera. The levator ani muscle creates a hammock-like structure by extending from the left tendinous arc to the right tendinous arc. The muscle has openings through which the vagina, rectum and urethra traverse. Contraction of the levator muscles tends to pull the rectum and vagina inwards towards the pubic symphysis. This causes narrowing and kinking of both vagina and rectum. The origin of levator ani muscles is fixed on the anterior end because the muscle arises anteriorly either from the bone or from the fascia which is attached to the bone. As a result, the anterior

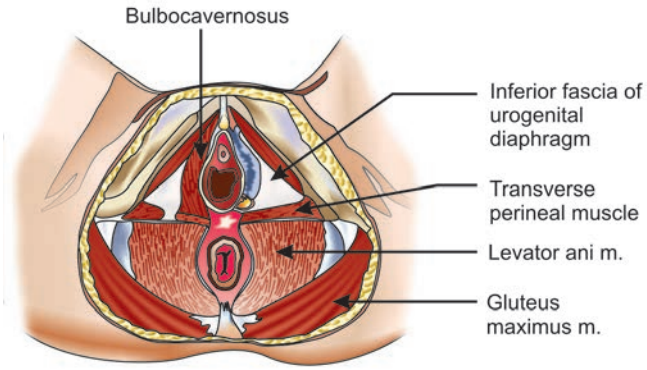


Fig. 22.4A: The female perineum

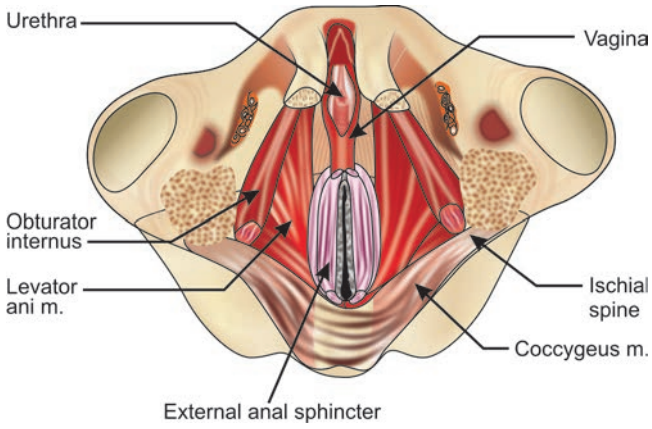


Fig. 22.4B: Muscles of the pelvic floor

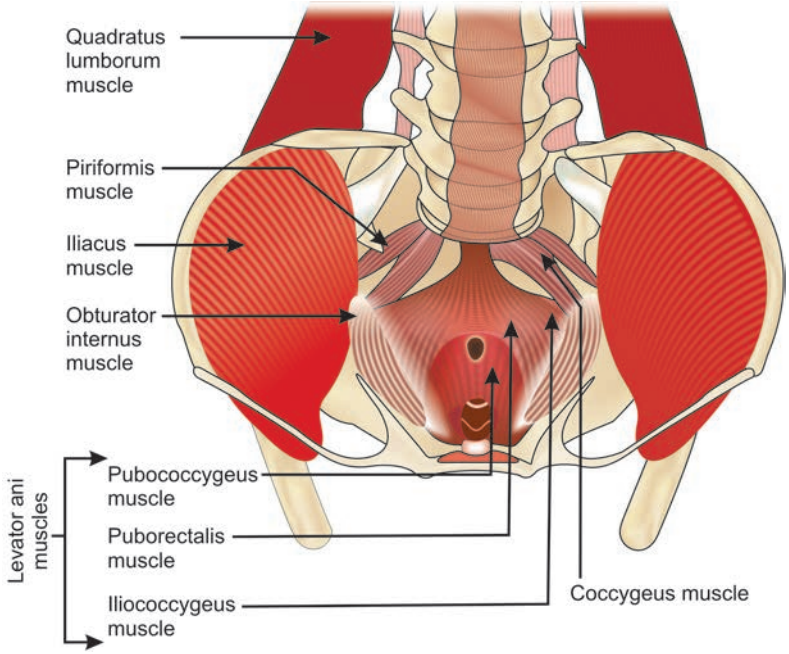


Fig. 22.5: Levator ani muscle

attachment of the muscle largely remains immobile. On the other hand, the levator ani muscles posteriorly get inserted into the anococcygeal raphe or into the coccyx, both of which are movable. Thus the contraction of levator ani muscles tends to pull the posterior attachment towards the pubic symphysis.

The pelvic diaphragm consists of two levator ani muscles, one on each side. Each L. ani muscle consists of three main divisions: Pubococcygeus, iliococcygeus and ischiococcygeus (figure 22.5). The pubococcygeus muscle originates from the posterior surface of the pubic bone. It passes backwards and lateral to the vagina and rectum to be inserted into the anococcygeal raphe and the coccyx. The inner fibers of this muscle which come to lie posterior to the rectum are known as the puborectalis portion of the muscle. These form a sling around the rectum and support it (figure 22.6). Some of the inner fibers of puborectalis fuse with the outer vaginal wall as they pass lateral to it. Other fibers decussate between the vagina and rectum in the region of perineal body. The decussating fibers divide the space between the two levator ani muscles into an anterior portion (hiatus urogenitalis), through which pass the urethra and vagina and a posterior portion (hiatus rectalis), through which passes the rectum. The iliococcygeus is fan-shaped muscle, which arises from a broad origin along white line of pelvic fascia. It passes backwards and inwards to be inserted into the coccyx. The ischiococcygeus muscle takes its origin from the ischial spine and spreads out posteriorly to be inserted into the front of coccyx.

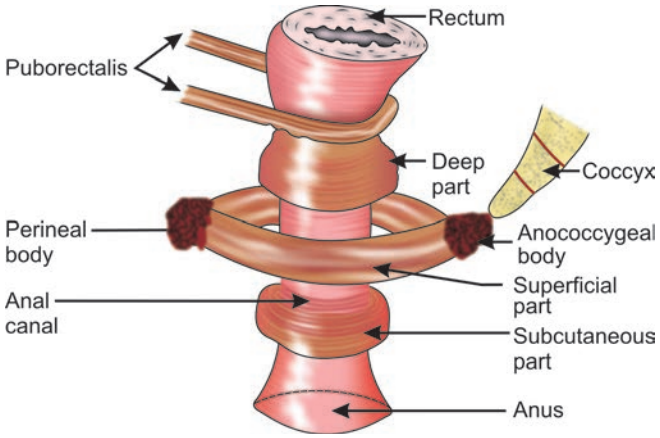


Fig. 22.6: Sling formed by levator ani muscles

The superior and inferior surfaces of the levator muscles are covered with tough fibrous tissue known as pelvic fascia, which separates the muscles from the cellular tissues of the parametrium above and from the fibrous and fatty tissues of ischiorectal fossa below. This fascia is composed of two components: Pelvic component (also known as the endopelvic fascia) and the vaginal component (also known as periurethral fascia at the level of the urethra, and the perivesical fascia at the level of the bladder). The "pelvic component" fuses with the "vaginal component" to get inserted into the tendinous arc. Within the two components of the levator fascia are present the various pelvic organs, such as the urethra, bladder, vagina and uterus to which it provides support.

The central tendinous point of the perineum or the perineal body

The perineal body is a pyramid-shaped fibromuscular structure lying at the midpoint between the vagina and the anus. It lies at the level of the junction between the middle-third and lower-one third of the posterior vaginal wall. Perineal body assumes importance in providing support to the pelvic organs as it provides attachment to the following eight muscles of the pelvic floor: Superficial and deep transverse perineal muscles, and the levator ani muscles of both the sides, bulbocavernosus anteriorly, and the external anal sphincter posteriorly.

The deep transverse perineal muscle

The deep transverse perineal muscles run transversely across the pelvic floor and lie within the urogenital diaphragm. They thus lie deep to the superficial transverse perineal muscles and are continuous with the sphincter urethrae muscle anteriorly. They originate from the medial surface of the ischiopubic ramus and get inserted into the midline raphe and the perineal body.

The superficial transverse perineal muscle

These muscles arise from the upper and innermost part of the ischial tuberosity and run transversely across the pelvic floor, while lying superficial to the deep transverse perineal muscles. Running medially, they get inserted into the perineal body.

Perineal tears occurring at the time of delivery and parturition tend to either divide the decussating fibers of levator ani or cause damage to the perineal body. Both these factors can cause the hiatus urogenitalis to become patulous and result in the development of prolapse. Conditions which result in reduced tone of levator muscles tend to increase the dimensions of hiatus urogenitalis, thereby increasing the tendency of pelvic organs to prolapse.

History

RISK FACTORS

The risk factors associated with the development of uterine prolapse, which need to be elicited at the time of taking history, are described below:

- Obstetrical trauma associated with multiple vaginal deliveries in the past is especially associated with development of prolapse in future. The factors during childbirth which are particularly likely to result in stretching and subsequent weakening of the pelvic support structures, such as the endopelvic fascia, levator muscles and perineal body are described in the section of obstetric history which follows later.
- While uterine prolapse is usually more common in multiparous women compared to the nulliparous ones, prolapse may also be sometimes seen in unmarried or nulliparous women. In nulliparous women prolapse can mainly be attributed to spina occulta and split pelvis, which may result in inherent weakness of the pelvic floor support.
- Decreased estrogen levels (e.g., menopause) resulting in loss of strength and elasticity of pelvic structures. As a result, prolapse is more common in post-menopausal women.
- Increased intra-abdominal pressure (e.g., obesity, chronic lung disease, asthma).
- History of smoking is particularly important. Not only does smoking act as a risk factor for the surgery, habitual smoking can have both direct and indirect effect in causing weakness of the pelvic connective tissues. Also, smoking is antiestrogenic in nature.

Medical History

- History of many medical conditions (e.g., obesity, chronic pulmonary disease, smoking, constipation, chronic lung disease, asthma), which may result in prolapse by causing an increase in intra-abdominal pressure needs to be asked.
- Abnormalities in connective tissue (collagen), such as Marfan disease, and Ehlers Danlos syndrome are associated with an increased risk of uterine prolapse.
- In neonates, uterine prolapse is secondary to congenital weakness in the pelvic musculature or to defects in innervation.

Obstetric History

Previous obstetric history is particularly important in cases of pelvic prolapse because it may reveal the exact pathology responsible for development of prolapse. Some of the points in the history which need to be asked are as follows:

- Route of delivery: Vaginal delivery or delivery by cesarean route.
- In case of vaginal delivery, the clinician needs to ask whether delivery was taken by dai (untrained midwife), trained midwife or a doctor? The clinician must also be asked about number of previous pregnancies and interval between successive deliveries. Interval between successive pregnancies is especially important because rapid succession of the pregnancies prevents proper puerperal rehabilitation, thereby resulting in a tendency to develop prolapse.

  In India and many other developing countries, a large number of deliveries are taken by untrained dais. These dais tend to adopt certain techniques which may serve as a risk factor for development of prolapse. Some of these techniques are as follows:

  - Asking the patient to bear down before full dilation of the cervix
  - The bladder is not emptied before taking the delivery.
  - The untrained dai usually does not give an episiotomy, which is a surgical incision and prevents perineal muscles from stretching and atonicity. As a result, the second stage of the labor may be prolonged resulting in undue stretching of the pelvic floor muscles.
  - The untrained dai does not make use of forceps or vacuum in the case of prolonged second stage of labor. Furthermore, ventouse extraction of the fetus before the cervix is fully dilated can result in overstretching of both the Mackenrodts ligaments and the uterosacral ligaments and thereby cause prolapse in the long run.
  - The untrained dai usually use Credes method of placental extraction, which involves giving vigorous downwards push on the uterus to expel the placenta. This method may weaken the ligaments and muscles, which support the genital tract.
  - The untrained dai may not stitch the lacerations or tears of the perineum, which occur during the child birth. Unless sutured immediately, these tears and lacerations may cause the widening of the hiatus urogenitalis.
  - Application of fundal pressure by the dai may also be responsible for prolapse.
- Whether delivery took place at home or hospital? Home delivery may force the women to resume the household activities soon after delivery without taking proper rest or doing pelvic floor exercises. This may further predispose the woman to develop prolapse in the long run.
- Whether squatting position was used during delivery? Squatting during delivery may cause excessive stretching of the pelvic floor muscles and ligaments.
- Did the women use the birthing ball to facilitate the process of normal vaginal delivery? Birthing ball, unlike the squatting position facilitates fetal descent by causing gentle stretching of the muscles of pelvic floor.
- The woman must be asked about the weight at birth of each baby she has delivered. Delivery of a large sized baby is likely to stretch the perineal muscles, resulting in patulous introitus and thereby prolapse.

Besides taking the history of various risk factors related to prolapse, the gynecologist also needs to take history of different symptoms related to prolapse, as described below.

SYMPTOMS OF PROLAPSE

Symptoms of prolapse are typically exacerbated by prolonged standing or walking and are relieved by lying down. As a result, the patients may feel better in the morning, with symptoms worsening throughout the day. Some of these symptoms include:

- Pelvic heaviness or pressure
- Protrusion of tissue: The patient often reports of experiencing a "bulge" passing through the vaginal introitus due to which the patient may experience difficulty while walking and urinating. The patient may complain of experiencing an annoying protrusion at the vaginal introitus. The patient may complain about a "bearing down sensation" or the feeling that "every thing is falling".
- Pelvic pain
- Sexual dysfunction, including dyspareunia, decreased libido and difficulty achieving orgasm.
- Lower back pain: There may be feeling of discomfort and aching in the lower back.
- Constipation: Rectocele is usually not a cause of constipation, but may be aggravated by it.
- Difficulty in walking.
- Urinary symptoms including increased urinary frequency, urgency and urinary incontinence may be present. Cystocele may be associated with voiding difficulties such as imperfect control of micturition and stress incontinence. If present, these symptoms should be investigated because advanced prolapse may contribute to lower urinary tract dysfunction, including hydronephrosis and obstructive nephropathy.
- Rarely the prolapsed uterus may become ulcerated (decubitus ulcer) resulting in purulent discharge, and bleeding.
- Vaginal spotting from ulceration of the protruding cervix or vagina, coital difficulty, lower abdominal discomfort and voiding and defecatory difficulties. Typically, the patient feels a bulge in the lower vagina or the cervix protruding through the vaginal introitus.

Assessment of quality of life is also helpful in determining appropriate treatment. A detailed sexual history is crucial and focused questions or questionnaires should include quality-of-life measures.

General Physical Examination

General physical examination helps in diagnosing serious complications related to uterine prolapse, including infection, urinary obstruction, hemorrhage, strangulation with uterine ischemia, urinary outflow obstruction with renal failure, etc.

- If urinary obstruction is present, the patient may exhibit suprapubic tenderness or a tympanitic bladder.
- If infection is present, purulent or blood stained cervical discharge may be noted.

Specific Systemic Examination

Diagnosis of uterine prolapse is made by performing complete pelvic examination. This must include a rectovaginal examination in order to assess the sphincter tone. The detailed description of pelvic examination has been given in chapter 16.

PER SPECULUM EXAMINATION

- The vaginal tissue must be evaluated for estrogen status on the per speculum examination. Some of the signs of reduced estrogen status include the following:
  - Loss of rugosity of the vaginal wall mucosa
  - Reduced vaginal and cervical secretions
  - Thinning and tearing of the perineal skin.
- Examination of the pelvic organ prolapse begins by asking the woman to attempt the valsalva prior to placing a speculum in the vagina. Patients who are unable to adequately complete a Valsalva maneuver are asked to cough.
- To perform the evaluation of prolapse, a standard Sim's speculum and an anterior vaginal wall retractor are used. The Sim's speculum is placed in the vaginal vault to visually examine the vagina and cervix. The speculum is then replaced into the posterior vaginal wall, allowing visualization of the anterior wall. The speculum is then everted in order to visualize the posterior wall. The point of maximal descent of the anterior, lateral and apical vaginal walls is noted in relation to the ischial spines and hymen. The level to which the cervix descends on staining can be described as "descends to two inches below the introitus" etc. The term "procidentia" should be reserved for the patients who have a total uterine prolapse with eversion of the entire vagina.
- The vaginal and cervical mucosa should be carefully examined for atrophy, hypertrophy and other lesions. Vaginal cytology and biopsy may be required, if any lesions are present.

PELVIC EXAMINATION

- Firstly, the vaginal examination is carried out the lithotomy position. The tone of pubococcygeus muscles on each side of the lower vaginal wall must be estimated. For this, two fingers are placed inside the vaginal introitus in such a way that each finger opposes the ipsilateral vaginal wall. The patient is then asked to contract these muscles as if she was attempting to stop the flow of urine during the act of voiding. Any protrusion felt on the vaginal fingers is noted. Following the evaluation of the lateral vaginal support system, the apex (cervix and apical vagina) is assessed. The examination is then repeated with the patient standing and in bearing down position in order to note the maximum descent of the prolapse. The prolapse can be exaggerated by having the patient strain during the examination or by having her stand or walk prior to examination. The patient is asked to strain as if she was attempting to defecate or she may also be asked to cough.
- Next, the strength and quality of pelvic floor contraction is assessed by asking the patient to tighten the levator muscles around the examining finger. The diameter of the vaginal introitus and length of perineal body must also be assessed.
- A bimanual examination must be performed in order to note the uterine size, mobility and adnexa. Bimanual examination also helps in ensuring that the pelvic organs are free and not restricted by adhesions or any pathology.

Lastly, a rectal examination is performed in order to assess the tone of external sphincter muscles, to note the presence of any palpable pathology, presence of blood on the examining finger, the presence of the rectocele, for differentiating between rectocele and enterocele, strength of the perineal body and for assessing the rectovaginal septum. The rectovaginal septum may feel to be unusually thin inbetween the examining fingers. The examiner needs to differentiate between rectocele and an entrocele. For this, the index finger of the clinician's left hand is placed in the rectum with the tip directed upwards. Two fingers of the right hand are then placed in the vagina. The patient is asked to strain downwards. If a bulge is felt between the examining fingers in the space between the rectum and upper posterior vaginal wall, it is most likely to be an enterocele. On the other hand, if the bugle is felt on the tip of the index finger in the rectum, the bulge is most likely to be a rectocele. The thickness of the perineum can be assessed by feeling the distance between the anal orifice and posterior fourchette, with the finger in the rectum and the thumb pressing against the perineum. Observation of the small bowel peristalsis behind the vaginal wall is definitively indicative of enterocele. In general, the bulges at the apical segment of the posterior vaginal wall implicate enterocele, whereas the bulges in the posterior wall are most likely to be rectocele. Assessment of both the resting and the contraction tone of pelvic floor muscles must also be done.

Speculum examination helps in answering three questions:

Whether the level of protrusion comes beyond the hymen; the presenting part of the prolapse (anterior, posterior or apical) and does the widening of the vaginal hiatus occur with increased intra-abdominal pressure? Answers to these

questions help the gynecologists to classify prolapse on the basis of POP-Q system.

- In patients with significant degree of uterine prolapse, it is imperative to exclude the potential urinary incontinence. By definition, potential urinary incontinence must be present only when the prolapse is reduced. To test for potential urinary incontinence, the bladder is retrograde filled to maximum capacity (at least 300 mL) with sterile water or saline while replacing and elevating the prolapsed part digitally or with an appropriately fitted pessary. The patient is then asked to cough. If the patient leaks urine, the urinary incontinence is suspected and the patient must be evaluated by performing a complete urodynamic test.
- In order to check the integrity of the sacral pathways, the bulbocavernous reflex and anal reflex are also evaluated. Presence of both these reflexes suggest normal sacral pathways. The bulbocavernous reflex is elicited by tapping or stroking lateral to the clitoris and observing the contractions of bulbocavernous bilaterally. Innervation of the external anal sphincter is evaluated by stroking lateral to the anus and observing the relative contraction of the anus.

Evaluation of the Degree of Prolapse

Baden-Walker Halfway system as described in table 22.1 previously is the system which is commonly used for evaluation of pelvic organ prolapse. Another important system which is often used for evaluation of pelvic organ prolapse is the POP-Q system for quantification of pelvic prolapse and is described below:

POP-Q system for quantification of pelvic prolapse

In 1966, the international continence society defined a system for quantification of pelvic organ prolapse (POP-Q system). This system is based on a series of site-specific measurements of the woman's pelvic organ support system in relation to the hymen in each of the segments. This system is based on the measurement of six points, which are located with the reference to the plane of the hymen: Two on the anterior vaginal wall (Aa & Ba), two in the apical vagina (C & D) and two on the posterior vaginal wall (Ap & Bp). All these six points are measured with the patient engaged in maximum protrusion and have been illustrated in figure 22.7.

Anterior vaginal wall points

Point Aa: This is the point on the anterior vaginal wall in the midline and lies 3 cm above the external urethral meatus, corresponding to the proximal location of the urethrovesical crease. In relation to the hymen, this point's position ranges

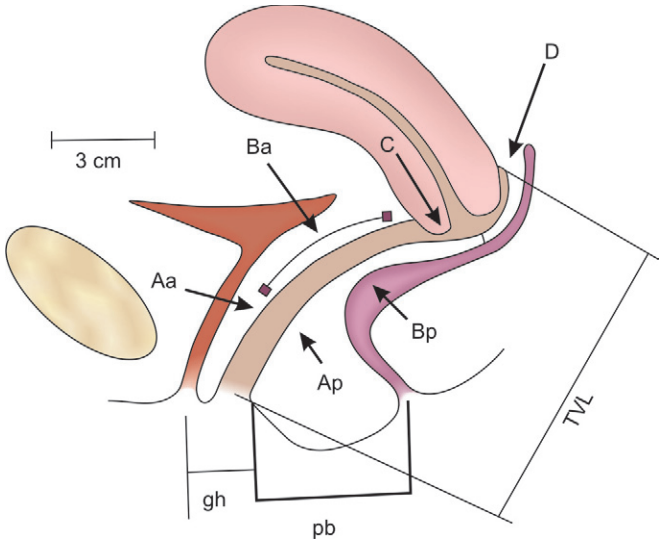


Fig. 22.7: POP-Q system for quantification of pelvic prolapse

Source: Bump RC, Mattiasson A, Bo K, Brubaker LP, DeLancey JO, Klarskov P, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol.* 1996;175(1):10–7.

by definition from –3 (normal support) to +3 cm (maximum prolapse of the point Aa).

Point Ba: This point represents the most distal edge of cervix or vaginal cuff. It is –3 cm in the absence of prolapse. In a woman with total vaginal eversion post-hysterectomy, Ba would have a positive value equal to the position of the cuff from the hymen.

Apical vaginal points

The apical points represent the most proximal locations of a normally positioned lower reproductive tract

Point C: This point either represents the most distal edge of the cervix or the leading edge of the vaginal cuff after total hysterectomy.

Point D: This represents the location of posterior fornix in a woman who still has a cervix. This point is omitted while making measurements, if cervix is absent. This point is located at the level of the attachment of uterosacral ligament to the proximal posterior cervix.

Posterior vaginal wall points

Point Ap: This point is located 3 cm proximal to the hymen on the posterior vaginal wall. Relative to the hymen, the position of this point may range from –3 (normal support) to +3 (maximum prolapse of the point Ap).

Point Bp: This point represents the most distal position of the upper portion of the posterior vaginal wall from the vaginal cuff. By definition, this point is at –3 cm in the absence of

prolapse. In a woman with total vaginal eversion post-hysterectomy, Bp would have a positive value equal to the position of the cuff from the hymen.

Total vaginal length, genital hiatus and perineal body

Total vaginal length (TVL) is the greatest depth of vagina (in cms) when points C&D are reduced to their fullest position.

In addition to the TVL, remaining measurements include those of the genital hiatus (gh) and the perineal body (pb). The genital hiatus is measured from the middle of the external urethral meatus to the mid-line of the posterior hymenal ring. The perineal body is measured from the posterior margin of the genital hiatus to the mid-anal opening.

Assessment of prolapse using the POP-Q system

While assessing the degree of prolapse using the POP-Q system, the hymenal plane is defined as zero (table 22.3). The anatomical position of these points from the hymen is measured in cm. Points above the hymen are described with a negative number, whereas the points below the hymen are described using a positive number. It is important to remember that these various measurements can change in accordance with the position of the patient, e.g. whether the patient was standing or in lithotomy position or whether she was asked to strain. Thus, it is important to mention the patient's position at the time of taking measurements.

If the POP-Q examination is performed, firstly the genital hiatus and the perineal body are measured during the Valsalva maneuver. The TVL is the only measurement made while the patient is not engaged in Valsalva maneuver. It is measured by placing the marked ring forceps at the vaginal apex and noting the distance to the hymen. The apical points C & D are then measured during maximal Valsalva effort. The anterior and posterior vaginal walls are next visualized and lastly the points Aa, Ba, Ap and Bp are respectively measured. The urethra is also evaluated during anterior vaginal wall assessment. If the posterior vaginal wall descends, attempts must be made to determine whether rectocele or enterocele is present.

POP-Q Staging System

The POP-Q staging system is shown in table 22.3.

Table 22.3: POP-Q staging system for pelvic organ prolapse

Stage of prolapse	*Definition*
Stage 0	No prolapse is demonstrated. Points Aa, Ap, Ba and Bp are all 3 cm above the hymenal ring (value = –3 and either points C or D are at a position above the hymen that is equal to or within 2 cm of TVL. Thus the quantitation value for point C or D is ≤ – [TVL – 2 cm]
Stage I	The criteria for stage 0 are not met, but all the points are >1 cm above the level of the hymen (i.e. its quantitation value is ≤ –1cm)
Stage II	The most distal portion of the prolapse protrudes to a point to or above 1cm above the hymen but no more than 1cm beyond the hymen (i.e. its quantitation value ≥ 1 cm but ≤ + 1 cm)
Stage III	The most distal portion of the prolapse protrudes at least one cm below the plane of hymen but protrudes no further than 2 cm less than the TVL (in cm), i.e. its quantitation value is > + 1 cm but < + [TVL – 2 cm]
Stage IV	Complete eversion of the total length of the lower genital tract is demonstrated. The distal portion of the prolapse protrudes to within 2 cm of the total vaginal length, i.e. its quantitation value is ≥ + [TVL– 2] cm.

Differential Diagnosis

Various symptoms related to prolapse could be contributed by several other disorders unrelated to uterine prolapse. For example, disorders such as rectal prolapse, presence of vulvar or vaginal cysts/masses, pelvic masses (both adnexal and uterine) or hernia (vaginal or femoral) could produce a sensation of something bulging or protruding through the vaginal introitus. Urinary symptoms such as urinary urgency, frequency or incontinence could be related to the disorders such as incompetence of the urethral sphincters, detrusor overactivity, bladder outlet obstruction, interstitial cystitis or urinary tract infection. Bowel symptoms such as incontinence of flatus/liquid/solid stools, feeling of incomplete emptying or difficulty in defecation, urgency to defecate, etc could be related to disorders such as the disruption of anal sphincters or neuropathy, diarrheal disorders, rectal prolapse, inflammatory bowel syndrome, rectal inertia, pelvic floor dyssynergia, hemorrhoids, anorectal neoplasm etc. Moreover, sexual symptoms such as dyspareunia, decreased lubrication, reduced sexual sensation and reduced arousal or orgasm could be related to disorders such as interstitial cystitis, levator ani syndrome, vulvodynia, etc. Back pain can also result due to lumbar disk herniation or musculoskeletal diseases.

Though the diagnosis of prolapse can be easily established on per speculum and pelvic examination and it is unlikely to confuse prolapse with any other pathology, congenital elongation of the cervix needs to be ruled out. In cases of congenital elongation of the cervix the vaginal portion of the cervix is elongated and there is no accompanying vaginal prolapse. As a result, the vaginal fornices are unusually deep. Many a times, decubitus ulceration over the prolapse may resemble an ulcerated cervical fibroid or polyp. A cervical fibroid or polyp can be easily differentiated from cases of

uterine prolapse as in case of cervical fibroids, the cervix is high up and is in a normal anatomical position.

Management

Diagnosis of uterine prolapse is made on pelvic examination. Investigations are directed towards identification of rare but serious complications related to uterine prolapse (infection, urinary obstruction, hemorrhage, strangulation) and for assessing the patient's suitability for anesthesia.

Investigations

The various laboratory investigations which may be required are as follows:

- Hemoglobin: Estimation of hemoglobin levels give an idea about the patient's anemic status.
- Urine examination: Urine analysis is important because it is essential to rule out urinary tract infection before undertaking surgery.
- Blood urea and creatinine levels: These tests of renal function may be indicated in cases with suspected urinary obstruction.
- Blood sugar
- X-ray chest
- ECG
- Urine culture: Urine culture is specifically indicated in cases of suspected urinary tract infection.
- High vaginal swab: High vaginal swabs are indicated in cases of vaginitis.
- Cervical cultures are indicated for cases complicated by ulceration or purulent discharge.
- A Pap smear cytology may be indicated in cases of suspected carcinoma, although this is a rare occurrence.
- Imaging Studies: A pelvic ultrasound examination may be useful in distinguishing prolapse from other pathologies, especially when other differential diagnoses are suspected on the basis of the history and physical examination. Ultrasound also serves as an important investigation modality for diagnosing hydronephrosis and for excluding presence of pelvic masses such as uterine fibroids, adnexal masses, etc.

Rx Treatment/Gynecological Management

PREVENTION

Several steps can be taken to prevent the development of uterine prolapse. Some of these steps are as follows:

- Steps must be taken to minimize obstetrical trauma during vaginal delivery.
- The second stage of labor must be properly supervised and managed. Earlier it was thought that the routine use of episiotomy in primigravida would help in preventing undue stretching of the pelvic floor muscles and subsequently prolapse in the long run. However, in the light of present evidence, routine use of episiotomy and its role in preventing prolapse have largely been questioned.
- Low forceps delivery should be undertaken in cases of delayed second stage of labor.
- A perineal tear must be immediately and accurately sutured after delivery.
- The patient must be advised to maintain a reasonable time interval between pregnancies using family planning methods so that too many births at too short intervals are avoided. This helps the pelvic muscles to recover their tone in between pregnancies.
- Antenatal physiotherapy, postnatal exercises, early postnatal ambulation and physiotherapy are highly beneficial in preventing prolapse. Adequate rest must be provided to the patient for first six months after delivery and there must be availability of home help for carrying out heavy domestic duties.
- The woman should be advised to maintain a healthy body weight. She should be instructed to exercise regularly for 20 to 30 minutes, three to five times per week. She should be especially advised to Kegel exercises, which may be done up to four times a day.
- Besides doing regular exercises, the woman must be advised to eat a healthy balanced diet containing appropriate amounts of protein, fat, carbohydrates and high amounts of dietary fiber (such as whole grain cereals, legumes and vegetables). A healthy, well-balanced diet can help maintain weight and prevent constipation, which may serve as a predisposing factor for development of prolapse.
- The patient should be advised to stop smoking. This helps in reducing the risk of developing a chronic cough, which is likely to put extra strain on the pelvic muscles.
- Prophylactic hormone replacement therapy (HRT) in menopausal women can avoid or delay the occurrence of prolapse. Use of estrogen replacement therapy, however, has no role in treatment of established cases of uterine prolapse.
- The woman should be instructed to use correct weight lifting techniques in order to avoid undue straining of the pelvic floor muscles.
- Pelvic floor (Kegel) exercises: Although routine use of Kegel exercises can improve the tone of pelvic floor

muscles and stress urinary incontinence, presently there is no high quality evidence in form of prospective, double blinded, randomized trials, which indicates that improvement of pelvic floor muscle tone leads to regression of uterine prolapse. The Kegel floor exercises must be done at least 50–200 times per day, each exercise attempt lasting for about 5–10 seconds.

NONSURGICAL MANAGEMENT

Expectant management including the pelvic floor exercises (Kegel's exercises) and pessaries are the current mainstays of nonsurgical management of patients with uterine prolapse. Nonsurgical management must be primarily used in cases with mild degree of uterovaginal prolapse with no or minimal symptoms. Since severe degree of prolpase may interfere with the functioning of urinary tract, such patients should not be managed expectantly.

Pessary Treatment for Prolapse

Peassaries are a nonsurgical method for supporting the uterine and vaginal structures. A small pessary may help in maintaining normal uterine position. Pessaries are usually used for attaining temporary relief in cases with symptomatic prolapse. Some indications for using pessaries are enumerated in table 22.4. One of the important indications for using pessary is in young women following child birth. Immediate surgical treatment must not be advised in a woman suffering from prolapse immediately following child birth. This is so as the possibility of recurrence of prolapse is high if the surgery is performed within 6 months of delivery. Furthermore, the symptoms of prolapse rapidly improve using conservative measures such as massage and abdominal and perineal exercises. The conservative measures should be advised following delivery for at least 3 to 4 months.

Presence of infection, such as acute pelvic inflammatory disease, recurrent vaginitis, etc, act as contraindication for pessary use. The two most common types of pessaries used include ring pessary and the donut pessary. Other types are the inflatable ball, cube and Gellhorn pessaries (figure 22.8). The Gellhorn pessary is most often used for patients with significant uterine prolapse and a large introital diameter who have not obtained relief with other pessaries. The Smith-Hodge pessary facilitates retrodisplacement of the uterus and should be used for patients with a well-defined pubic notch and adequate vaginal width. However, the use of pessary requires frequent care and monitoring by a gynecologist. Pessaries may cause vaginitis, bleeding, ulceration, urinary incontinence, urinary obstruction with retention, fistula formation and erosion into the bladder or rectum. Most complications result from a retained pessary that had been long forgotten inside the vagina.

Table 22.4: Current indications for use of pessary

A young woman planning a pregnancy in future
During early pregnancy, immediately after delivery and during lactation
Temporary use while clearing infection and decubitus ulcer prior to the actual surgery
Women unfit for surgery
Women who do not desire surgery

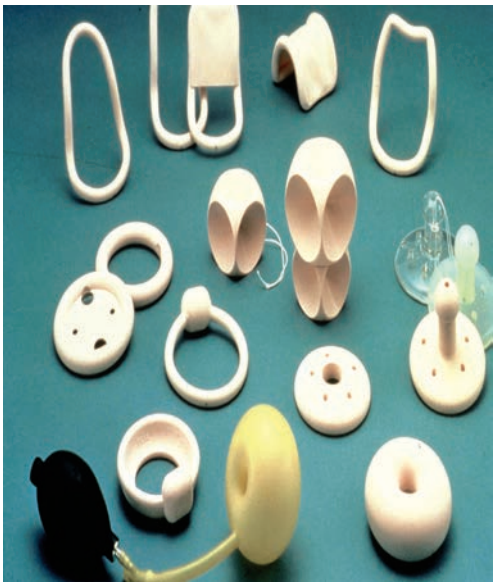


Fig. 22.8: Different types of pessaries used for treatment of uterine prolapse

Expectant Management

Expectant management involves taking steps to improve conditions which are likely to result in prolapse. This involves treatment of the underlying conditions such as chronic cough, obesity, constipation, etc. Administration of HRT in postmenopausal woman helps in improving the tone of the pelvic floor muscles. Postmenopausal women may be administered HRT in form of conjugated equine estrogens in the dosage of 0.625 mg, three-four weeks prior to the surgery. Daily application of estrogen cream may also prove to be useful. Expectant management also involves regular use of pelvic floor exercises or Kegel's exercises. Antibiotic therapy may be indicated for rare cases of prolapse complicated by infection. Steps must also be taken to heal decubitus ulcers prior to surgery. For curing decubitus ulcers, the patient is admitted in the hospital a week prior to the surgery. The prolapsed organs are replaced and packed in position by a tampon or gauze

soaked in acriflavine-glycerine, which is changed everyday. This action helps in healing the ulcer by restoring back the circulation to the prolapsed organs. There is usually no need to impregnate the tampon with antibiotics.

SURGERY: DEFINITIVE TREATMENT

The surgery helps in providing relief against symptoms of prolapse and helps in restoring pelvic anatomy, sexual functioning and human physiologic function (micturition and defecation). Since uterine prolapse is not a life-threatening condition, surgery is indicated only if the patient feels that her condition is severe enough that it warrants correction. Mild prolapse, which is rarely symptomatic, does not require surgical correction. Surgery is usually advised in women over 40 unless it is contraindicated or is hazardous on account of some medical disorders.

Since the surgical treatment for various types of prolapse can be performed together at the time of surgery, it is very important that the physician carefully inspects the vagina for other prolapses. All forms of vaginal relaxation should be treated at the same time as the hysterectomy or uterine suspension. It is possible to have vaginal prolapse surgery without the need for hysterectomy or uterine suspension if there is no prolapsed uterus. The main challenge for the pelvic surgeon is to recreate normal pelvic anatomy while restoring normal physiological functioning as far as possible. Experienced gynecologic surgeons can re-evaluate the anatomy intraoperatively, noting the strength and consistency of the various support structures (e.g., uterosacral ligaments). If these structures are found to be weak, it may be necessary to use other, stronger reattachment sites, such as the sacrospinous ligament or the presacral fascia, for the correction of the defect. In addition, make every attempt to prevent the possibility of recurrence of pelvic organ prolapse. For example, when performing a retropubic urethropexy for urinary incontinence, a concomitant colpocleisis may avoid the formation of an enterocele in the future. Surgical options which can be used in cases of prolapse are enumerated in table 22.5 below. The choice of surgery depends on numerous factors:

- Degree of prolapse
- Areas specific for prolapse
- Desire for future pregnancies
- Desire to maintain future sexual function
- Other medical conditions
- Preservation of vaginal function
- The woman's age and general health
- Patient's choice (i.e., surgery or no surgery)
- Medical condition and age
- Severity of symptoms

Table 22.5: Surgical options which can be used in cases of prolapse

Vaginal hysterectomy, posterior culdoplasty, colporrhaphy.
Vaginal hysterectomy, closure of enterocele sac, total colpectomy, colporrhaphy, colpocleisis.
Combined vaginal colporrhaphy and abdominal hysterectomy.
Moschcowitz culdoplasty, sacral colpopexy and suprapubic urethrocolpopexy.
Manchester operation
Le fort colpocleisis and colporrhaphy
Vaginal repair and uterine suspension

- Patient's suitability for surgery
- Presence of other pelvic conditions requiring simultaneous treatment, including urinary or fecal incontinence
- Presence or absence of urethral hypermobility
- History of previous pelvic surgery.

Although the choice of procedure largely depends on the surgeon's preference and experience, the gynecologist needs to consider numerous factors such as the patient's general health status, degree and type of uterine prolapse, requirement for preservation or restoration of coital function, concomitant intrapelvic disease, and the patient's desire for preservation of menstrual and reproductive function. A careful preoperative evaluation should be carried out in order to identify all concomitant defects associated with uterine prolapse, which should be repaired in order to avoid recurrence of prolapse in future. In patient with advanced degree of prolpase, additional procedures like sacrospinous ligament fixation, sacral colpopexy or colpectomy with colpocleisis may be required to provide adequate support to the vaginal vault.

Preoperative Treatment

Before undertaking the surgical treatment for prolapse, the following steps need to be taken:

- Medical treatment for chronic cough or constipation must be administered.
- If decubitus ulceration is present over the prolapsed tissue, it first needs to be treated by the application of glycerine acriflavine pack or ring pessaries. Both these strategies help by repositioning the uterus to the normal anatomical position, thereby relieving the kinking of uterine blood vessels, cervical congestion and ulceration. The surgery must be undertaken only when the decubitus ulceration has regressed.
- Surgery must be undertaken only when the associated UTI and PID have been aggressively treated.
- Pre-operative estrogen therapy must be given, especially to the elderly postmenopausal patients in whom vaginal epithelium is thin and inflamed.

- Aseptic vaginal douches should be administered a day before surgery.
- Full dose of antibiotics (80 mg of gentamycin, 1 gram of ampicillin, and 500 mg of metronidazole) must be administered two hours before surgery to prevent postoperative pelvic infections.

Principles of Surgery for Pelvic Organ Prolapse

- At the time of clinical examination when the patient is made to bear down, the site of primary damage appears first followed by the sites of secondary damage. The gynecologist must take special note of this site of primary damage. The primary site of damage should be identified first and over-repaired to reduce the chances of recurrence.
- The gynecologist must repair all relaxations even if they are minor in order to prevent recurrence in the future. The strength of the various support structures should be evaluated. Even the relatively weak structures can be used, but they must not be used to provide dependable support at the time of reconstruction surgery.
- As far as possible, the surgeon must try to create a normal anatomy. Normal vaginal length should be maintained because a shortened vagina is likely to prolapse again.
- The vagina should be suspended in its normal posterior direction over the levator plate and rectum, pointing into the hollow of the sacrum, towards S3 & S4. The surgeon should avoid suspending the vaginal vault anteriorly to the abdominal wall.
- The cul-de-sac should be closed and rectocele repaired in all cases. A posterior colpoperineorrhaphy should be preferably performed in all cases where possible. Repair of the lower posterior vaginal wall provides some support to the anterior vaginal wall and also lengthens the vagina.
- When performed in properly selected patients, anterior colporrhaphy serves as an effective procedure for treating stress incontinence which may be commonly associated with anterior cystocele. An anterior cystocele involves defect in the support of the bladder neck, urethrovesical junction and proximal urethra. A posterior cystocele on the other hand occurs above interureteric ridge and involves the proximal (posterior) vaginal wall. A vaginal hysterectomy may not always be indicated in a patient in whom the primary aim is to repair a cystocele. In fact, a vaginal hysterectomy with anterior colporrhaphy may produce a variety of disorders of the bladder function including stress urinary incontinence, detrusor instability and other voiding difficulties.
- Removal of uterus helps in facilitating the repair of an enterocele. The choice of surgery for repair of enterocele and massive eversion of vagina include perineorrhaphy. A hysterectomy with colporrhaphy and colopexy works for the patient with prolapse who wishes to preserve coital interest. Colpocleisis can be considered for patients in whom preservation of the sexual functioning is not important. When the uterosacral ligaments are long and strong, the addition of Mc Call or New Orleans type of culdoplasty will help to re-establish the vaginal length. The Mc Call's culdoplasty involves attaching the uterosacral-cardinal ligament complex to the peritoneal surface. The sutures are attached in such a way, so that when they are tied, the uterosacral-cardinal ligaments are drawn toward the midline. This helps in closing off the cul-de-sac. Additionally, when the sutures are tied, the posterior vaginal apex is drawn up to a higher position, thereby supporting the vaginal vault. The main disadvantage of this type of culdoplasty is a possible increased incidence of kinking or ligating the ureter, because it is so close to the uterosacral ligament.

DESCRIPTION OF VARIOUS SURGICAL PROCEDURES

Different types of available surgical options such as hysterectomy, repair of anterior defects, repair of posterior defects, enterocele repair, Manchester repair and obliterative procedures such as Le Fort colpocleisis would now be described.

Hysterectomy

Surgical removal of uterus or hysterectomy can be done via the vaginal route (vaginal hysterectomy) or through the abdomen (abdominal hysterectomy). Vaginal hysterectomy with pelvic floor repair is suitable for women over the age of 40 years, those who have normal sized uterus and those who have completed their families and are no longer interested in retaining their child bearing and menstrual functions. A Kelly stitch may be necessary to relieve the patient of her stress incontinence, if this is present. Indications for hysterectomy in case of prolapse uterus are listed in table 22.6.

Table 22.6: Indications for hysterectomy in case of prolapse uterus

Removal of a nonfunctioning organ in postmenopausal women
Uterine or cervical pathology (e.g., large fibroid uterus, endometriosis, pelvic inflammatory disease, endometrial hyperplasia, carcinoma)
Bulky uterus
Patient desires removal of the uterus

Anterior Repair

Anterior colporrhaphy

Anterior colporrhaphy operation is one of the most commonly performed surgeries to repair a cystocele and cystourethrocele. This surgery is usually performed under general or regional anesthesia.

Principles of anterior colporrhaphy

Anterior colporrhaphy comprises the following steps: Excision of a portion of relaxed anterior vaginal wall; mobilization of bladder; pushing the bladder upwards after cutting the vesicocervical ligament; and permanently supporting the bladder by tightening the pubocervical fascia.

Steps of surgery

- A speculum is inserted into the vagina to expose it during the procedure. Traction is applied on the cervix using allies forceps in order to expose the anterior vaginal wall.
- An inverted T-shaped incision is made in the anterior vaginal wall, starting with a transverse incision in the bladder sulcus.
- Through the midpoint of this tranverse incision, a vertical incision is given which extends up to the urethral opening.
- The vaginal walls are reflected to either side to expose the bladder and vesicovaginal fascia. Bladder is pushed upwards and the vaginal skin is separated from the underlying fascia.
- The overlying vesicovaginal and pubocervical fascia is plicated with interrupted 0 catgut to correct the vaginal wall laxity and to close the hiatus through which the bladder herniates.
- Redundant portion of the vaginal mucosa is cut on either side.
- Cut margins of vagina are apposed together.
- In women suffering from stress incontinence, a Kelly suture to plicate the bladder neck helps to correct stress incontinence.

Disadvantage

Anterior Colporrhaphy is still today the most commonly performed procedure to treat cystoceles, despite of the several disadvantages. Some of these are as follows:

- Failure rates in the range of 30% to 50%.
- It has poor cure rates.
- Requirement for a repeat procedure.
- The surgery can result in constriction of vagina.
- Constriction and/or shortening of vagina can result in dyspareunia. The surgery is not a true repair, it is just a compensatory procedure, associated with plication of the weakened tissue.
- Tightening of tissue under the bladder neck can result in voiding dysfunction.

The figures 22.9A to D illustrate the sequence of events in the repair of a midline defect cystocele. The patient has a cystocele due to weakness of the pubocervical fascia in the midline.

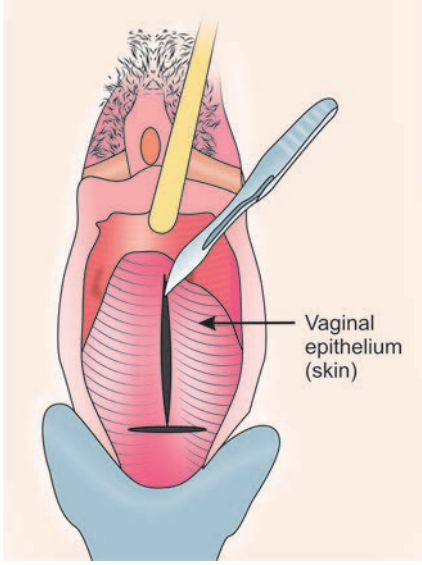


Fig. 22.9A: Skin incision is given over the skin overlying the cystocele

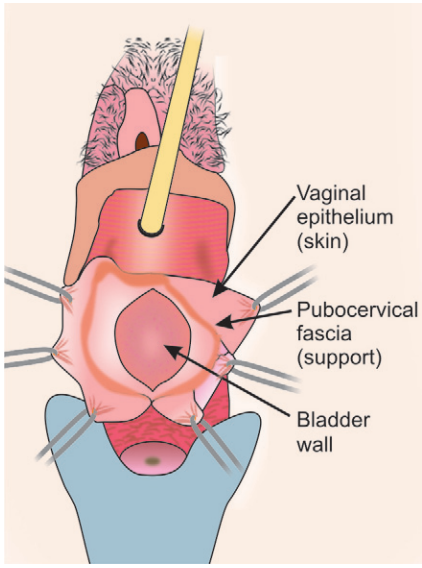


Fig. 22.9B: Dissection of the underlying fascia until the midline defect in pubocervical fascia is visualized

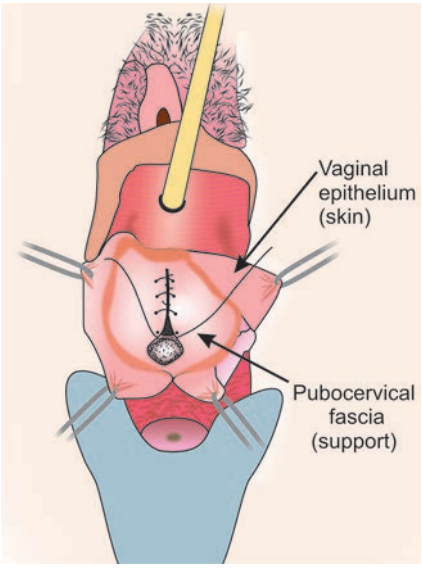


Fig. 22.9C: The tissue under the bladder is plicated and pulled together in the midline, thus reducing the bulge. Following the reduction, excess vaginal skin is then cut off which can create a shortened or constricted vagina

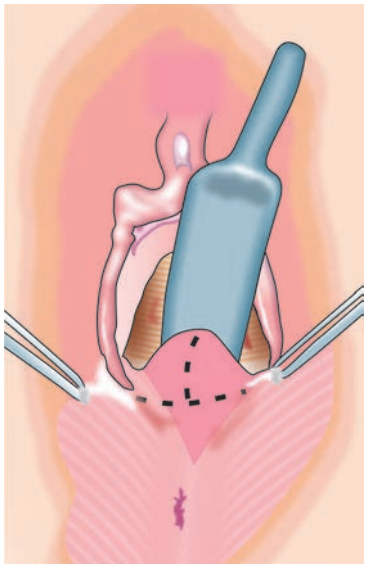


Fig. 22.10A: Rectocele identified and skin incised: A bulge is apparent on the bottom (posterior) floor of the vagina. The dotted line represents the skin incision about to be performed in this posterior repair procedure

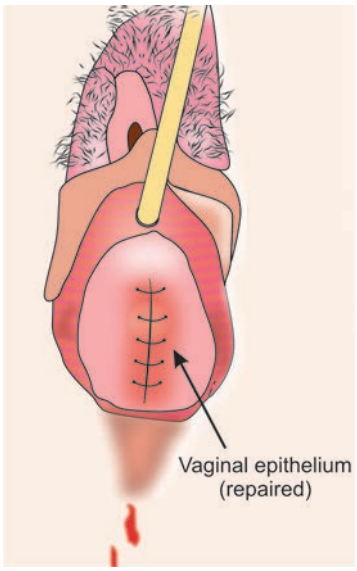


Fig. 22.9D: Closure of the vaginal epithelium

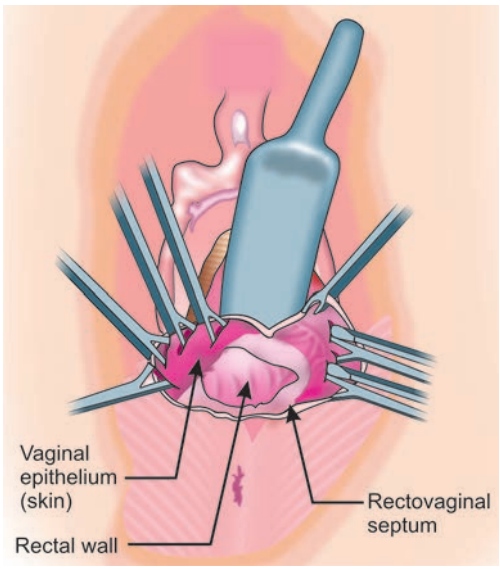


Fig. 22.10B: Identification of the fascia break: The rectocele exists because of a break in the supportive layer known as the rectovaginal fascia. The defect is readily identified and the rectal wall is found protruding through this break in the rectovaginal fascia

Posterior Repair

Posterior colporrhaphy and colpoperineorrhaphy

While repairing the rectocele, most surgeons also perform a posterior colporrhaphy. This process involves nonspecific midline plication of the rectovaginal fascia after reducing the rectocele. The lax vaginal tissue over the rectocele is excised. The medial fibers of the levator ani are then pulled together, approximated and sutured over the top of rectum. This helps in restoring the caliber of the hiatus urogenitalis, and strengthening the perineal body. An adequate amount of perineum is also created which helps in separating the hiatus urogenitalis from the anal canal.

Though this surgery is quite effective in the treatment of the rectocele, these patients often suffer from dyspareunia following surgery. The surgical procedure for rectocele repair is shown in figures 22.10A to F.

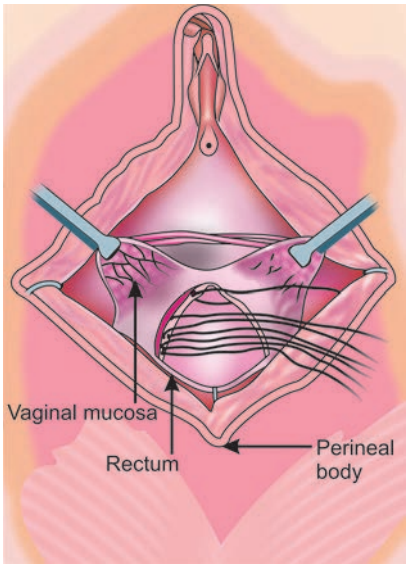


Fig. 22.10C: The rectovaginal fascia is reattached to the perineal body where the distal defect was located

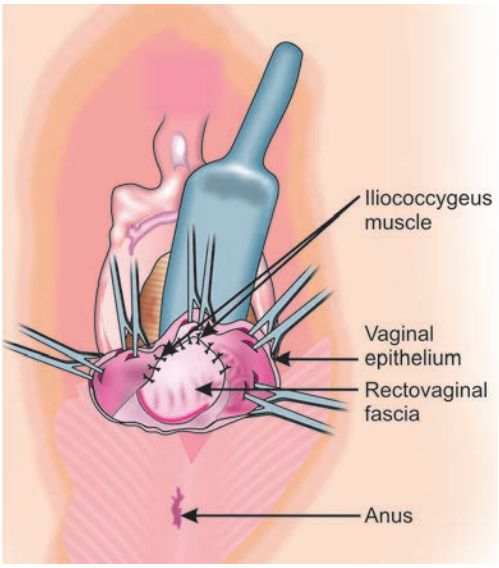


Fig. 22.10E: The rectovaginal fascia is reattached to the iliococcygeal muscles bilaterally with permanent sutures

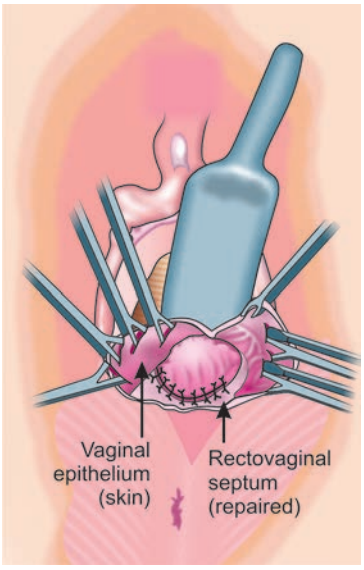


Fig. 22.10D: The rectovaginal fascial defect has been repaired

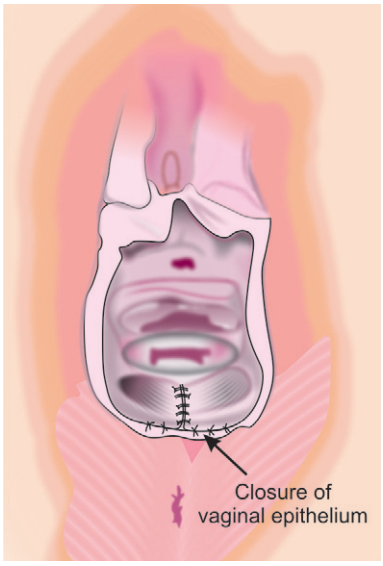


Fig. 22.10F: Closure of the vaginal epithelium (skin) completes the operation

Manchester Repair

Manchester repair is performed in those cases where removal of the uterus is not required.

Indications

Indications of Manchester operation are as described below:

- Child bearing function is not required.
- Malignancy of the endometrium has been ruled out by performing a D&C.
- Absence of urinary tract infection.
- Presence of a small cystocele with only first or second degree prolapse.
- Absence of an enterocele.
- Symptoms of prolapse are largely due to cervical elongation.
- Patient requires preservation of the menstrual function.

Procedure

The procedure for Manchester repair (also called Fothergill operation) is described in figures 22.11A to E and it comprises of the following steps:

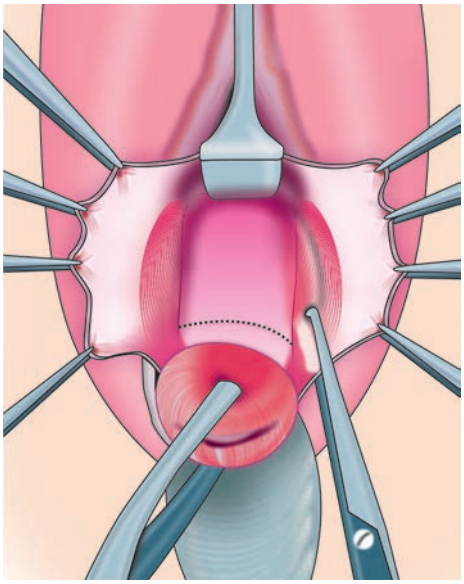


Fig. 22.11A: The bladder is dissected from the cervix. A circular incision is given over the cervix. The base of cardinal ligment is exposed, clamped and cut

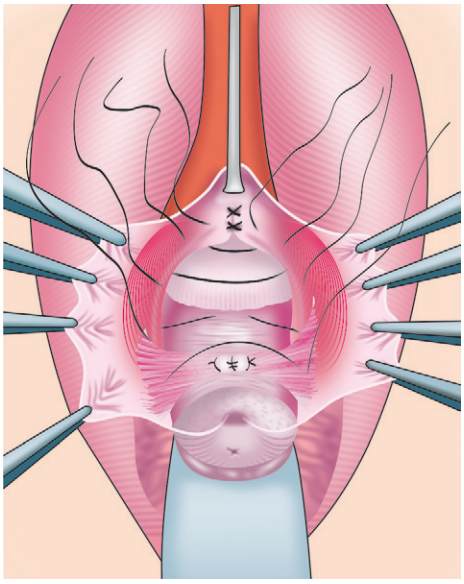


Fig. 22.11C: Approximation of pubovesicocervical fascia in the midline

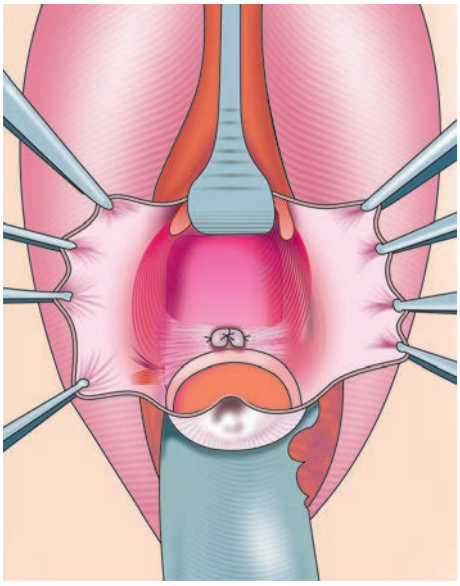


Fig. 22.11B: The cervix is amputed and posterior lip of cervix is covered with a flap of mucosa. The base of cardinal ligament is sutured over the anterior surface of cervix

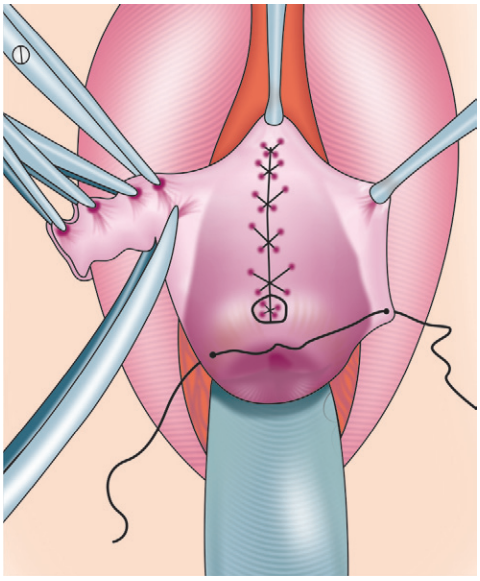


Fig. 22.11D: The fascial approximation has been completed and excessive vaginal mucosa has been excised

- Anterior colporrhaphy is firstly performed.
- The bladder is dissected from the cervix. A circular incision is given over the cervix.
- The attachment of Mackenrodt ligaments to the cervix on each side are exposed, clamped and cut.
- The vaginal incision is then extended posteriorly round the cervix.
- The cervix is amputed and posterior lip of cervix is covered with a flap of mucosa.
- The base of cardinal ligament is sutured over the anterior surface of cervix.
- The raw area of the amputated cervix is then covered.
- Colpoperineorrhaphy is ultimately performed to correct the posterior and perineal defects.

Shirodhkar's Modification of Manchester Repair

In Shirodhkar's modification of Manchester repair, firstly an anterior colporrhaphy is performed. The cardinal ligaments

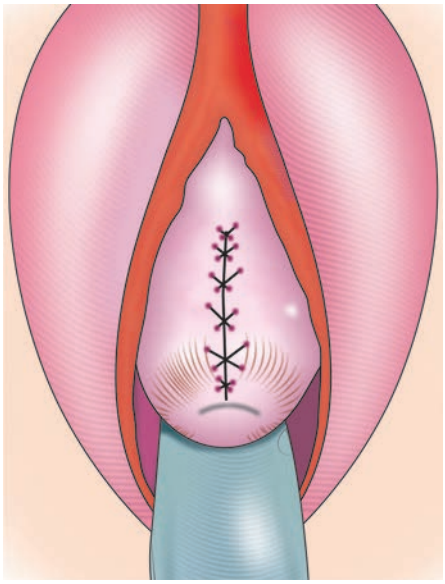


Fig. 22.11E: Vaginal mucosa has been closed

are exposed and the pouch of Douglas is opened. The uterosacral ligaments are identified and divided close to the cervix. The amputated uterosacral ligaments are then crossed and stitched in front of cervix. Since in this procedure, the cervix is not amputated, the complications related to childbirth can be largely avoided. A high closure of the peritoneum of the pouch of Douglas is carried out.

Uterine Suspension

Vault prolapse is a delayed complication of both abdominal and vaginal hysterectomy when the supporting structures, i.e. paravaginal fascia and levator ani muscles become weak and deficient. It may also result from failure to identify and repair an enterocele during hysterectomy. Uterine suspension procedures involve putting the uterus back into its normal position. Various types of uterine suspensions can be performed either via the abdominal or vaginal route. This may be done by reattaching the pelvic ligaments to the lower part of the uterus to hold it in place (e.g. sacrospinous colpopexy). Another technique uses special materials which act like sling in order to support the uterus in its proper position (abdominal sacral colpopexy). Recent advances include performing these procedures laparoscopically, thereby considerably reducing postoperative pain and facilitating speedy recovery.

Abdominal sacral colpopexy

This procedure comprises of suspending the vault to the sacral promontory extraperitoneally using various grafts such as harvested fascia lata, abdominal fascia, dura mater, marlex, prolene, goretex, mersilene, or cadaveric fascia lata. Injury to the ureter, bladder, sigmoid colon and middle sacral artery should be avoided. Bleeding is the most serious complication of sacral colpopexy due to injury to the presacral venous plexus or the middle sacral artery while operating in the presacral space.

The aim of surgery is to restore the normal pelvic anatomy as far as possible. At the end of the surgery, normal vaginal length should be maintained with its axis directed towards S3-S4 vertebra. Abdominal sacral colpopexy has the highest cure rate for vault prolapse, probably because of the use of graft tissue with high strength and not relying on the patient's own tissue which may not be strong enough to hold up the vaginal vault. As a result, sacral colposcopy can also be considered in patients who have had previous failed operations, older patients with poor tissue or patients with large defects or severe prolapse.

Transvaginal sacrospinous ligament fixation

In this method, the vaginal apex is attached, using permanent sutures, to the sacrospinous ligament. The posterior vaginal wall is opened vertically, following which a window space is created between the vagina and the rectum towards the right sacrospinous ligament. Using Deschamps ligature carrier, a synthetic ligature is used for fixing the vaginal vault to the sacrospinous ligament, 3–5 cm away from the ischial spine (figures 22.12A and B). The suture must be placed through the ligament, rather than around it. The two most serious complications from sacrospinous ligament fixation are hemorrhage and nerve injury as a result of damage to the pudendal neurovascular bundle. Thus, the surgeon must try to avoid injuring the pudendal bundle and the inferior gluteal vessels as far as possible.

Obliterative Procedures

For patients who cannot undergo long surgical procedures and who are not contemplating sexual activity, obliterative procedures, such as the Le Fort colpocleisis or colpectomy and colpocleisis, are viable options.

Le Fort Colpocleisis

In the Le Fort colpocleisis, a patch of anterior and posterior vaginal mucosa is removed. The cut edge of the anterior vaginal wall is sewn to its counterpart on the posterior side. As the approximation is continued on each side, the most dependent portion of the mass is progressively inverted. A tight perineorrhaphy is also performed to help support the inverted vagina and prevent recurrence of the prolapse. The main problem specific to these obliterative operations is that they limit coital function. Neither corrects an enterocele because they are both extraperitoneal procedures. Also, there is a 25% incidence of postoperative urinary stress incontinence caused by induced fusion of the anterior and posterior vaginal walls and flattening of the posterior urethrovesical angle. In addition, if

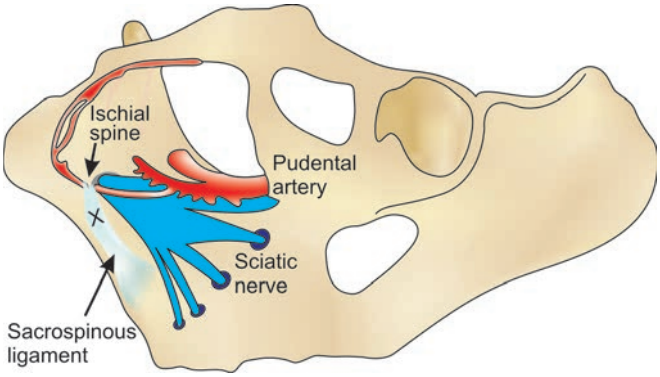


Fig. 22.12A: The sacrospinous ligament must be penetrated 3-5 cm medial to the ischial spine at the point marked by "X"

the uterus is retained, the patient can later bleed from many causes, including carcinoma.

Indications for Le Fort colpocleisis

Colpocleisis is an excellent operation for the treatment of uterine prolapse or complete vaginal vault prolapse for patients that are:

- Not sexually active
- Have no future plans for sexual activity
- Medically fragile
- Elderly patients who do not require preservation of their sexual functioning.

Procedure

The procedure involves excision of rectangular strips of mucosa from the upper portions of anterior and posterior vaginal walls. The exposed submucosal fascia is then closed together. In those frail elderly women who do not wish to be sexually active in the future, colpocleisis acts as a simple, safe and effective surgical procedure that reliably relieves these women of their symptoms without the potential hazards of vaginal suspension. The procedure is called a total colpocleisis for patients who do not have a uterus and have complete vaginal vault prolapse and a Le Fort colpocleisis for those patients who still have a uterus. Total colpocleisis procedure is often coupled with a tension free vaginal tape (TVT) sling procedure for urinary incontinence. The colpocleisis procedure is done through the vagina and essentially closes the vagina on the inside. The patient can no longer engage in sexual intercourse due to the closing up of the vagina. The completed procedure usually leaves the patients with a much shortened vagina. As a result, the patient becomes incapable of engaging in sexual intercourse. Colpocleisis is an extremely effective operation which has the advantages listed in table 22.7. The surgical technique of colpocleisis is shown in figures 22.13A to E. The procedure is associated with disadvantages such as loss of sexual activity and development of

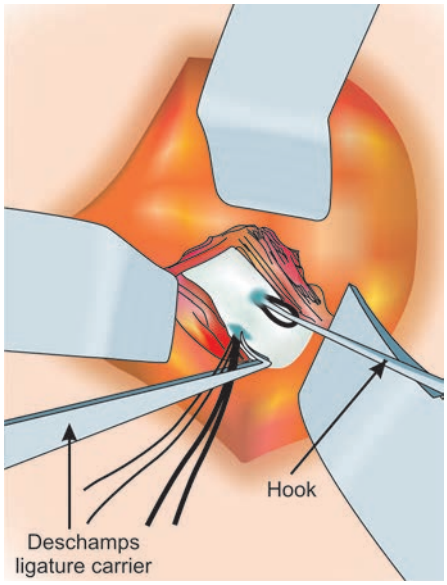


Fig. 22.12B: The sacrospinous ligament has been penetrated by the blunt end of a long Deschamps ligature carrier at a point 3-5 cm medial to the ischial spine, away from the pudental nerve and vessels and sciatic nerve

Table 22.7: Advantages of colpocleisis

Closes the vagina together
Inhibits the patient from future sexual intercourse
90% to 95% cure rate
Can be performed using local anesthesia, epidural, or spinal
No requirement for general anesthesia
A quick procedure which takes only 45 minutes to perform
Minimal pain or complications
Can be coupled with TVT sling (incontinence) operation

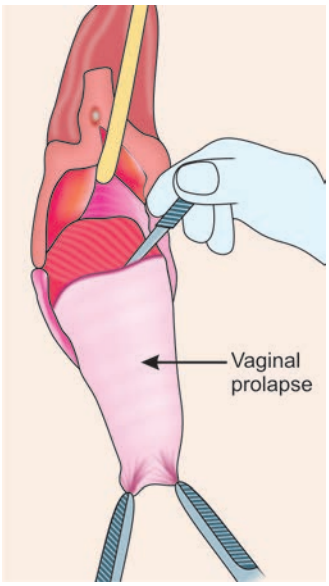


Fig. 22.13A: Incision over the mucosa of anterior vaginal wall

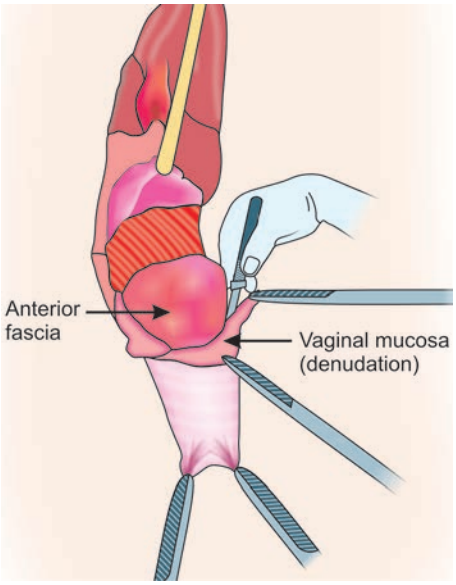


Fig. 22.13B: Incision and removal of skin: Mucosa is removed from the prolapse to expose the anterior fascia (pubocervical fascia) and posterior fascia (rectovaginal fascia)

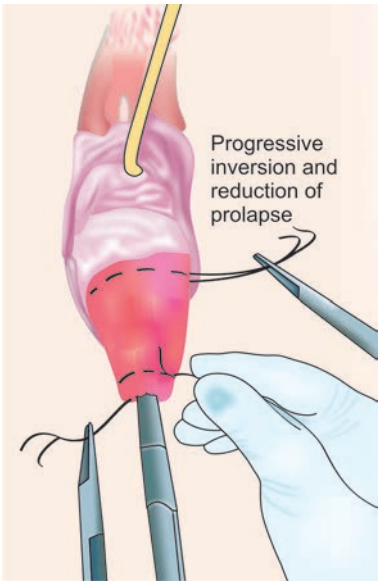


Fig. 22.13D: Reducing the prolapse: The most protruding portion of the vagina is inverted (pushed in upon itself) and the last suture placed is tied. The suture holds the rest of the vagina from coming back out or prolapsing

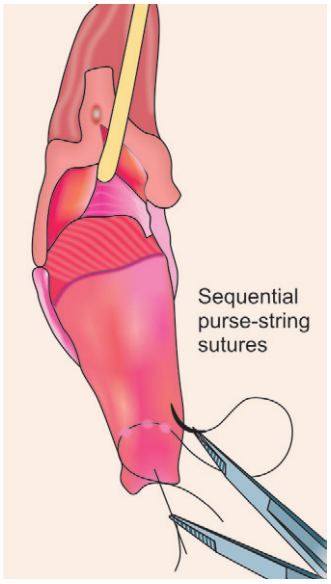


Fig. 22.13C: Suturing: The mucosa has been removed and the underlying strong tissue (pubocervical and rectovaginal fascia) are identified. The tissue is sewn together in a circular fashion (like the drawstrings on a purse)

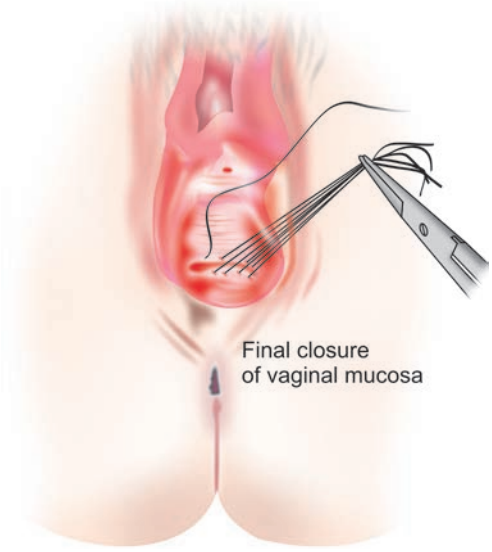


Fig. 22.13E: Final closure of vaginal mucosa. After multiple circular sutures are placed and the prolapse is progressively reduced, the prolapse is completely reduced back into the patient's vagina and pelvis. The skin edges from the original incision are then closed using sutures

stress or urge incontinence. Le Fort's procedure should only be used when there is a good reason not to perform any of the usual procedures for prolapse. This operation is recommended only to the patients who are no longer sexually active nor have plans for future sexual intercourse. The procedure should never be done before the woman and her partner fully understand that the procedure would result in termination of intravaginal sexual intercourse.

Complications

Uterine prolapse if not corrected, can interfere with bowel, bladder and sexual functions and result in the development of the following complications:

- Ulceration
- Infection/urosepsis (including due to pessary use)
- Urinary incontinence

- Constipation
- Fistula
- Postrenal failure
- Decubitus ulceration.

Important Questions and Answers

Q.1. What would be the next step of the management in the above mentioned case study?

Ans. In the above mentioned case study, the prolapse significantly interfered with the patient's day to day functioning and prevented her from standing for prolonged periods. Therefore, it needs to be treated. Since the patient was above 40 and did not want to preserve her uterus, a transvaginal hysterectomy was planned. The anesthetists promptly gave their clearance since the patient did not have any history of previous medical disorders. No other hazards to contraindicate surgery could be identified. In order to prevent the recurrence of prolapse, the surgical treatment for various types of defects must be performed together at the time of surgery. It is very important that the physician carefully inspects the vagina for other prolapses. At the time of hysterectomy in this patient, the following repairs were planned: Anterior colporrhaphy, posterior colporrhaphy and a Mc Call's culdoplasty. Mc Call's culdoplasty was performed in this patient in order to obliterate the cul-de-sac and to prevent the future development of both vaginal vault prolapse and enterocele.

22

Q.2. What essential precaution should be taken in this patient?

Ans. Preventing vaginal vault prolapse by supporting the vaginal cuff is an essential part of hysterectomy. Closure of cul-de-sac at the time of vaginal hysterectomy helps prevent future development of enterocele as well as vaginal vault prolapse.

Q.3. What are the methods for preventing vaginal prolapse at the time of hysterectomy?

Ans. Various methods for preventing vaginal prolapse at the time of hysterectomy are as follows:

Culdoplasty (obliteration of cul-de-sac)

- Mc Call culdoplasty (has been described previously in the text)
- Moschcowitz culdoplasty (has been described previously in the text)
- Halban cul-de-sac closure (figure 22.14): While both the Mc Call culdoplasty and Moschowitz culdoplasty are performed via the vaginal route, Halban culdoplasty is performed via the abdominal route.

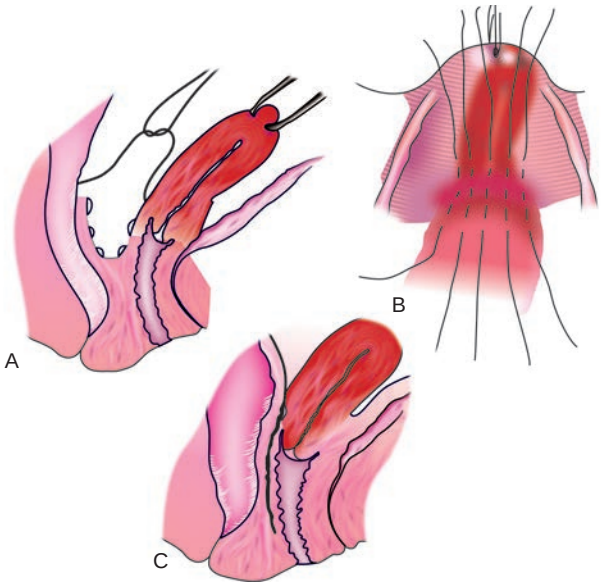


Fig. 22.14: Halban's culdoplasty with uterus in situ. (A) Lateral view showing the attachment of the suture to sigmoid, upper vagina, and lower uterine segment. (B) Superior view of the cul-de-sac (C) Lateral view of completed closure

Suspension of vagina

Vaginal procedure:

- Transvaginal sacrospinous colpopexy

Abdominal procedure:

- Abdominal sacrocolpopexy

Q.4. Had uterovaginal prolapse been also present in the patient, what extra precaution at the time of surgery would have been required?

Ans. If uterovaginal prolapse had also been present, it is a good idea to also shorten the cardinal-uterosacral ligament complex at the time of Mc Call's culdoplasty. This would help in eliminating any laxity that is present.

Bibliography

1. Brown, Jeanette S, L Elaine Waetjen, Leslee L Subak, David H Thom, Stephen Van Den Eeden and Eric Vittinghoff. Pelvic Organ Prolapse Surgery in the United States, 1997. American Journal of Obstetrics and Gynecology. 2002;186:712-6.
2. Bump RG, Mattiasson A, Bo K, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor function. Am J Obstet Gynecol. 1996;175:10.
3. Cruikshank SH, Cox DW. Sacrospinous fixation at the time of transvaginal hysterectomy. Am J Obstet Gynecol. 1990;162:1611.
4. DeLancey JOL. Anatomic aspects of vaginal eversion after hysterectomy. Am J Obstet Gynecol. 1992; 166:1717.
5. Elancey JO. Anatomy and biomechanics of genital prolapse. Clin Obstet Gynecol. 1993;36(4):897-909.

6. Feldman GB, Birnbaum SJ. Sacral colpopexy for vaginal vault prolapse. Obstet Gynecol. 1979;53:399.
7. Hagen S, Stark D, Maher C. Conservative management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2004;CD003882.
8. Handa VL, Harris TA, Ostergard DR. Protecting the pelvic floor: Obstetric management to prevent incontinence and pelvic organ prolapse. Obstet Gynecol. 1996;88(3):470-8.
9. Jones HW, Rock JA, (eds). Surgery for correction of defects in pelvic support and pelvic fistulas. Telinde's Operative Gynecology. pp 720-723, 10th edition, 2008. Philadelphia: JB Lippincott.
10. Kaser O, Ikg FA, Hirsch HA. Atlas of Gynecologic Surgery. pp 6.1-6.9, 2nd ed. New York, Thieme-Stratton, 1985.
11. Lee RA, Symmonds RE. Surgical repair at posthysterectomy vault prolapse. Am J Obstet Gynecol. 1972; 112:953.
12. Lentz, GM. Anatomic defects of the abdominal wall and pelvic floor: abdominal and inguinal hernias, cystocele, urethrocele, enterocele, rectocele, uterine and vaginal prolapse and rectal incontinence: Diagnosis and Management. In: Katz VL, Lentz GM, Lobo RA, Gershenson DM (eds) Katz: Comprehensive Gynecology. 5th ed. Philadelphia, PA: Mosby Elsevier; 2007:chap 20.
13. Loret de Mola JR, Carpenter SE. Management of genital prolapse in neonates and young women. Obstet Gynecol Surv. 1996;51(4):253-60.
14. McCall ML. Posterior culdoplasty. Obstet Gynecol 1957;10: 595.
15. Morley GW. Treatment of uterine and vaginal prolapse. Clin Obstet Gynecol. 1996;39(4):959-69.
16. Moschcowitz AV. The pathogenesis, anatomy and cure of prolapse of the rectum. Surg Gynecol Obstet. 1912;15:7.
17. Nichols DH, Milley PS, Randall CL. Significance of restoration of normal vaginal depth and axis. Obstet Gynecol. 1970;36: 251.
18. Randall CL, Nichols DH. Surgical treatment of vaginal inversion. Obstet Gynecol. 1971;38:327.
19. Ranny B. Enterocele, vaginal prolapse, pelvic hernia: Recognition of treatment. Am J Obstet Gynecol. 1981;140:852.
20. Rinne KM, Kirkinen PP. What predisposes young women to genital prolapse?. Eur J Obstet Gynecol Reprod Biol. 1999; 84(1):23-5.
21. Rush CB, Entman SS. Pelvic organ prolapse and stress urinary incontinence. Med Clin North Am. 1995;79(6):1473-9.
22. Ryan, Kenneth J., et al. Kistner's Gynecology and Women's Health. 7th ed. St. Louis, MO: Mosby, Inc., 1999.
23. Sanai T, Yamashiro Y, Nakayama M. End-stage renal failure due to total uterine prolapse. Urology. 2006;67(3):622.e5-7.
24. Silva WA, Kleeman S, Segal J. Effects of a full bladder and patient positioning on pelvic organ prolapse assessment. Obstet Gynecol. 2004;104(1):37-41.
25. Symmonds RE, Williams TJ, Lee RA, et al. Posthysterectomy enterocele and vaginal vault prolapse. Am J Obstet Gynecol. 1981;140:852.
26. Walsh, Patrick C, et al. Campbell's Urology. 8th ed. Philadelphia: Elsevier Science, 2002.
27. Weber AM, Walters MD, Piedmonte MR. Sexual function and vaginal anatomy in women before and after surgery for pelvic organ prolapse and urinary incontinence. Am J Obstet Gynecol. 2000;182(6): 1610-5.

Chapter

23

Pelvic Pain

Case Study

A 25-year-old nulliparous patient presented with complains of chronic pelvic pain since last two years. The pain is mainly present in the lower back and abdomen and typically exacerbates at the time of menstrual periods. During this time, the pain becomes severe enough to interfere with the quality of life. The patient gives history of experiencing mild to-moderate pain at the time of sexual intercourse. The patient also gives history of experiencing primary infertility. On bimanual pelvic examination, localized areas of tenderness were felt in the pelvic region. However, no nodularity or thickness of uterosacral ligaments, cul-de-sac or rectovaginal septum was felt.

Introduction

The International Association for the study of pain has defined pain as an unpleasant sensory and emotional experience associated with actual or potential damage to the tissues. This implies that pain is associated with both a sensory and an emotional component. American College of Obstetrics and Gynecology has defined chronic pelvic pain (CPP) as cyclic or non-cyclic pain, emanating from the pelvic area, which has been present for six months or more. The pain often localizes to the pelvis, infraumbilical part of anterior abdominal wall, lumbosacral area of the back or buttocks and often leads to functional disability. It may also be present in the perineal region and produce discomfort in the anus, rectum, coccyx and sacrum. It is often associated with symptoms such as premenstrual pain, dysmenorrhea, dyspareunia, exercise related pain, or cramping, with or without menstrual exacerbation of sufficient severity to cause functional disability or require medical care. The pain may be a steady or it may come and go. It can feel like a dull ache, or it can be sharp and may be generalized or localized. The pain may be mild, or it may be severe enough to negatively affect health related quality of life.

CPP is not a disease, but a symptom, which rarely reflects a single pathologic process. Different neurophysiological mechanisms may be involved in the pathophysiology of CPP. Patient's history is crucial and is generally of utmost importance for reaching a correct diagnosis. Chronic pelvic pain is common in women in the reproductive and older age groups and causes disability and distress. In many cases no obvious cause for the pain can be found even after conducting numerous investigations including laparoscopy. Since the pathophysiology of chronic pelvic pain is not well understood, its treatment is often unsatisfactory and limited to symptom relief.

Identifying the Cause of Pelvic Pain

The most important question for the patient and the clinician is to identify the cause of pain. In general the three most common sources of pain include:

Pain of somatic origin

This type of pain arises from skin, muscles and bone tissue and is commonly described by the patients as throbbing, stabbing or burning type of pain.

Visceral origin

This type of pain arises from internal organs and tends to be diffuse and more generalized.

Neuropathic origin

The pain of neuropathic origin arises from damaged nerve fibers and may be described as numbness, pins and needles and may produce electric current like sensations.

The main contributing factors in women with CPP are identified by history and physical examination in most cases. Many disorders of the reproductive tract, urological organs, gastrointestinal, musculoskeletal and psychoneurological systems may be associated with CPP. The various gynecological and non-gynecological causes for CPP have been enumerated in table 23.1 and are described in the section of differential diagnosis of this chapter.

Since CPP can be caused due to numerous pathologies and pathology in one organ can commonly lead to dysfunction in the other, women with chronic pelvic pain may have

Table 23.1: Causes of chronic pelvic pain

Gynecological causes	*Gastrointestinal causes*
Endometriosis, chocolate cyst of ovary	Irritable bowel syndrome
Ovarian adhesions, polycystic ovarian disease	Chronic intermittent bowel obstruction
Chronic pelvic inflammatory disease, pelvic and tubal adhesions	Diverticulitis, colitis, appendicitis
Pelvic tuberculosis	Carcinoma rectum
Uterine fibroids and adenomyosis	
Benign or malignant ovarian tumors	
Renal causes	*Musculoskeletal disease*
Ureteric or bladder stones	Abdominal wall myofasical pain
Urinary tract infection, interstitial cystitis, radiation cystitis	Degenerative joint disease including muscle strains and pain
Bladder malignancy	Disc herniation, rupture or spondylosis
Psychiatric/neurological cause	*Miscellaneous causes*
Abdominal epilepsy, abdominal migraines	Familial Mediterranean fever
Depression, sleep disturbances, somatization	Herpes zoster
Nerve entrapment, neurologic dysfunction	Porphyria

more than one cause for pain and other overlapping symptoms. Thus a comprehensive evaluation of multiple organ systems and psychological state is essential for complete treatment. Most important causes for CPP include endometriosis, symptomatic leiomyomas, interstitial cystitis and irritable bowel syndrome. Diagnosis and treatment of pain in relation to endometriosis would be discussed in this chapter. Evaluation and management of pain secondary to that of leiomyomas has been discussed in chapter 18. The most common symptoms related to endometriosis are dysmenorrhea, dyspareunia and low back pain which worsens during menses.

Endometriosis is one of the most common causes of chronic pelvic pain in women belonging to the reproductive age groups and may be associated with infertility in nearly 30% to 40% cases. Endometriosis is characterized by occurrence of endometrial stroma and glands outside the uterus in the pelvic cavity, including all the reproductive organs as well as on the bladder, bowel, intestines, colon, appendix and rectum (figure 23.1). In normal women, endometrial glands and stroma are largely limited to the uterus. Other common sites for endometriotic lesions include uterine scars, uterosacral ligaments and pelvic side walls. The ectopic endometrial tissue, both the glands and the stroma, are capable of responding to cyclical hormonal stimulation and has the tendency to invade the normal surrounding tissues. Endometriosis is a disease, which is largely encountered in the women belonging to the reproductive age group. The pathogenesis of endometriosis is yet not clear. Retrograde menstrual flux is considered as an essential element in the pathogenesis of endometriosis. However, it is yet not clear

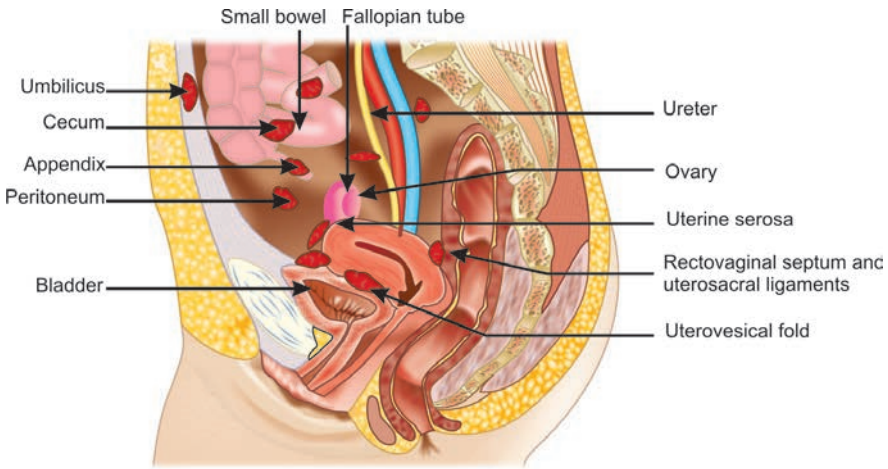


Fig. 23.1: Common sites of endometriotic lesions

why endometriosis develops only in a limited number of women, despite the fact that retrograde menstruation is seen in almost all women. Endometriosis is an estrogen dependant disease, characterized by the regression of lesions following treatment with drugs that block estradiol synthesis. The patients with endometriosis typically present with menstrually related pain, often in association with menorrhagia and deep dyspareunia.

History

Taking proper history and conducting appropriate physical examination in a woman can help in narrowing the differential diagnosis and guide further tests and investigations. The most important part of history is taking a detailed history regarding pain. The following characteristics related to pain need to be enquired:

- The exact area of pain localization: The pain may be localized to the pelvis, lower back, perineal region or the lower abdomen.
- The severity and duration of pain: The clinician needs to assess whether the pain is acute or chronic in nature and whether it is mild or severe in intensity. A significant number of women with endometriosis remain asymptomatic. The clinician must remember that the degree of visible endometriosis may have no correlation with the degree of pain or other symptoms. However, the pain may correlate with the depth of tissue infiltration caused by the endometriotic lesion. Though the endometriotic lesions commonly cause chronic pelvic pain, at times, there may be acute exacerbations of pelvic pain caused by chemical peritonitis due to leakage of old blood from an endometriotic cyst.
- The aggravating or relieving factors for pain must be enquired.
- Timing during the day when the pain occurs or increases in intensity.
- Correlation of pain with menstrual cycles: CCP due to endometriosis is commonly associated with dysmenorrhea and low back pain that worsens during menses. The diagnosis of endometriosis should be considered especially if a patient develops dysmenorrhea after years of pain-free menstrual cycles. Secondary dysmenorrhea has been observed to occur twice as commonly in women with endometriosis in comparison to controls. Pain due to endometriosis typically commences prior to menses.
- The patient needs to be asked if the pain follows any cyclic pattern and whether it remains same all the time or varies at different times of the day. Cyclic pain is the pain that accompanies bleeding at the time of menstruation. Cyclical pain associated with hormonal changes taking place during the menstrual cycle is likely to result from endometriosis or adenomyosis, while a nonhormonal pattern of pain may be more indicative of a musculoskeletal pathology or other conditions such as adhesions, IBS, or interstitial cystitis. However, the clinician should be careful before reaching any conclusion because pain caused by IBS and interstitial cystitis may sometimes also fluctuate based on hormone levels.
- The affect the pain has on the patient's quality of life needs to be assessed.
- Relation of pain to bowel movements or urination needs to be asked.
- The clinician needs to take history regarding any correlation between the symptoms of pain and the sexual intercourse. Relation of pain with deep penetration during intercourse or dyspareunia needs to be asked. Deep dyspareunia may result due to scarring of the uterosacral ligaments, nodularity of the rectovaginal septum, obliteration of cul-de-sac and/or uterine retroversion. All these reasons are also responsible for producing lower backache. These symptoms may get exaggerated during menses. A woman presenting with a combination of dysmenorrhea, CPP and dyspareunia is most likely to be suffering from endometriosis.

Other questions which need to be asked at the time of taking history include:

- The patient's age
- Any previous history of STD or PID
- Symptoms indicative of malignancy such as unexplained weight loss, hematochezia, perimenopausal irregular bleeding, postmenopausal vaginal bleeding, or postcoital bleeding, should prompt an investigation to rule out malignancy.

Obstetric History

Injury to the ilioinguinal nerve or hypogastric nerves during Pfannenstiel incision for cesarean section delivery may be the cause of lower abdominal pain. In a nulliparous woman with infertility, pain may be due to endometriosis, pelvic adhesions or PID. History of using oral contraceptive pills or any other methods of birth control need to be asked.

Surgical History

Prior history of abdominal surgery increases the woman's risk for developing pelvic adhesions, especially if infection, bleeding or large areas of denuded peritoneal surfaces were involved. Certain disorders may persist and therefore information regarding prior surgeries for endometriosis, adhesive surgery or malignancy must be sought.

Psychosocial History

It is important to investigate all contributing factors related to the pain including psychological, social and environmental causes.

Previous Treatment History

The patient needs to be asked if she has ever undergone an assessment or treatment for pain in the past. The patient needs to be asked if she has been taking any medicines. She also needs to be asked if she has ever suffered from psychiatric disorders like depression or anxiety.

General Physical Examination

Initial examination begins with the assessment of the woman's general appearance including the woman's facial expression, pallor, degree of agitation and vital signs. Altered vital signs such as elevated temperature, hypotension and tachycardia could be indicative of presence of underlying intraabdominal pathology. Constant low grade fever is commonly present in inflammatory conditions such as diverticulitis and appendicitis. Higher temperature may be associated with conditions such as advanced stages of PID, pyelonephritis or advanced peritonitis.

Evaluation of the patient's pulse and blood pressure may help in assessment of hypovolemia. Reduced blood pressure (hypotension) and tachycardia may indicate the underlying hypovolemia. If hypovolemia is present, an intravenous access must be established prior to completion of the examination.

Evaluation of the patient's posture

Evaluation of the patient's posture may point towards underlying musculoskeletal pathology. Patient's posture should be evaluated in three directions: Anterior, posterior and lateral. The back must be examined posteriorly for presence of structural deformities such as scoliosis, kyphosis, lordiosis etc and symmetry of the shoulders, gluteal folds and knee creases. Asymmetry may be indicative of underlying musculoskeletal disease. The clinician must also evaluate the mobility of spine by asking the patient to bend in forward and sideways direction at the waist. Limitation in forward flexion may be indicative of underlying orthopedic or musculoskeletal disease. The clinician can assess the abnormal tilting of the pelvic bones by simultaneously placing the medial side of his/her open palm on each side of patient's pelvis between the anterior superior iliac spine and posterior superior iliac spine. In normal individuals, the anterior superior iliac spine lies about 1 cm below the level of posterior superior iliac spine. Distances greater than this may be suggestive of abnormal tilt and could be associated with osteoarthritis and other orthopedic problems.

Specific Systemic Examination

ABDOMINAL EXAMINATION

Both abdominal and pelvic examinations must proceed slowly and gently because both the abdominal and pelvic components of the examination may be painful. The abdominal examination can help identify areas of tenderness and the presence of masses or other anatomical findings which may help in reaching the accurate diagnosis. The method of performing abdominal examination has been described in details in chapter 16. The abdomen must be inspected for the presence of previous surgical scar marks. Presence of previous surgical scars increases the possibility of post-operative adhesions, which could be an important cause of pelvic pain. Anterior abdominal wall must also be inspected for the signs of hernia. Hernias involving the anterior abdominal wall or pelvic floor may be associated with CPP. Palpation of the abdomen must systematically explore each abdominal quadrant and begin away from the area of indicated pain. Superficial palpation of the anterior abdominal wall by the clinician may reveal sites of tenderness or knotty muscles which may reflect nerve entrapment or myofascial pain syndromes. Deep palpation of the lower abdomen may identify pathology originating from the pelvic viscera. Palpation of the outer pelvis, back and abdomen may reveal trigger points that may indicate a myofascial component to the pain.

Following inspection and palpation, auscultation must be done. Presence of high-pitched bowel sounds are characteristic of bowel obstruction.

However, a lack of findings during the abdominal or pelvic examination does not rule out intra-abdominal pathology because many patients with a normal abdominal and pelvic examination may subsequently show pathologic findings on laparoscopic examination. Carnett's sign can be performed to distinguish whether the pain is due to an intra-abdominal pathology or pathology in the anterior abdominal wall.

Carnett's Sign for Patients with Pelvic Pain (Figure 23.2)

The test is performed with the patient lying supine on the table. While the clinician places a finger on the painful, tender area of the patient's abdomen, the patient is instructed to raise her head and shoulders while tensing the anterior abdominal wall muscles. A positive test occurs when the pain increases

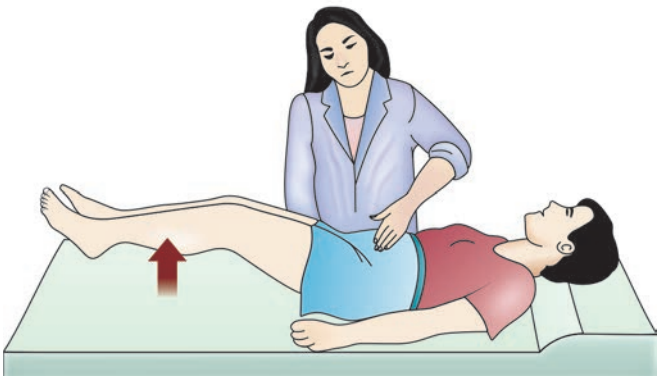


Fig. 23.2: Performing Carnett's sign for patients with pelvic pain

during this maneuver and is typical of anterior abdominal wall pathology and indicates myofascial cause of the pain. On the other hand, tenderness originating from inside the abdominal cavity usually decreases with this maneuver. In addition, Valsalva maneuver during head and shoulder elevation may display diastasis of the rectus abdominis muscle or hernias. Diastasis recti can be differentiated from the case of ventral hernias. With diastasis, the borders of rectus abdominis muscle can be palpated bilaterally along the entire length of the protrusion.

PELVIC EXAMINATION

Detailed description of the method for conducting the pelvic examination has been described in chapter 16. The pelvic examination should commence with inspection of the external genitalia.

Per Speculum Examination

- Vagina and vulva must be inspected for presence of generalized changes and any local lesions. Findings of purulent vaginal discharge or cervicitis may be indicative of PID.
- Presence of bluish-black puckered spots, which are tender to touch may be noted on per speculum examination. This feature of endometriosis is pathognomonic of endometriosis. Bleeding through the vagina could be due to pregnancy related complications, benign or malignant reproductive tract neoplasia or acute vaginal trauma. Cervical motion tenderness is commonly associated with peritoneal irritation and may be seen with PID, appendicitis and diverticulitis.

Bimanual Pelvic Examination

Tenderness upon pelvic examination is best detected at the time of menses when the endometrial implants are likely to be largest and most tender. Since the pelvic examination must be performed slowly and gently, it should begin with a single-digit of one-hand. A moistened cotton swab should be used to elicit point tenderness in the vulva and vagina. Following the single-digit examination, a bimanual examination should be performed. During the pelvic examination, it is important to determine whether any manipulations reproduce the pain especially upon the palpation of the uterus or rectum. The bimanual examination may reveal the following findings:

- Nodularity and thickening of the uterosacral ligaments and the cul-de-sac may be present in cases of moderate to severe endometriosis. Women with minimal or mild endometriosis may have focal tenderness of the uterosacral ligaments or cul-de-sac without palpable nodules.
- Pain with deep palpation of the vaginal fornices may be observed with endometritis and cervical motion tenderness may be noted with PID.
- The uterus may be fixed in retroversion, owing to adhesions. Besides endometriosis, immobility of the uterus could be related to pelvic inflammatory disease, malignancy or adhesive disease from prior surgeries. Evaluation of adnexa may reveal masses or tenderness.
- A bluish nodule may be seen in the vagina due to infiltration from the posterior vaginal wall.
- Myofascial tenderness involving the puborectalis and coccygeus muscles may be noted by firmly sweeping the index finger across these muscles.
- Tenderness of urethra and bladder are potential indicators of urethral diverticulum or interstitial cystitis respectively. The patient should be checked for point tenderness along the bladder or other musculoskeletal structures.
- The size of the uterus must be assessed on pelvic examination. While an irregularly enlarged uterus is indicative of leiomyomas, a regularly enlarged uterus with softening could indicate adenomyosis or pregnancy.
- Adnexal tenderness with or without enlargement may indicate ovarian endometriosis. On the other hand, failure to reproduce localized tenderness during the pelvic examination may point toward a nongynecologic disorder. A tender adnexal mass may be suggestive of ectopic pregnancy, tuboovarian abscess, or ovarian cyst with torsion, hemorrhage or rupture.

Finally a rectovaginal examination must be performed. This should include the palpation of rectovaginal septum. A rectal examination may show rectal or posterior uterine masses, presence of nodules in the uterosacral ligaments, cul-de-sac or rectovaginal septum and/or pelvic floor point tenderness. Nodularity of the rectovaginal septum could also be due to neoplasia. Palpation of hard stools or hemorrhoids on rectovaginal examination may indicate gastrointestinal disorders.

Table 23.2: Significance of selected findings on history, physical examination, and diagnostic investigations

Finding	*Possible significance*
History	
Hematochezia	Gastrointestinal malignancy/bleeding
History of pelvic surgery, pelvic infections, or use of intrauterine device	Adhesions
Nonhormonal pain fluctuation	Adhesions, interstitial cystitis, irritable bowel syndrome, musculoskeletal causes
Pain fluctuates with menstrual cycle	Adenomyosis or endometriosis
Perimenopausal or postmenopausal irregular vaginal bleeding	Endometrial cancer
Postcoital bleeding	Cervical cancer or cervicitis (e.g., chlamydia or gonorrhea)
Unexplained weight loss	Systemic illness or malignancy
Physical examination	
Lack of uterus mobility on bimanual examination	Endometriosis, pelvic adhesions
Nodularity or masses on abdominal, bimanual pelvic and/or rectal examination	Adenomyosis, endometriosis, hernias, malignancy, tumors
Pain on palpation of outer back and outer pelvis	Abdominal/pelvic wall source of pain, trigger points
Point tenderness of vagina, vulva, or bladder	Adhesions, endometriosis, nerve entrapment, trigger points, vulvar vestibulitis
Positive Carnett's sign	Myofascial or abdominal wall cause of pain
Diagnostic studies	
Abnormal urine analysis or urine culture	Bladder malignancy, infection
Elevated leukocyte count, increased level of C-reactive protein	Infection, systemic illness, or malignancy (elevated/decreased white blood cell count or anemia)
Elevated erythrocyte sedimentation rate	Infection, malignancy, systemic illness
Positive culture tests for gonorrhea or chlamydia	Pelvic inflammatory disease
Transvaginal ultrasound abnormalities	Adenomyosis, endometriosis/endometriomas, malignancy

Differential Diagnosis

The etiology of chronic pelvic pain in women is poorly understood. Although a specific diagnosis is not found in the majority of cases, the four most commonly diagnosed pathologies include endometriosis, adhesions, irritable bowel syndrome and interstitial cystitis. The various causes for CPP are listed in table 23.1. Various points in the history, clinical examination and results of laboratory investigations can point towards the specific cause of pelvic pain (table 23.2).

Management

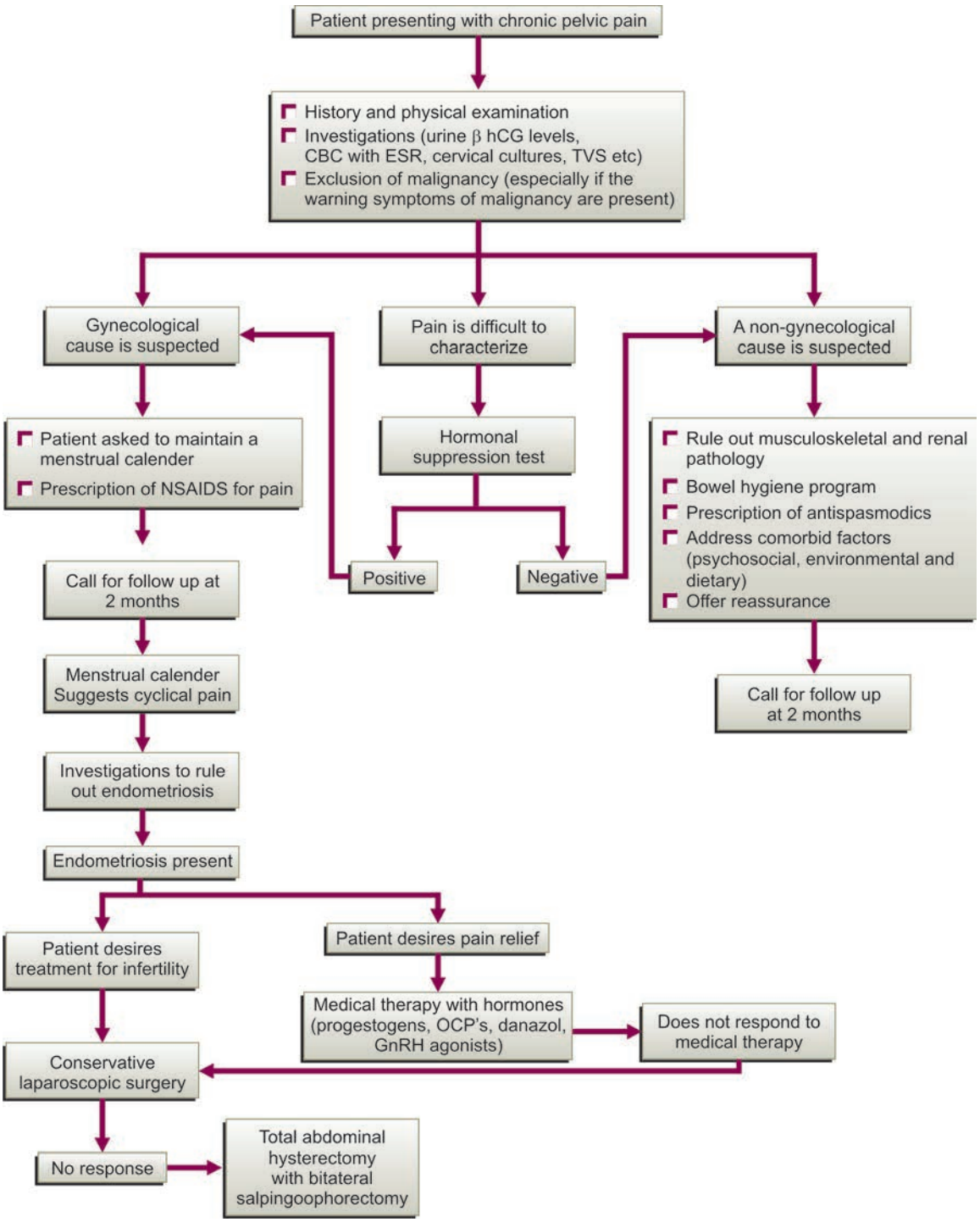
The discovery of exact pelvic pathology or cause of pain helps the clinician in instituting the therapy appropriate to the etiology. The management plan for a patient suffering from CPP is described in flow chart 23.1. The treatment needs to be individualized and must be decided after taking various parameters into consideration. Some of these include patient's age, requirement for preserving future reproductive function, main presenting complain for which the patient sought treatment (for e.g., pain or infertility), severity of symptoms, extent of disease and patient's attitude toward her problem.

Warning signs of malignancy include unexplained weight loss, hematochezia, perimenopausal, postmenopausal or postcoital bleeding.

Investigations

Since CPP can be caused due to numerous pathologies and pathology in one organ can commonly lead to dysfunction in the other, women with chronic pain may have more than one cause of pain and overlapping symptoms. Thus, a comprehensive evaluation of multiple organ symptoms and psychological state is essential for complete treatment. The main issue in evaluating patient with chronic pelvic pain is distinguishing between gynecologic and nongynecologic causes of the pain. This would enable the gynecologist to institute the most appropriate course of further investigations and management. A definite diagnosis and the cause of the

Flow chart 23.1: Algorithm for the management of chronic pelvic pain in women



pain cannot always be elicited clinically. If the gynecological cause of pain cannot be established with surety, the gynecologist can make use of the hormonal suppression test to distinguish between the gynecological and nongynecological causes of pain. The hormonal suppression test is a functional study that provides a practical means of making this distinction and uses progestogens to create a hypoestrogenic environment. If the pain emanates from a gynecologic source or is exacerbated by normal menstrual physiology, the symptoms should improve significantly with hormone suppression.

Negative investigations at least assure the woman that no serious condition prevails and also help in eliminating the cancer phobia. Other investigations which may facilitate diagnosis are described below:

Urine β hCG Levels

Determination of urine β hCG levels is important to rule out pregnancy related complications.

Complete Blood Count

Elevated leukocyte count points towards infection, whereas reduced hemoglobin level suggests anemia, which could be the result of chronic or acute blood loss.

Urine Analysis/Urine Culture

Urine analysis helps in excluding out the presence of possible urolithiasis, cystitis and urinary tract infection.

Cervical Cultures

Vaginal swabs may help in detecting infection such as gonorrhea and Chlamydia.

Serum Cancer Antigen 125 Test (CA 125)

CA 125 levels may be increased to values greater than 35 IU/ml in nearly 80% cases of endometriosis. Serial measurement of CA antigen 125 have a low sensitivity in detecting endometriosis, but the progressively decreasing serum CA 125 level is a useful prognostic indicator of treatment outcome. However, normal posttreatment values do not mean that endometriosis is absent. Increased CA 125 levels may be associated with numerous conditions such as tuberculosis, PID, malignant epithelial ovarian tumors, chronic liver disease, etc.

Imaging Studies

Ultrasound examination (both transabdominal and transvaginal) is the most commonly used investigation which may help in revealing the pelvic pathology responsible for producing pain. Imaging investigations such as CT and MRI may be helpful in some cases. Though these diagnostic modalities help in identifying the individual lesions, these modalities are not helpful in assessing the extent of endometriosis. Doppler ultrasound may be used for diagnosis of pelvic congestion.

Ultrasound imaging

Ultrasound examination forms the diagnostic modality of choice in most cases of CPP due to gynecological causes. Transvaginal sonography is a useful method for identifying the classic chocolate cyst of the ovary and typically shows a cyst containing low-level homogenous internal echoes consistent with old blood. The cyst wall may be thickened and irregular. There may be multiple cysts in different phases of evolution.

CT/MRI examination

In cases, where sonographic findings are equivocal or nondiagnostic, CT examination must be widely used to reach the correct diagnosis. MRI is too costly imaging modality and therefore cannot be recommended as an investigation for routine use. However, MRI examination may be helpful in detecting rectovaginal endometriosis and cul-de-sac obliteration in more than 90% of cases where ultrasound examination proved to be nonconclusive.

Endoscopy

Endoscopic investigations such as cystoscopy, laparoscopy, sigmoidoscopy and colonoscopy may also be employed depending upon the symptoms of each individual patient. In patients with CPP and urinary symptoms, cystoscopy is typically advised. If gastrointestinal symptoms are dominant, flexible sigmoidoscopy or colonoscopy may be warranted. For many women with a likely gynecological cause for their chronic pelvic pain, laparoscopy may be performed.

Diagnostic laparoscopy

Diagnostic laparoscopy remains the gold standard for diagnosis of pelvic pathology. Laparoscopy detects small nodules of endometriosis which may remain undetected clinically. Laparoscopy can also detect pelvic adhesions and small inflammatory pelvic masses. Therapeutic treatment such as adhesiolysis and cauterization of endometriotic lesions can be applied in the same sitting.

Radiological Investigations to Rule Out the Presence of Non-gynecological Causes of CPP

Radiological studies may be required in case of non-gynecological causes of CPP. These investigations must be ordered in accordance with the patient's history and examination.

Some such investigations include barium studies (especially if gastrointestinal pathology is suspected), radiography of joints (if musculoskeletal pathology is suspected) and intravenous pyelography (in case of renal pathology). In patients with bowel symptoms, barium enema may indicate internal or external obstructive lesions, malignancy and diverticular disease or irritable bowel disease.

Rx *Treatment/Gynecological Management*

In many women with CPP, treatment begins with identification of a source of pain and treatment is dictated by the

diagnosis. However, in other cases pathology may be identified and treatment is directed towards dominant symptoms. Treatment should be directed at the underlying cause of the pelvic pain. The patient should be given a menstrual calendar to document the correlation of pain with the menstrual cycle. She should be advised to return after 2 months to review her symptoms and the calendar. Such record of pain also guides the gynecologist regarding the severity of pain and to decide whether the pain is sufficiently severe and truly disrupts the patient's quality of life to justify proceeding with more invasive diagnostic modalities or surgery.

If a nongynecological cause of pelvic pain is suspected, the patient should be instructed to follow a course of proper bowel hygiene for at least two months. If her symptoms get alleviated, she should continue this program for 6 more months. However, if the menstrual calendar suggests a gynecologic etiology (e.g., endometriosis) for pelvic pain, exploratory laparoscopy can be considered. At the time of laparoscopy, the following procedures can be undertaken: Destruction of endometrial implants, uterosacral transection, lysis of adhesions and evacuation of endometriomas. These simple laparoscopic procedures may help in relieving symptoms in the majority of appropriately selected patients.

Treatment for endometriosis may be expectant, or either medical or surgical. Each modality of treatment is associated with its own specific advantages and disadvantages which are described in table 23.3. Perhaps the strongest reason for beginning with surgical treatment is the apparently lower recurrence rate compared with medical treatment. One of the main criteria which help the gynecologist decide the next step in management is the patient's main presenting complain, i.e. whether the patient's main complaint is infertility or pelvic pain. The likelihood of subsequent conception can be significantly increased by undertaking surgery in infertile patients.

Table 23.3: Advantages and disadvantages associated with different treatment modalities

Treatment	*Advantages*	*Disadvantages*
Surgical Therapy	Beneficial for infertility Possibly better long-term results Definitive diagnosis and treatment Associated with a much lower rate of recurrance	Expensive Invasive
Medical	It is associated with reduced initial cost and is effective for providing relief from pain.	Adverse effects are commonly present; it is unlikely to improve fertility and is associated with a high recurrence rate.

Since medical treatment has not been shown to help these patients conceive, surgical treatment is usually preferred in patients desiring fertility. Furthermore, pregnancy is contraindicated in patients receiving medical treatment and is in fact unlikely, because the drugs that are used may interfere with ovulation and endometrial implantation. However, some authorities do believe that endometriosis should be suppressed prophylactically by using continuous medical therapy such as combined oral contraceptives, GnRH analogs, medroxyprogesterone, or danazol in order to cause regression of asymptomatic disease and enhance subsequent fertility. On the other hand, both medical and surgical approaches have been used successfully for reducing the pain associated with endometriosis. Algorithm for treatment of patients with endometriosis is described in flow chart 23.2.

Staging of Endometriosis

Before initiating treatment for endometriosis, it is important to classify the disease as minimal, mild, moderate or severe (table 23.4). The American Fertility Society's revised staging for endometriosis is currently the most widely used staging system. In this scoring system, point scores are assigned based on the number of lesions, their bilaterality, size of the lesions, depth of endometrial implants, presence and extent of adnexal adhesions and degree of obliteration of the pouch of Douglas (table 23.5). It however, does not take into account the complaints like infertility or pelvic pain. This classification is a fairly accurate method of recording laparoscopic findings and can help standardize the patient's findings and document the patient's baseline condition and subsequent progress. Staging is based on location, diameter and depth of lesions and density of adhesions. Stages range from minimal to severe disease. Despite this standardization, the correlation between stage and extent of disease remains controversial.

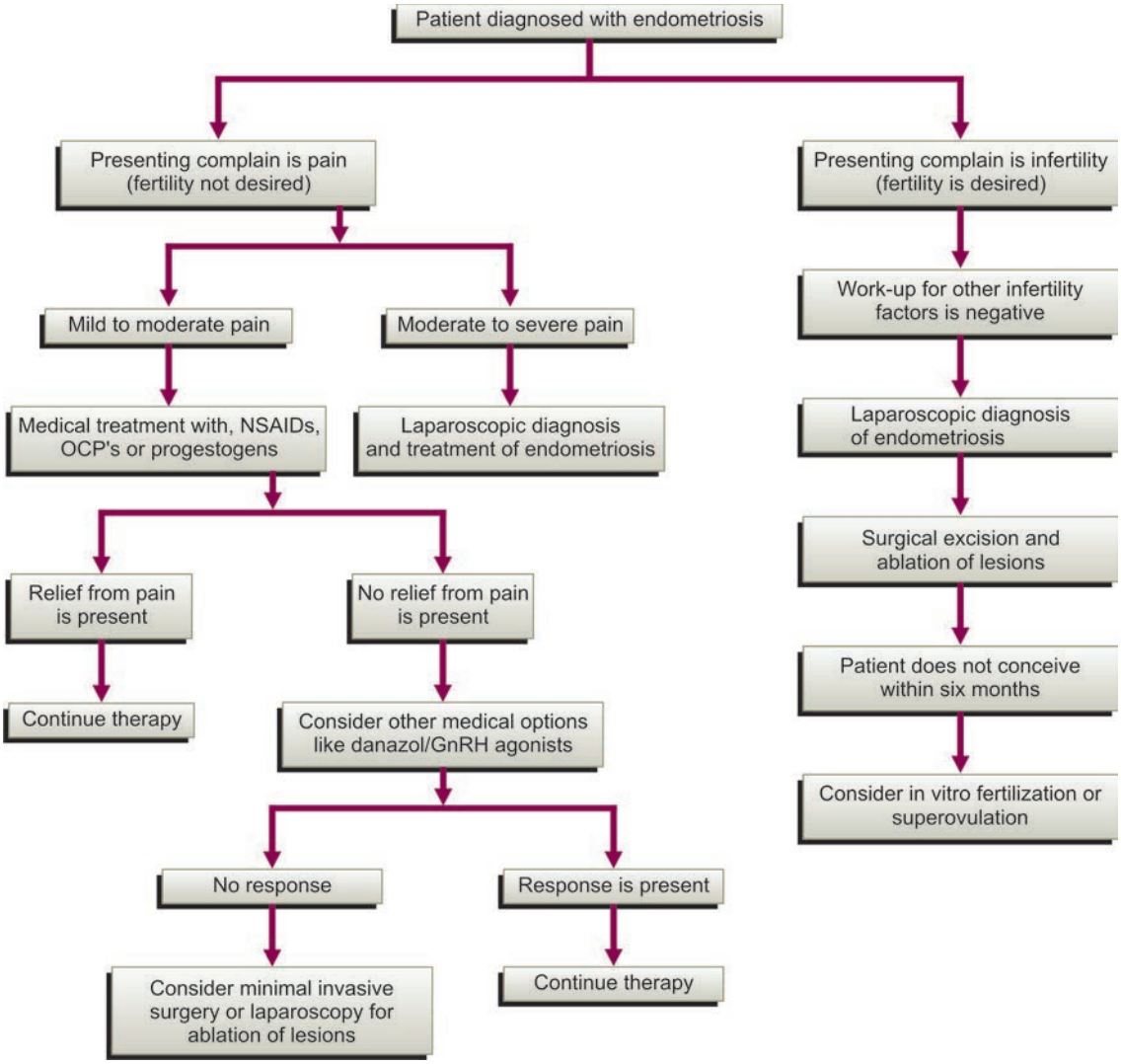
Treatment for Mild-to-Moderate Cases

For patients with mild disease, hormonal treatment (e.g., GnRH analogs, danazol and medroxyprogesterone) has been shown to be effective in reducing pain, but has no impact on fertility. However, for severe endometriosis, the efficacy of hormonal treatment has not yet been established. Since no

Table 23.4: Stage of endometriosis in accordance to the points assigned

Stage of enometriosis	*Points*
Stage I (minimal)	1–5
Stage II (mild)	6–15
Stage III (moderate)	16–40
Stage IV (severe)	> 40

Flow chart 23.2: Algorithm for treatment of patients with endometriosis



pharmacologic method appears to restore fertility, medical treatment should be reserved for use in patients with pain or dyspareunia. Medical treatment comprises of oral analgesic agents such as NSAIDs, progesterone therapy, oral contraceptive agents, GnRH agonists, danazol and mirena IUCD. The various medical treatment options would be described next in details.

MEDICAL TREATMENT

Analgesics

Oral analgesics, such as acetaminophen, non-steroidal antiinflammatory drugs (NSAIDs) and opioid analgesics, are commonly used as the first line treatment modality for alleviation of mild to moderate pelvic pain. However, there is lack of adequate evidence in form of prospective randomized, controlled studies that show a specific benefit of NSAIDs in providing relief against chronic pelvic pain. If satisfactory relief is not obtained with NSAIDS, mild opioid drugs such as codeine or hydrocodone may be added. Initially, long acting opioid drugs with scheduled dosing must be used in order to provide adequate pain relief. If pain persists, stronger opioid drugs such as morphine, fetanyl, methadone, oxycodone and hydromorphone can replace the milder ones. Close and regular surveillance is required while administering the opioid drugs.

Antidepressants and Anticonvulsants

Tricyclic antidepressants have been shown to reduce neuropathic pain independent of their antidepressant effect. Amitriptyline and its metabolite nortriptyline have best

Table 23.5: Revised American Fertility Society classification of endometriosis (1996)

PERITONEUM			
Endometiosis	*< 1 cm*	*1–3 cm*	*> 3 cm*
Superficial	1	2	4
Deep	2	4	6
OVARY			
Right superficial	1	2	4
Right deep	4	16	20
Left superficial	1	2	4
Left deep	4	16	20
POSTERIOR CUL-DE-SAC OBLITERATION			
	Partial		*Complete*
	4		40
OVARY			
Adhesions	*< 1/3 enclosure*	*1/3–2/3 enclosure*	*> 2/3 enclosure*
Right filmy	1	2	4
Right dense	4	8	16
Left filmy	1	2	4
Left dense	4	8	16
TUBE			
Right filmy	1	2	4
Right dense	4*	8*	16
Left filmy	1	2	4
Left dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, the point assignment is changed to 16

Source: Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril. 1997;67:817-21.

documented efficacy in the treatment of neuropathic and non-neuropathic pain syndromes. A recent randomized, controlled, open-label study showed that gabapentin (Neurontin), alone or in combination with amitriptyline, provides significant pain relief in women with chronic pelvic pain. SSRI do not appear to be as effective as tricyclic antidepressants. In addition to antidepressants, anticonvulsants have also been used in the treatment of CPP. Of these, gabapentin and carbamazepine are most commonly used to reduce the neuropathic pain. Injections of botulinum toxin type A into the pelvic floor muscles have been also shown to be beneficial.

Hormonal Therapy

Medical treatment is designed to interfere with ovulation and provides effective pain relief. However, the recurrence rate following cessation of therapy is high. Moreover, this type of treatment does not usually resolve infertility. The hormonal medication is usually continued until the patient remains amenorrheic for at least 2 months. Following this, a repeat pelvic examination and consultation are scheduled.

In case, the hormonal therapy serves to be helpful in bringing about pain relief, the physician may consider laparoscopic exploration/surgery (with or without ultrasonography) or continued therapy with hormonal suppression or OCPs. However, if treatment with hormones does not improve the patient's symptoms, it is indicative of a probable nongynecologic source of pain. In these cases, the clinician must carry out further GI and urologic workup of the patient, possibly including a psychological counseling. Several authors have emphasized the importance of ruling out psychogenic or somatization disorders before proceeding with laparoscopy or other operative management, reducing the potential for unnecessary hysterectomy.

The hormonal preparations commonly used include oral contraceptive pills and oral progestogens.

Combined oral contraceptives

Administration of oral contraceptive pills (OCPs) suppresses LH and FSH and prevents ovulation. They also have direct effects on endometrial tissue, rendering it thin and compact. They bring about the decidualization and atrophy of endometrial implants, along with reduced retrograde menstrual reflux, owing to the reduction in menstrual volume, thereby bringing about significant pain relief. Initially, a trial of continuous or cyclic COCPs should be administered for 3 months. If pain is relieved, this treatment must be continued for 6–12 months. Continuous noncyclical administration of OCPs, for 3–4 months also helps in avoiding any menstruation and associated pain in nearly 75% patients. The OCPs can be discontinued after 6 to 12 months if pregnancy is desired.

Progestational agents

All progestational agents act by causing decidualization and atrophy of the endometrium. Progestins are similar to combination OCPs regarding their effects on FSH, LH and endometrial tissue. Progestins can be considered to be as effective as OCP's in reducing the symptoms of endometriosis. If effective, these agents can be used safely for long periods of time. Progestins can be given orally on a daily basis or in form of weekly/monthly intramuscular injections and have been observed to show proven efficacy in pain suppression, when administered in both oral and injectable depot preparations. Oral regimens may include daily administration of norethisterone in the dosage of 5–20 mg; dydrogesterone in dosage of 10–30 mg or medroxyprogesterone acetate in the dosage of 10 to 20 mg daily. Depot medroxyprogesterone

has also been administered intramuscularly in the dosage of 50 mg intramuscularly weekly, 100 mg every two weeks for two months, followed by 200 mg monthly dose for four-six months. Megestrol acetate has been used in doses of 40 mg with similarly good results. The levonorgestrel intrauterine system (LNG-IUS) has also been shown to reduce endometriosis associated pain.

Progestational agents can cause adverse effects such as weight gain, fluid retention, depression, breakthrough bleeding, irregular menses or amenorrhea, reduced libido, mental depression and breast tenderness. Besides these side effects, fertility may be impaired for as long as two years following prolonged hormonal therapy. Also, the time to resumption of ovulation is longer and variable with depot preparations.

Danazol

Danazol, a synthetic androgen is the derivative of ethinyl testosterone, which has been shown to be highly effective in relieving the symptoms of endometriosis by inhibiting pituitary gonadotropins (FSH and LH). This may result in the development of a relative hypoestrogenic state. Endometrial atrophy is the likely mechanism which provides relief of pain from endometriosis. Danazol acts by inhibiting the midcycle follicle stimulating hormone (FSH) and luteinizing hormone (LH) surges and preventing steroidogenesis in the corpus luteum. It can be considered as a highly effective drug for treatment of endometriosis. However its use may be associated with numerous side effects (table 23.6), which may largely preclude its use. The adverse effects caused by danazol are primarily related to estrogen deficiency and the androgenic effects.

Danazol therapy is started when the patient is menstruating, usually on the first day of the menses. The initial dosage should be 800 mg per day, given in two divided oral doses, but this dosage can be titrated down as long as amenorrhea persists and pain symptoms are controlled. Patients with less severe symptoms may be given 200 to 400 mg per day, in two divided oral doses. Treatment is usually administered for six months, but can be extended to nine months in responsive patients with severe disease.

Table 23.6: Adverse effects caused by danazol

Cause of side efffect	*Side effect caused*
Estrogen deficiency	Headache, flushing, sweating, atrophic vaginitis and breast atrophy
Androgenic effect	Acne, edema, hirsutism, deepening of the voice and weight gain

GnRH agonists

GnRH analogs [e.g., leuprolide (lupron), goserelin (zoladex)] produce a hypogonadotropic-hypogonadic state by inhibiting the secretion of gonadotropins by causing the down-regulation of pituitary gland. They act by inhibiting the midcycle FSH and LH surge and preventing steroidogenesis in the corpus luteum. Currently, goserelin and leuprolide acetate are the most commonly used GnRH agonists. The efficacy of GnRH agonists is comparable to danazol in relieving pain. However, these drugs mainly help in suppressing pain and may show no improvement in infertility. Treatment is usually restricted to monthly injections for 6 months. Similar to danazol, GnRH agonists are contraindicated in pregnancy and may result in hypoestrogenic side effects. Their use is specifically associated with the loss of trabecular bone density, which is restored by 2 years after cessation of therapy. Other prominent adverse effects include hot flushes and vaginal dryness. There has been much recent research regarding whether the simultaneous use of add-back therapy (hormone replacement therapy preparations, progestins, tibolone maleate and bisphosphonates) would be helpful in preventing osteoporosis and other hypoestrogenic symptoms associated with the use of GnRH agonists. Leuprolide is used in the dosage of a single monthly 3.75 mg depot injection given intramuscularly. Gosarelin, in a dosage of 3.6 mg, is administered subcutaneously every 28 days. The dose of goserelin is 3.6 mg SC q28d or 10.8 mg SC q12wk for 6 months. A nasal spray of nafarelin (synarel) is also available and is used twice daily. The response rate is similar to that with danazol; about 90% of patients experience pain relief. The pregnancy rate after the use of these agents is no different from that in untreated patients.

SURGICAL TREATMENT

If the medical therapy does not prove to be successful, the gynecologist may have to resort to surgical treatment. Surgical treatment is the preferred approach for treatment of infertile patients with advanced endometriosis. The benefit of surgery in these patients may be entirely due to the mechanical clearance of adhesions and obstructive lesions. Surgical care can be broadly classified as conservative when reproductive potential is retained, semiconservative when reproductive ability is eliminated but ovarian function is retained and radical when both the uterus and ovaries are removed. Age, desire for future childbearing and deterioration of quality of life are the main considerations when deciding on the extent of surgery. Besides removing the endometriotic lesions, the minimal invasive surgery is also useful in restoration of patient's fertility.

Laparoscopic Surgery

Laparoscopy can help in establishing the diagnosis of endometriosis by identifying the following lesions: Endometriotic nodules or lesions having blue-black or a powder burned appearance (figures 23.3 and 23.4). However, the lesions can be red, white, or nonpigmented. Peritoneal defects and adhesions are also indicative of endometriosis. Laparoscopy can also detect presence of blood (figure 23.5) or endometriotic deposits in cul-de-sac and its obliteration.

Besides diagnosis of endometriotic lesions at various locations, laparoscopy can also help in treating the patient. Powder burn lesions over the uterine surface may be amenable to laser obliteration (figures 23.6 and 23.7). Some of the endometrial lesions are cystic or nodular and can be excised. Laproscopic surgery can also be used for excision

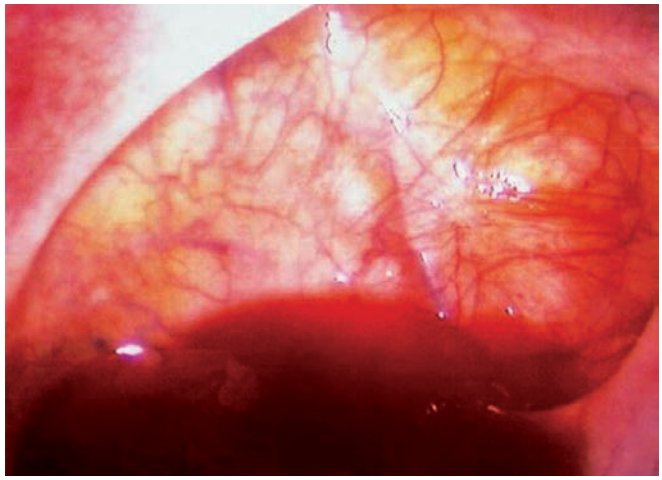


Fig. 23.5: Presence of blood in cul-de-sac

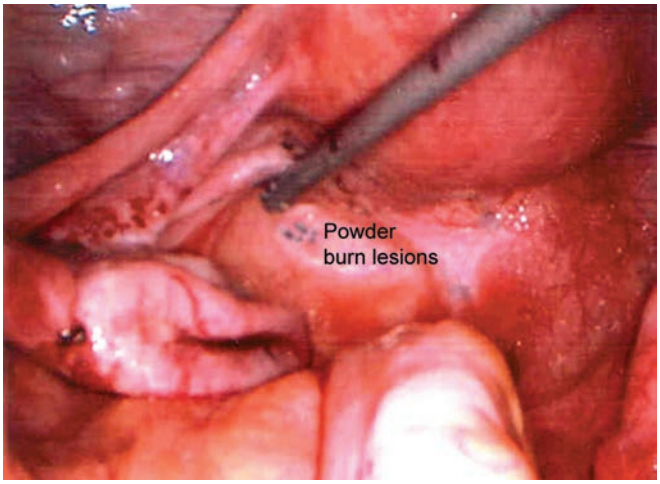


Fig. 23.3: Power burn lesions over endometrial surface

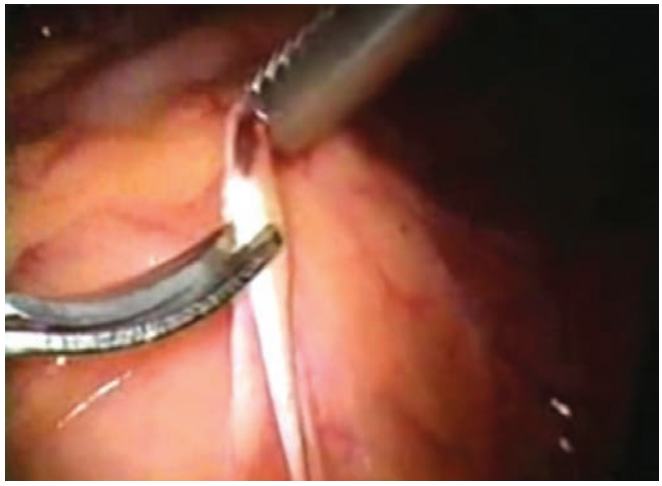


Fig. 23.6: Laparoscopic excision of nodular endometrial lesions overlying the round ligament

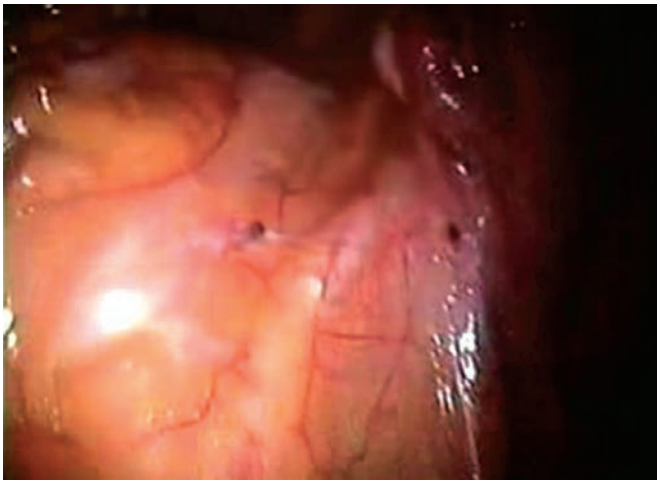


Fig. 23.4: Nodular endometrial lesions

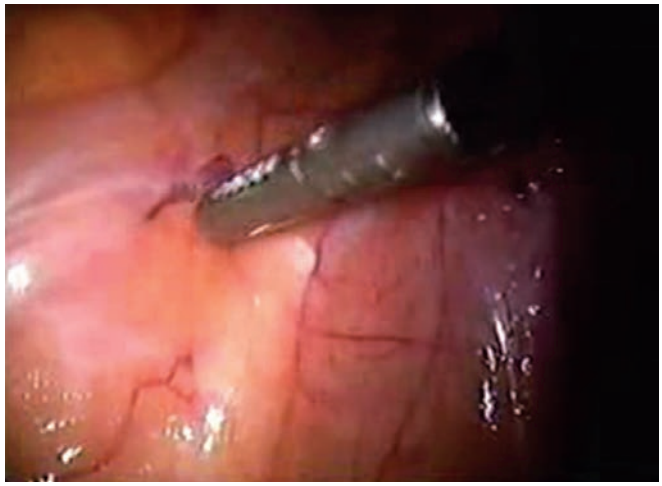


Fig. 23.7: Laparoscopic ablation of nodular endometrial lesions overlying the uterus

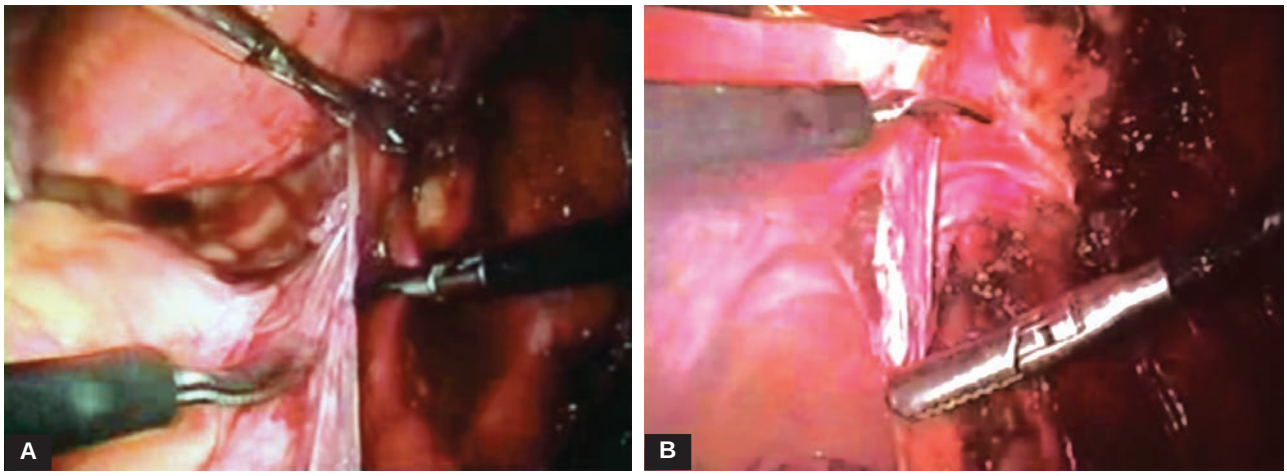


Fig. 23.8: Laparoscopic excision of endometrial adhesions

of adhesions (figures 23.8 A and B). Until recently, surgery in infertile patients with limited disease was thought to be no better than expectant management. However, according to the recent evidence, surgery has been found to significantly improve the fertility rates among infertile women with minimal or mild endometriosis. Infertile patients with documented endometriosis can also benefit from the same reproductive techniques such as superovulation, in vitro fertilization, etc.

The usefulness of conservative surgery for pain relief is unclear, but it appears that immediate postoperative efficacy is at least as high as that with medical treatment and long-term outcomes may be considerably higher. Since laparoscopy is much more expensive in comparison to the medical treatment, some physicians advocate that the overall costs can be reduced by making aggressive use of empiric medical treatment before surgery is considered. Definitive surgery, which includes hysterectomy and oophorectomy, is reserved for use in women with intractable pain who no longer desire pregnancy. Women who have undergone oophorectomy must be treated with estrogen replacement therapy in order to prevent the side effects related to premature menopause. When the diagnosis of endometriosis is made at laparoscopy, surgical ablation of the lesions is frequently performed.

Surgical treatment improves pregnancy rates and is the preferred initial treatment for infertility caused by endometriosis. Surgery also appears to provide better long-term pain relief than medical treatment. Bilateral oophorectomy and hysterectomy are treatment options for patients with intractable pain, if childbearing is no longer desired.

Conservative Surgery

The aim of conservative surgery is to destroy visible endometriotic implants and lyse peritubal and periovarian adhesions that are a source of pain and may interfere with ovum transport. The laparoscopic approach is the widely used method for conservative treatment of endometriosis. Ablation can be performed with laser or electrodiathermy. Ovarian endometriomas can be treated by drainage or cystectomy. Tubal flushing with oil-soluble media has been shown to improve pregnancy rates in women with endometriosis-associated infertility.

Presacral neurectomy may be used to relieve severe dysmenorrhea. The nerve bundles are transected at the level of the third sacral vertebra and the distal ends are ligated. Some authors advocate prophylactic ligation of the middle sacral artery and vein in order to prevent potential vascular injury. Constipation is a long-term adverse effect of this procedure.

Nodularity of the uterosacral ligaments may contribute to dyspareunia and low back pain. The transmission of neural pathways is via the Lee-Frankenhäuser plexus. Laparoscopic uterine nerve ablation (LUNA) is performed to interrupt the pain fibers. Potential complications of this procedure include uterine prolapse and pelvic denervation. A systematic review of trials of LUNA found no advantage in terms of pain relief when compared to placebo. However, when combined with laparoscopic ablation, LUNA significantly reduced pain attributed to endometriosis.

Semi-conservative Surgery

The indication for this type of surgery is mainly in women who have completed their childbearing, are too young to undergo surgical menopause and are debilitated by the symptoms. Such surgery involves hysterectomy and cytoreduction of pelvic endometriosis. Ovarian endometriosis can be removed surgically because the remaining functioning ovarian tissue which is left behind is sufficient for hormone production.

Radical Surgery

This involves total hysterectomy with bilateral oophorectomy and cytoreduction of visible endometriosis. Adhesiolysis is performed to restore mobility and normal intrapelvic organ relationships. Ureteric obstruction may warrant surgical release or excision of a damaged segment. Bowel resection and anastamosis may be required in cases of intestinal obstruction.

Important Questions and Answers

Q.1. What is the next step of management in the above mentioned case study?

Ans. In this patient, the history points towards the likelihood of endometriosis as the likely diagnosis. However, since the main complaint of the patient is infertility rather than chronic pelvic pain, she must undergo a thorough basic evaluation for other causes of infertility before diagnostic laparoscopy is undertaken.

Q.2. Explain the pathogenesis of endometriosis.

Ans. The exact pathogenetic mechanism of endometriosis is not yet clear. Endometriosis is not well understood and is probably multifactorial in origin. Some likely pathogenetic mechanisms for endometriosis are described below:

Retrograde menstruation

The most widely accepted theory for pathogenesis of endometriosis involves retrograde menstruation (figure 23.9). According to this theory, reflux of degenerated menstrual endometrium through the fallopian tubes occurs during menstrual cycles. This tissue subsequently gets implanted on the pelvic peritoneum and the surrounding structures and starts growing. These refluxed cells implant in the pelvis, bleed in response to cyclic hormonal stimulation and increase in size along with progression of symptoms at the time of menses. Although retrograde menstruation seems to be the most likely cause involved in the pathogenesis of endometriosis, this theory does not explain the full spectrum of the disease. For example, this theory is unable to expain the presence of endometrial implants at remote sites such as the lung, pleura, endocardium, etc.

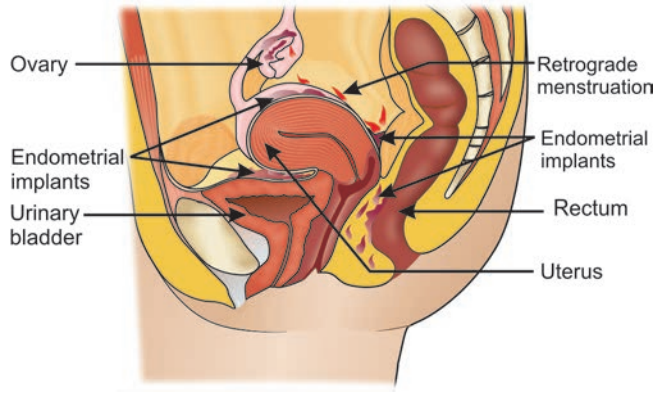


Fig. 23.9: Basic anatomy of retrograde menstruation

Theory of coelomic metaplasia

According to this theory, peritoneal epithelium can be "transformed" into endometrial tissue under the influence of some unknown stimulus. The possible stimulus could be the chronic inflammation or chemical irritation from refluxed menstrual blood. According to another theory, müllerian remnants can differentiate into endometrial tissue. Such transformation appears likely, because embryologically the müllerian ducts arise from these same tissues. Coelomic metaplasia is also believed to explain the occurrence of endometriosis in women who have undergone total hysterectomy and are not taking estrogen replacement.

Metastatic theory of lymphatic and vascular spread

Metastatic deposition of endometrial tissues at ectopic sites via lymphatic and vascular route has been postulated as another theory responsible for the pathogenesis of endometriosis. This pathway may explain the occurrence of endometriosis at distant, noncontiguous sites such as lung, pleura, etc. Ovarian endometriosis is also believed to be caused by lymphatic spread, although superficial ovarian endometriosis may also be due to implantation via retrograde menstruation.

Immunological defects

Immunological defects such as impaired activity of T cells and natural killer cells are believed to increase the susceptibility of a woman to endometriosis. Humoral antibodies to endometrial tissue have also been found in sera of women with endometriosis. The peritoneal fluid in women with endometriosis may show the presence of macrophages and natural killer cells.

Genetic factors

Familial tendency for endometriosis may be found in as many as 15% to 20% individuals with endometriosis.

Q.3. Describe the various lesions of endometriosis.

Ans. The common sites for the occurrence of endometriosis include the ovaries, the pouch of Douglas, uterosacral ligaments and serosal surface of the uterus, bladder, sigmoid colon, appendix, cecum, uterine scars, etc. The ovary is the most common site for endometriosis. Lesions can vary in size from spots to large endometriomas. The classic lesion is a chocolate cyst of the ovary that contains old blood that has

undergone hemolysis. On gross microscopic examination, the tunica albuginea appears to be thickened. Red vascular lesions may be well marked on the under surface of the ovary. Once intracystic pressure inside the chocolate cyst rises, the cyst perforates, spilling its contents within the peritoneal cavity. This can cause severe abdominal pain typically associated with endometriosis exacerbations. The inflammatory response may result in the development of adhesions which may further increase the disease related morbidity.

Endometriotic lesions can also involve the uterine serosa and the anterior surface of the bladder. Involvement of uterine serosa and formation of dense adhesions can lead to fixed retroversion of the uterus. Posteriorly, the disease may cause obliteration of the cul-de-sac and form dense adhesions between the posterior vaginal wall or cervix and the anterior rectum. This can be responsible for producing severe dyspareunia, dyschezia and alteration of bowel habits. Deep endometriotic nodules can also cause infiltration of the uterosacral ligaments and rectovaginal septum. Through contiguous spread, endometriosis may invade the rectovaginal septum and the anterior rectal wall. It may also involve the upper rectum and sigmoid colon, resulting in cyclical rectal bleeding (hematochezia). The ileum, appendix and cecum may also be involved, resulting in intestinal obstruction.

In the beginning, the endometriotic lesions appear as red colored, papular vesicles. With the passage of time, these lesions progressively change their appearance from dark red to bluish-black appearance. Scarring in the surrounding tissues may give it a puckered appearance. Old inactive lesions of endometriosis may appear as powder burnt areas.

Q.4. Can endometriosis be encountered in postmenopausal women?

Ans. Since the progression of endometriotic lesions appears to be dependent on the hormone estrogen, it appears likely that with the drop in estrogen level during menopause, these lesions would disappear. However endometriosis may sometimes be encountered in the women past their menopause. Postmenopausal endometriosis may be typically encountered in women who are on hormone (estrogen) replacement therapy (HRT).

Bibliography

1. ACOG Committee on Practice Bulletins-Gynecology. ACOG Practice Bulletin No. 51. Chronic pelvic pain. Obstet Gynecol. 2004;103(3):589-605.
2. American College of Obstetricians and Gynecologists. Endometriosis. ACOG technical bulletin no. 184. Washington, D.C.: ACOG. 1993.
3. Carter JE, Trotter JP. GnRH analogs in the treatment of endometriosis. Clinical and economic considerations. The Female Patient. 1995;20:13-20.
4. Chen FP, Chang SD, Chu KK, Soong YK. Comparison of laparoscopic presacral neurectomy and laparoscopic uterine nerve ablation for primary dysmenorrhea. J Reprod Med. 1996;41(7): 463-66.
5. Dmowski WP, Lesniewicz R, Rana N, Pepping P, Noursalehi M. Changing trends in the diagnosis of endometriosis: A comparative study of women with pelvic endometriosis presenting with chronic pelvic pain or infertility. Fertil Steril. 1997;67:238-43.
6. Eskenazi B, Warner M. Epidemiology of endometriosis. Obstet Gynecol Clin North Am. 1997; 24:235-58.
7. Foley KM, Posner J.B. Pain and its management. In: Cecil Textbook of medicine. 18th edition. W. B. Saunders Company. 1988;104-12.
8. Gambone JC, Mittman BS, Munro MG, Scialli AR, Winkel CA; Chronic Pelvic Pain/Endometriosis Working Group. Consensus statement for the management of chronic pelvic pain and endometriosis: Proceedings of an expert-panel consensus process. Fertil Steril. 2002;78(5):961-72.
9. Gambone JC, Reiter RC. Nonsurgical management of chronic pelvic pain: A multidisciplinary approach. Clin Obstet Gynecol. 1990;33:205-11.
10. Howard F. Evaluation of chronic pelvic pain in women. In: UpToDate, Rose, BD (Ed), Waltham, MA: UpToDate, 2007.
11. Howard FM. Chronic pelvic pain. Obstet Gynecol. 2003;101(3): 594-611.
12. Hull ME, Moghissi KS, Magyar DF, Hayes MF. Comparison of different treatment modalities of endometriosis in infertile women. Fertil Steril. 1987;47:40-44.
13. Kiesel L, Schweppe KW, Sillem M, Siebzehnrubl E. Should add-back therapy for endometriosis be deferred for optimal results? Br J Obstet Gynaecol. 1996;103(14 suppl):15-17.
14. Lu PY, Ory SJ. Endometriosis: Current management. Mayo Clin Proc. 1995;70:453-63.
15. Mahmood TA, Templeton A. The impact of treatment on the natural history of endometriosis. Hum Reprod. 1990;5:965-70.
16. Marcoux S, Maheux R, Berube S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. N Engl J Med. 1997;337:217-22.
17. Mathias JR, Ferguson KL, Clench MH. Debilitating "functional" bowel disease controlled by leuprolide acetate, gonadotropin-releasing hormone (GnRH) analog. Dig Dis Sci. 1989;34: 761-66.
18. Menses S, Simons DG. Muscle Pain: Understanding Its Nature, Diagnosis and Treatment. Baltimore, Lippincott Williams & Wilkins, 2001, pp. 121.
19. Merskey H, Bogduck N (Eds). Classification of Chronic Pain. Second edition. Washington, IASP Press. 1994.
20. Moen MH, Magnus P. The familial risk of endometriosis. Acta Obstet Gynecol Scand. 1993;72:560-64.
21. Moghissi KS. Add-back therapy in the treatment of endometriosis: The North American experience. Br J Obstet Gynaecol. 1996;103(14 suppl):14.
22. Mounsey AL, Wilgus A, Slawson DC. Diagnosis and management of endometriosis. Am Fam Physician. 2006;74(4): 594-600.
23. Olive D, Schwartz LB. Endometriosis. N Engl J Med. 1993;328: 1759-69.

24. Petta CA, Ferriani RA, Abrao MS, et al. Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis. Hum Reprod. 2005;20(7): 1993-98.
25. Prior A, Whorwell PJ. Gynaecological consultation in patients with the irritable bowel syndrome. Gut. 1989;30:996-98.
26. Quan M. Chronic pelvic pain. J Fam Prac. 1987;25:283-88.
27. Rapkin AJ. Adhesions and pelvic pain: a retrospective study. Obstet Gynecol. 1986;68:13-15.
28. Redwine DB. Conservative laparoscopic excision of endometriosis by sharp dissection: life table analysis of reoperation and persistent or recurrent disease. Fertil Steril. 1991;56:628-34.
29. Revised American Fertility Society classification of endometriosis. Fertil Steril. 1985;43:351-52.
30. Roseff SJ, Murphy AA. Laparoscopy in the diagnosis and therapy of chronic pelvic pain. Clin Obstet Gynecol. 1990;33: 137-43.
31. Royal College of Obstetricians and Gynaecologists. Guideline No. 41: The initial management of chronic pelvic pain. London, U.K.:RCOG;2005.
32. Selak V, Farquhar C, Prentice A, Singla A. Danazol for pelvic pain associated with endometriosis. Cochrane Database Syst Rev. 2001;(4):CD000068.
33. Siegel S, Paszkiewicz E, Kirkpatrick C, Hinkel B, Oleson K. Sacral nerve stimulation in patients with chronic intractable pelvic pain. J Urol. 2001;166(5):1742-45.
34. Stones RW, Mountfield J. Interventions for treating chronic pelvic pain in women. Cochrane Database Syst Rev. 2000;(4): CD000387.
35. Stovall DW, Bowser LM, Archer DF, Guzick DS. Endometriosis-associated pelvic pain: Evidence for an association between the stage of disease and a history of chronic pelvic pain. Fertil Steril. 1997;68:13-8.
36. Telimaa S, Ronnberg L, Kauppila A. Placebo-controlled comparison of danazol and highdose medroxyprogesterone acetate in the treatment of endometriosis after conservative surgery. Gynecol Endocrinol. 1987;1:363-71.
37. Vercellini P, Cortesi I, Crisgnani PG. Progestins for symptomatic endometriosis: A critical analysis of the evidence. Fertil Steril. 1997;68:393-401.
38. Viera AJ, Hoag S, Shaughnessy J. Management of irritable bowel syndrome. Am Fam Physician. 2002;66(10):1867-74.
39. Waller KG, Shaw RW. Gonadotropin-releasing hormone analogues for the treatment of endometriosis: Long-term followup. Fertil Steril. 1993;59:511-15.
40. Wood DP, Wiesner MG, Reiter RC. Psychogenic chronic pelvic pain: diagnosis and management. Clin Obstet Gynecol. 1990; 33:179-95.

Chapter

24

Abdominal Lump (Ovarian Cancer)

Case Study

A 60-year-old, para 3 woman presented to the gynecology OPD with the complaints of a lump in the abdomen, which has been increasing in size since past six months. There also has been anorexia, bloating sensation, vague pain in the left iliac fossa, fatigue, weakness and increased frequency of micturition since last one month. Patient has experienced severe weight loss of nearly 10 Kgs over past six months. There was no significant personal history or family history of cancers. The woman has been menopausal since last 10 years and never had any gynecological problems in the past. On per abdominal examination, a small mass of the size of a lemon was palpable in the left iliac fossa. The mass appeared fixed with restricted mobility. The abdomen was soft and non tender with no evidence of ascites. Vaginal examination revealed the presence of a solid, nodular, irregular shaped, fixed mass of size of a lemon arising from left ovary. An ultrasound examination revealed an ovarian mass of size 6 cm having mixed echogenicity, thick wall and papillary projections. CA 125 levels were performed which were found to be elevated (> 35 IU/L).

Introduction

There can be various causes for presence of an abdominal lump in a patient presenting to the gynecological OPD. Some of these causes are listed below in table 24.1.

Extrapelvic Masses

Of the various causes for the presence of abdominal mass listed above, cancer ovary as the cause for the presence of abdominal mass would be primarily discussed in this chapter. It is important for the gynecologist to detect the presence of ovarian malignancy at an early stage because detection of malignancy at an early stage is associated with a far better prognosis. If the malignancy is diagnosed at stage I, there is an almost 90% survival rate at 5 years; but if diagnosed at an advanced stage, as are most cases, the 5 year survival rate is <30%. Furthermore, ovarian malignancy often remains undetected due to its nonspecific presentation.

Table 24.1: Causes for an abdominal lump

Pelvic masses
Adenomyosis
Endometrial hyperplasia and cancer
Bladder cancer
Ovarian masses (benign and malignant)
Ectopic pregnancy
Uterine fibroids (especially pedunculated subserous fibroids
Extrapelvic masses
Distended bladder (hypogastric region)
Cholecystitis (right hypochondriac region)
Colon cancer (iliac, hypogastric and umbilical regions)
Bowel obstruction (iliac, hypogastric and umbilical regions)
Diverticulitis (iliac, hypogastric and umbilical regions)
Gallbladder tumor (right hypochondriac region)
Hydronephrosis (lumbar regions)
Cancer of the kidneys (lumbar regions)

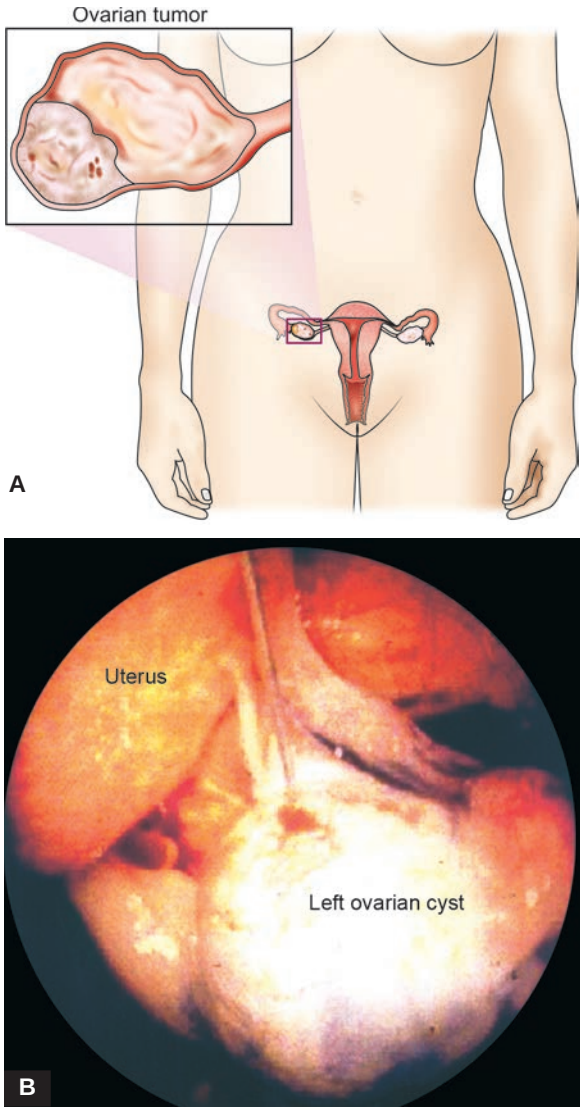
Ovarian Masses

Ovarian cysts are the most common ovarian masses encountered among women belonging to the reproductive age group. Ovarian cysts can be either neoplastic or nonneoplastic in nature (figures 24.1A and B). Ovarian neoplasms (tumors) can be benign or malignant in nature. Most ovarian tumors (80% to 85%) are benign and occur in the women between 20–44 years.

Nonneoplastic cysts of ovary are extremely common and can occur at any age (early reproductive age until perimenopause). These cysts are also known as functional cysts and include folicullar cysts, corpus luteum cysts and theca lutein cysts.

Functional cysts

These cysts develop due to accumulation of fluid in unruptured graafian follicles or follicles that have ruptured and sealed. Fluid accumulation in these follicles results in development of cysts. These cysts may be multiple and are usually small in size (1.1–1.5 cm). However, sometimes they can grow up to 3–4 cm in size. Spontaneous rupture of these cysts can cause pelvic pain and bleeding.



Figs 24.1A and B: (A) Ovarian tumor in right ovary (B) Cystic ovarian tumor in left ovary

All the functional cysts of the ovary are benign and usually do not cause any symptoms or require surgical management. Follicular cyst is the most common functional cyst of the ovary, which rarely becomes larger than 7–8 cm in size. Corpus luteum cysts are less common than follicular cysts. Luteal cysts tend to have thicker wall in comparison to the follicular cysts. Corpus luteum cysts may sometimes rupture, resulting in the development of hemoperitonium and requiring surgical treatment. Theca lutein cysts are the least common of the functional ovarian cysts. They may be associated with multiple gestations, diabetes, Rh isoimmunization or ovulation induction by use of clomiphine citrate, hCG, hMG or GnRH analogues. Theca lutein cysts may be quite large (up to 30 cm), are mulicystic and regress spontaneously. Most follicular ovarian masses resolve spontaneously in 4–8 weeks. Persistence of an ovarian lesion for more than 6–12 weeks is an important sign indicating the presence of neoplastic ovarian masses.

Neoplastic growths of the ovary can be either benign or malignant in nature. Histological classification of neoplastic ovarian growths is shown in table 24.2.

TYPES OF OVARIAN NEOPLASTIC GROWTH

Ovarian cancer is the fourth most common cancer in women (after breast, lung and bowel). Ovarian cancer is the most common in women over 50 and the highest rates occur in women over 65. Human ovarian tumors are divided into three major categories, which are named according to their histological patterns and directions of differentiation: Epithelial tumors; sex cord-stromal tumors; and germ cell tumors. Most ovarian cancers (approximately two thirds) are of epithelial type, which originate from the coelomic epithelium or mesothelium of the ovary.

Epithelial Tumors

Epithelial tumors are of the following histopathological types:

- Serous tumors which are similar to the epithelium of fallopian tube (most common subtype);
- Mucinous tumors which are similar to the endocervical mucosa;
- Endometrial tumors which are similar to the endometrium,
- Clear cell (mesonephroid) tumors
- Brenner tumors which contain cells similar to the transitional epithelium of the bladder.

The WHO classification of different types of the epithelial tumors has been detailed in table 24.2. Most malignant ovarian cancers are derived from the surface epithelium of the ovary. Serous and mucinous cystadenocarcinomas are the most common types of invasive epithelial ovarian cancers accounting for nearly 65% to 70% of cases. Nonepithelial ovarian cancer (e.g. germ cell tumors such as ovarian teratomas and sarcomas) are much less common. Germ cell tumors usually affect younger women and tend to behave very differently from other types of ovarian cancer. While germ cell tumors may account for 15% to 20% cases of malignant ovarian tumors, sex cord stromal tumors account for 5% to 10% cases. Metastatic ovarian cancer arising from nonovarian primary may account for further 5% of the cases.

As mentioned in table 24.2, ovarian tumors could be either benign, malignant or have a borderline potential. Benign growths are noncancerous whereas malignant growths are cancerous. The borderline ovarian tumors are a group of tumors with low malignant potential lying in between the

Table 24.2: Histological classification of neoplastic ovarian growths

I. Common epithelial tumors

A. *Serous Tumors*
1. Benign
   a. Cystadenoma and papillary cystadenoma
   b. Surface papilloma
   c. Adenofibroma and cystadenofibroma
2. Of borderline malignancy (carcinomas of low malignant potential)
   a. Cystadenoma and papillary cystadenoma
   b. Surface papilloma
   c. Adenofibroma and cystadenofibroma
3. Malignant
   a. Adenocarcinoma, papillary adenocarcinoma and papillary cystadenocarcinoma
   b. Surface papillary carcinoma
   c. Malignant adenofibroma and cystadenofibroma

B. *Mucinous Tumors*
1. Benign
   a. Cystadenoma
   b. Adenofibroma and cystadenofibroma
2. Of borderline malignancy (carcinomas of low malignant potential)
   a. Cystadenoma
   b. Adenofibroma and cystadenofibroma
3. Malignant
   a. Adenocarcinoma and cystadenocarcinoma
   b. Malignant adenofibroma and cystadenofibroma

C. *Endometrioid Tumors*
1. Benign
   a. Adenoma and cystadenoma
   b. Adenofibroma and cystadenofibroma
2. Of borderline malignancy (carcinomas of low malignant potential)
   a. Adenoma and cystadenoma
   b. Adenofibroma and cystadenofibroma
3. Malignant
   a. Carcinoma
      i. Adenocarcnoma
      ii. Adenoacanthoma
      iii. Malignant adenofibroma and cystadenofibroma
   b. Endometrioid stromal sarcomas
   c. Mesodermal (müllerian) mixed tumors, homologous and heterologous

D. *Clear Cell (Mesonephroid) Tumors*
1. Benign
2. Of borderline malignancy (carcinomas of low malignant potential)
3. Malignant: Carcinoma and adenocarcinoma

Table contd...

Table contd...

E. *Brenner Tumors*
1. Benign
2. Of borderline malignancy (proliferating)
3. Malignant

F. *Mixed Epithelial Tumors*
1. Benign
2. Of borderline malignancy
3. Malignant

G. *Undifferentiated Carcinoma*

H. *Unclassified Epithelial Tumors*

II. Sex cord stromal tumors

A. *Granulosa-Stromal Cell Tumors*
1. Granulosa cell tumor
2. Tumors in the thecoma-fibroma group
   a. Thecoma
   b. Fibroma
   c. Unclassified

B. *Androblastomas, Sertoli-Leydig Cell Tumors*
1. Well-differentiated
   a. Tubular androblastoma, Sertoli cell tumor (tubular adenoma of Pick)
   b. Tubular androblastoma with lipid storage, Sertoli cell tumor with lipid storage (folliculome lipidique of Lecene)
   c. Sertoli-Leydig cell tumor (tubular adenoma with Leydig cells)
   d. Leydig cell tumor, hilus cell tumor
2. Of intermediate differentiation
3. Poorly differentiated (sarcomatoid)
4. With heterologous elements

C. *Gynandroblastoma*

D. *Unclassified*

III. Germ cell tumors

A. Dysgerminoma

B. Endodermal Sinus Tumor

C. Embryonal Carcinoma

D. Polyembryoma

E. Choriocarcinoma

F. Teratomas
1. Immature
2. Mature
   a. Solid
   b. Cystic
      i. Dermoid cyst (mature cystic teratoma)
      ii. Dermoid cyst with malignant transformation
3. Monodermal and highly specialized
   a. Struma ovarii
   b. Carcinoid

Table contd...

Table contd...

c. Struma ovarii and carcinoid
d. Others
G. Mixed Forms
IV. Lipid (Lipoid) cell tumors
V. Gonadoblastoma
A. Pure
B. Mixed with Dysgerminoma or Other Form of Germ Cell Tumor
VI. Soft tissue tumors not specific to ovary
VII. Unclassified tumors
VIII. Secondary (Metastatic) tumors
IX. Tumor like conditions
A. Pregnancy Luteoma
B. Hyperplasia of Ovarian Stroma and Hyperthecosis
C. Massive Edema
D. Solitary Follicle Cyst and Corpus Luteum Cyst
E. Multiple Follicle Cysts (Polycystic Ovaries)
F. Multiple Luteinized Follicle Cysts and/or Corpora Lutea
G. Endometriosis
H. Surface-Epithelial Inclusion Cysts (Germinal Inclusion Cysts)
I. Simple Cysts
J. Inflammatory Lesions
K. Parovarian Cysts

24

benign and malignant tumors. These tumors usually occur at an earlier age (i.e. 30–50 years) in comparison to the invasive ovarian malignancy which occurs in older women between the age of 50 and 70 years. While borderline tumors remain confined to the ovary for a long period of time, they can also metastasize. Nearly 20% to 25% of borderline malignant tumors may spread beyond the ovary. The criteria for the diagnosis of borderline tumors are as follows:

- Epithelial proliferation with papillary formation and pseudostratification
- Nuclear atypia and increased mitotic activity
- Absence of true stromal invasion (i.e. without any tissue destruction)

Serous tumors

Serous cysadenomas and cystadenocarcinomas are amongst the commonest cystic ovarian neoplasms accounting for nearly 50% of all the ovarian neoplasms. Out of these, 60% to 70% are benign, whereas 20% to 25% are malignant. These tumors are characterized by the presence of papillary excrescences both on the surface and within the loculi. In case of the carcinoma, the papillary excrescences are coarse and friable and may spread to the peritoneal surface. The benign tumors may contain straw-colored fluid, while this fluid may be blood stained in case of malignant tumors.

Mucinous tumors

Mucinous tumors are multiloculated which commonly contain loculi filled with mucinous contents. If the tumor ruptures, it may result in the formation of pseudomyxoma peritonei.

Sex Cord-Stromal Cell Tumors

All ovarian tumors in this category are derived from the sex cord and stromal components of the developing gonad. In a normal woman, the embryonic sex cords develop into the sertoli cells in the testis and granulosa cells in the ovary. On the other hand, the stroma or mesenchyme develops into the leydig cells of the testis and the theca and corpus lutein cells of the ovary. As a result, the sex cord stromal tumors in the ovary may contain one or more of different types of cells: Granulosa cells, theca cells, lutein cells, sertoli cells, leydig cells and fibroblasts, in varying combinations. The most common tumors in this category are the fibromas, which are composed entirely of fibroblasts. Next in frequency is the granulosa cell tumor, generally an estrogenic neoplasm, followed by thecomas.

Fibromas

These tumors are relatively common (4% of all ovarian tumors) and are unilateral in 90% cases. These are solid, spherical, encapsulated, grayish-white, well differentiated lesions. These tumors are composed of well differentiated fibroblasts. As the name suggests, the fibroma has a firm consistency and is composed of a network of spindle shaped cells. Ovarian fibromas greater than 6 cm in size may be associated with ascites and right sided hydrothorax in nearly 40% cases. This is also known as Meig's syndrome. Meig's syndrome may also be associated with other solid ovarian tumors such as granulosa cell tumors and Brenner's tumors.

Granulosa cell tumors

These tumors can occur at any age and are composed of cells which are identical to the granulosa cells of the graafian follicle. Functionally active granulosa cell tumors are responsible for producing estrogen. This can cause precocious sexual development in young girls. In adult women, this can cause endometrial hyperplasia, fibrocystic disease of the breast, endometrial carcinoma, etc. In postmenopausal women, this tumor can cause postmenopausal bleeding. There is strong evidence that feminizing tumors of the ovary are associated with carcinoma endometrium in postmenopausal women. The histopathological examination may show the presence

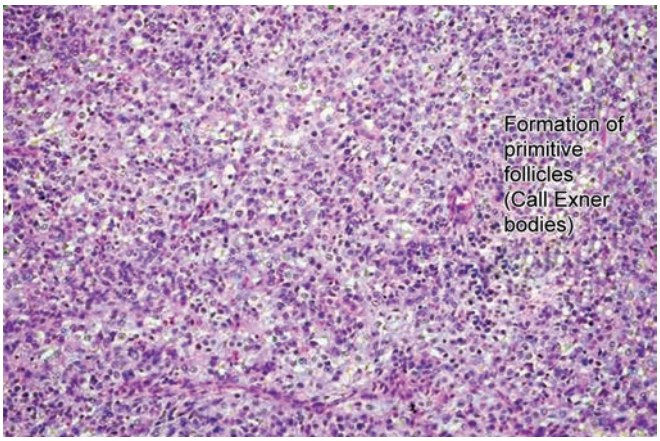


Fig. 24.2: Histopathological pattern of granulosa cell tumor

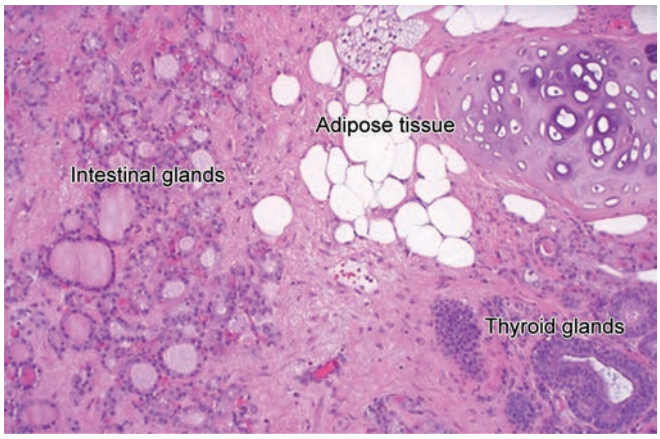


Fig. 24.3: Histological picture of a mature teratoma showing adipose tissue and intestinal glands at the right and thyroid tissue on the left.

of Call Exner bodies which can be considered as primitive follicles comprising of granulosa cells arranged haphazardly around a space containing eosinophilic fluid (figure 24.2). The anaplastic type of granulosa cell tumor is associated with nearly 65% chances of malignancy.

Germ Cell Tumors

Germ cell tumors arise from totipotent germ cells. Germ cell tumors tend to affect only one ovary and most are curable even if they are diagnosed at an advanced stage. Different types of germ cell tumors include the following:

Teratomas

Ovarian teratomas are a complex group of tumors that are subdivided into three major categories: Immature, mature, and monodermal and highly specialized. The majority of germ cell tumors are benign cystic teratomas, also known as dermoids.

Immature teratomas

Immature teratomas primarily contain immature tissues, most commonly of neuroectodermal origin. However, they may sometimes also contain varying quantities of mature tissue as well. Immature teratomas are essentially malignant.

Mature teratomas

Unlike the immature teratomas, the mature teratomas are exclusively composed of mature tissues (figure 24.3). Mature teratomas could be either solid or cystic (dermoid cysts). In most cases, the tumor contains elements derived from all three germ layers. The dermoid cysts are benign ovarian masses, which may appear as masses having various sonographic appearances ranging from anechoic to echogenic due to variety of internal contents. The solid areas may be due to the presence of hair follicles in combination with the calcified elements within dermoid. These materials are responsible for producing echogenicity within the cyst. These cysts may contain hair, which because of its high echodensity may produce a typical acoustic shadow. Other types of tissues which may be present include teeth, bone, cartilage, thyroid tissues, bronchial tissues and sebaceous material. Though dermoid cysts are usually benign in nature, epidermoid carcinoma may occur in approximately 2% of cases.

Monodermal tumors

The best known monodermal and highly differentiated teratoma of the ovary is the struma ovarii, which is also known as the thyroid tumor of the ovary and is composed entirely of the thyroid tissue. Another common monodermal tumor of the ovary is carcinoid tumor.

Dysgerminoma

These germ cell tumors are the female homologue of the testicular seminoma. Dysgerminomas are usually malignant and commonly affect both the ovaries. This tumor is more common in women in their twenties. The tumor has a typical elastic, rubbery consistency and has a firm smooth capsule. The cut surface of the tumor is yellowish-grayish with areas of degeneration and hemorrhage. Though the tumor does not secrete any hormones, it can secrete tumor markers such as lactate dehydrogenase (LDH), placental alkaline phosphatase and β hCG. Chemotherapy comprises of intravenous bleomycin, etoposide and cisplatin.

Yolk sac tumors

One of the most highly malignant forms of primitive germ cell tumor is the endodermal sinus tumor or yolk sac tumor, which summarizes yolk sac development. This tumor

characteristically contains papillary units termed as Schiller-Duval bodies. These are composed of papillary projections surrounding the central blood vessels protruding into a network of spaces lined by primitive neoplastic cells. Yolk sac tumors characteristically produce α-fetoprotein, which can be detected in the patient's serum.

History

RISK FACTORS FOR OVARIAN CANCER

Each year, about 6,600 women in the UK are diagnosed with ovarian cancer. The causes responsible for development of ovarian cancer are not yet completely understood. Some factors are known to affect a woman's chance of developing ovarian cancer – these need to be elicited at the time of taking history and are described below:

Age

Ovarian cancer is more common in the women belonging to the age group between 50–70 years, with the peak incidence of the disease occurring at the age of 62 years. The risk of developing ovarian cancer is very low in young women and increases as women get older. Over eight out of ten (85%) ovarian cancers occur in women over the age of 50.

Personal history of cancer

Women who have previously had cancer of the breast, uterus, colon, or rectum are at a higher risk of developing ovarian cancer in future.

Lifestyle factors

Body mass index: Having an increased body mass index (overweight or obese) is associated with an increased risk of developing ovarian cancer. However, future research is required to significantly prove this fact.
Diet: Eating a diet high in animal fats and low in fresh fruit and vegetables may increase the woman's risk of developing ovarian cancer.

Family history

Genetic history: BRCA-1, a gene locus on chromosome 17 has been found to be associated with breast/ovarian cancers.

Women who have a mother, daughter, or sister with ovarian cancer are at an increased risk of developing the disease. This risk is even higher in women who have two or more first-degree relatives with ovarian cancer. Hereditary ovarian cancers tend to occur in women who are about 10 years younger in comparison to those with nonhereditary tumors. Also, women with a family history of cancer of the breast, uterus, colon, or rectum may have an increased risk of developing ovarian cancer. Two syndromes which are associated with a high risk of ovarian cancer include breast/ovarian cancer syndrome and the Lynch II syndrome. Breast/ovarian familial cancer syndrome may exist in a family, in which there is a combination of epithelial ovarian and breast cancer, affecting a mixture of first and second degree relatives. Women with this syndrome tend to develop these tumors at young age. Lynch II syndrome is associated with a high occurrence of ovarian malignancies in patients with hereditary non-polyposis coli. Nearly 5% to 10% cases of ovarian cancers may be caused by an inherited genetic defect. Prophylactic oophorectomy may be considered in some women who are an increased risk of developing ovarian cancer.

Menstrual and obstetric history

- Patients with a history of early menarche and late menopause are associated with an increased risk for ovarian cancer.
- Women with a history of nulliparity or low parity are at an increased risk for development of ovarian cancer. On the other hand, women who have had children in the past or breast feed their babies are at a reduced risk. Multiparity acts as a protective factor in the development of ovarian cancers. Breast feeding the children may also act as a protective factor against development of cancer.
- Women with endometriosis are at an increased risk of developing ovarian cancer.
- *Infertility and fertility treatments:* Presently it is not clear if the risk of ovarian cancer is increased by taking treatment with ovulation inducing drugs for infertility, or undergoing hormone replacement therapy. More research would be required in future to find out whether the risk of ovarian cancer is increased by these above mentioned factors.
- *Menopausal hormone replacement therapy (HRT):* Some studies have shown that women who take unopposed estrogen in form of HRT for 10 or more years may be at an increased risk of developing ovarian cancer. However, when HRT is stopped, the risk of ovarian cancer gradually reduces to the level similar to the women who haven't taken HRT.
- *Oral contraceptive pills*: Women taking the contraceptive pill are at a reduced risk of developing ovarian cancer.

History of menstrual cycles

It is important to take the history regarding the menstrual cycles in the woman because ovarian tumors, even bilateral do not affect the menstrual cycles. The only tumors causing

menorrhagia are granulosa cell tumors and theca cell tumors because both these types of ovarian tumors are associated with increased estrogen secretion. On the other hand, masculinizing tumors may cause amenorrhea and virilization. Post-menopausal bleeding may occur in cases of benign Brenner tumors and feminizing tumors of the ovary.

SYMPTOMS OF OVARIAN CANCER

Most women with early-stage cancer of the ovary don't have any symptoms for a long time. This is an important cause for late diagnosis of ovarian cancer. A few symptoms which do develop are quite nonspecific and may be indicative of other gastrointestinal pathologies. Some of the symptoms which could be suggestive of ovarian cancer and need to be elicited while taking the history include the following:

- Abdominal bloating/distension: Quite often ovarian malignancy may present as a large intraabdominal mass and ascites. Both these could be responsible for producing abdominal distension and bloating.
- Pelvic or abdominal pain or dyspareunia
- Loss of appetite or early satiety
- Pressure symptoms, such as increased urinary urgency and frequency could result due to an ovarian tumor placed in the uterovesical pouch. On the other hand, a tumor impacted in the Pouch of Douglas may cause constipation.
- Nausea, vague indigestion, constipation or diarrhea.
- Feeling of tiredness, unexplained loss of weight, anemia and cachexia.
- Rapidly increasing abdominal swelling and dyspnea due to development of ascitis.
- Pain: Normally the benign ovarian tumors cause no abdominal pain and are comfortably placed in the abdominal cavity which is distensible. Large intraabdominal tumors on the other hand, may cause abdominal discomfort and difficulty in walking. Acute abdominal pain may develop if the ovarian tumor undergoes torsion, rupture or hemorrhage. If the tumor undergoes torsion, the woman may develop acute abdominal pain, vomiting and at times low grade fever.
- Rarely there may be abnormal vaginal bleeding (postmenopausal bleeding or menorrhagia). Presence of estrogen secreting granulosa cell tumors may produce menometrorrhagia and episodes of DUB.
- Presence of ascites, omental metastases or bowl metastases in the late stages of the disease may produce symptoms such as abdominal distension, bloating, constipation, nausea, early satiety, etc.
- Presence of lump in the abdomen: This could be related to the presence of ovarian malignancy per se or development of omental cake due to infiltration of the omentum by malignant cells.

General Physical Examination

Findings on general physical examination such as anemia, unexplained weight loss, unilateral non-pitting edema of the leg, pleural effusion and hepatic enlargement are suggestive of advanced stage of the malignant disease. The lymph nodes must be palpated because they (especially the supraclavicular nodes) could often be enlarged in presence of malignancy.

Specific Systemic Examination

ABDOMINAL EXAMINATION

Abdominal examination of the swelling

The typical ovarian cyst forms an abdominal swelling which is detected on inspection. The method of examination of an intraabdominal swelling has been detailed in chapter 16. The movement of abdominal wall over the swelling can be observed when the patient takes a deep inspiration. On abdominal palpation, the upper and lateral limits of the tumor can be defined. However in most of the cases it is impossible to identify the lower pole of the tumor except in case of a small cyst with a long pedicle. The surface of the ovarian tumor is smooth although it may be slightly bossed with multilocular cysts. Small cysts are generally movable from side to side, but large, especially the malignant ones may be fixed. The consistency of the cystic tumor is tense and cystic and a fluid thrill can be elicited. All patients with a possible ovarian cyst should be examined carefully for the presence of ascites because the presence of the ascites is a strong indicator that the tumor is malignant. In some cases even benign tumors may be associated with ascites, e.g. Meigs syndrome associated with fibroma, brenner tumor and occasionally granulosa cell tumor.

Ascites

Abdominal distension due to ascites is a common feature associated with malignant ovarian growth. In most of the cases, ascites can be differentiated from large ovarian growths on abdominal examination (chapter 16). With a large ovarian cyst, the percussion note over the tumor is dull, where as both the flanks are resonant. In cases of ascites, the note is dull over the flanks, while the abdomen in the midline is resonant. The physical signs of shifting dullness and fluid thrill may be obtained. A sample of ascitic fluid must be taken to look for malignant cells.

PELVIC EXAMINATION

Detailed description of pelvic examination has been done in chapter 16. Pelvic examination helps in assessment of the adnexa for presence of any lumps or mass. The most important sign of an ovarian tumor is presence of pelvic mass on physical examination**.** Presence of a solid, irregular, fixed pelvic mass is highly suggestive of an ovarian malignancy. In addition, if there is presence of an upper abdominal mass or ascites, the diagnosis of ovarian cancer is almost certain. As a general rule, under normal circumstances ovaries must become non palpable in women who are at least one year past menopause. Presence of any palpable pelvic mass in these patients should arouse the suspicion of malignancy. The method of conducting pelvic examination has been described in details in chapter 16. The physical signs on bimanual examination vary according to the size of the ovarian tumor. With small tumors, the uterus can be palpated without difficulty and the ovarian mass be outlined bimanually. A large ovarian cyst usually displaces the uterus to the opposite side and it may get difficult to outline the uterus with larger sized cysts. Even with a large cyst, the lower pole of the tumor should be palpable through one of the fornices. The lower pole of the ovary appears firm and rounded in appearance with a characteristic feel and fluctuations can usually be obtained between the finger placed in the vagina and external hand. The ovarian mass needs to be differentiated from uterine mass on bimanual examination. The cardinal sign which helps in distinguishing a mobile ovarian tumor from a uterine tumor is that when the ovarian tumor is raised up by the abdominal hand, the cervix remains stationary to the vaginal fingers. However, in case of a mass of uterine origin, rising up of tumor by abdominal hand results in simultaneous movement of the vaginal fornices. In all cases, the pouch of Douglas should be examined carefully for presence of any nodules. The vaginal examination may reveal fixed nodules in the pouch of Douglas. A common site for metastasis is the pouch of Douglas and these deposits are often palpable on vaginal examination. Presence of hard nodules in the POD is a strong indicator of malignancy.

Differential Diagnosis

Different types of ovarian tumors have been described earlier in the text. Various other common causes of abdominal lump which need to be excluded before establishing the correct diagnosis of an ovarian tumor are enumerated in table 24.1 at the beginning of the chapter.

Myomas, especially peduculated uterine leiomyomas can commonly result in an abdominal lump. The myoma can be differentiated from ovarian cyst based on clinical examination. A myoma is usually hard and firm, whereas a typical ovarian cyst has a cystic consistency.

Management

Management for ovarian cancer includes taking history, conducting physical examination and evaluation of serum CA-125 levels in combination with imaging (ultrasound, MRI and CT). Neither imaging results nor CA-125 levels alone are sufficiently accurate in diagnosing ovarian cancer. The staging of ovarian cancer is done on exploratory laparotomy.

Investigations

Blood Tests

The following blood tests can be done:

- CBC with platelet count
- Kidney and liver function tests
- CA 125 test

CA 125 levels

CA 125 is a surface glycoprotein found on the surface of ovarian cancer cells and on some normal tissues. A high CA 125 level could be a sign of cancer or other conditions. The CA 125 test should not be used as a stand alone test to diagnose ovarian cancer. This test is approved by the Food and Drug Administration for monitoring a woman's response to ovarian cancer treatment and for detecting its return after treatment. Values of CA 125 greater than 35 IU/ml are found in over 80% of cases with nonmucinous epithelial ovarian cancers. Estimation of CA 125 levels is associated with low specificity because it can also be raised in presence of benign conditions like endometriosis, tuberculosis, leiomyomas, liver or kidney disease, pelvic inflammatory disease, etc. In case of premenopausal women, if the adnexal mass does not show any feature of malignancy (i.e. the mass is freely mobile, cystic in consistency and of regular contour) a period of observation of no more than two months can be allowed during which hormonal suppression with oral contraceptive pills can be used. A benign mass would regress, while a malignant mass would be persistent and mandates surgical removal.

Imaging Studies

Ultrasound

Ultrasonography, (both transabdominal and transvaginal) is accurate in differentiating tumors of the ovary from other types of tumors of the pelvis, in more than 90% of the patients

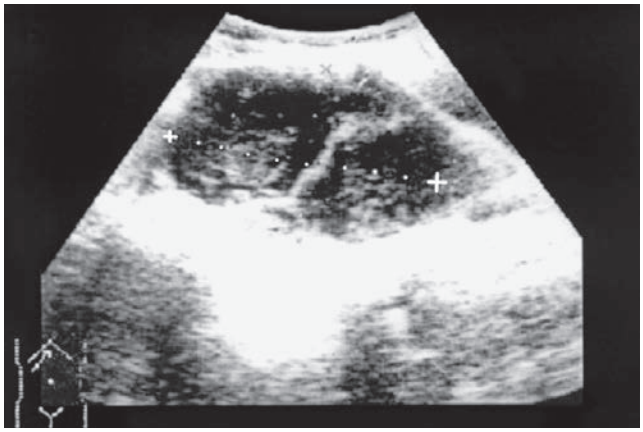


Fig. 24.4: TAS showing a multiloculated mass with presence of cystic areas along with a few brightly echogenic areas. Differential diagnosis of mucinous cystadenoma and dermoid cyst were established

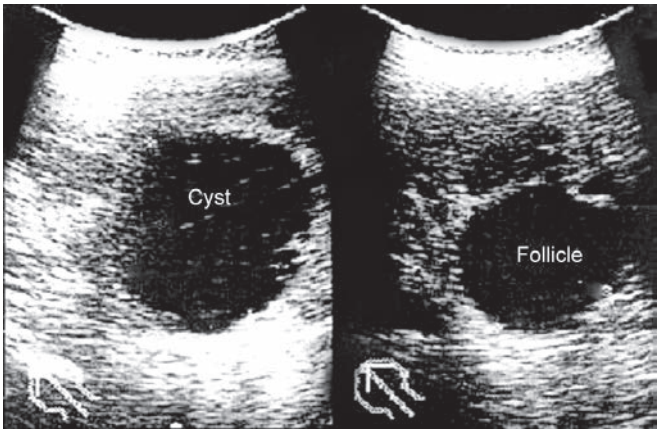


Fig. 24.7: TVS revealing the presence of an ovarian cyst (with multiple internal echoes) on the right side. On the left side the ovary is normal with presence of a dominant follicle

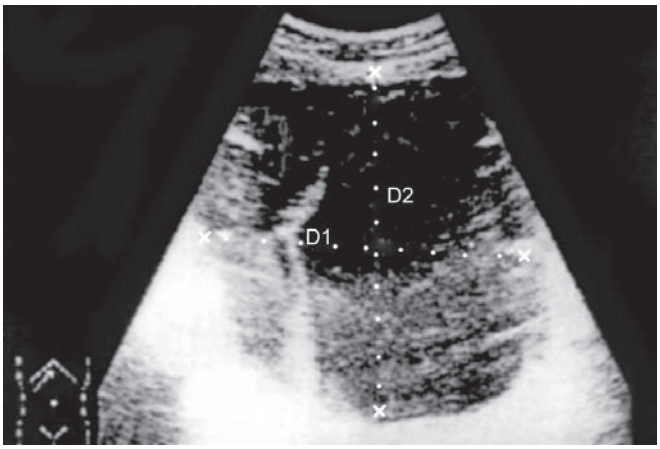


Fig. 24.5: TAS showing presence of a large thin walled cyst of right ovarian origin with multiple septa and numerous internal echoes

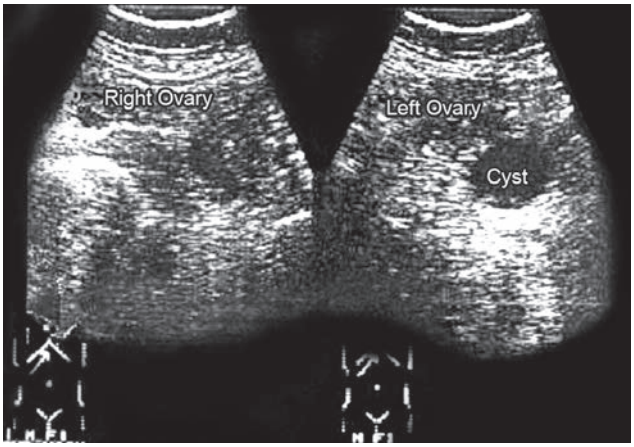


Fig. 24.8: TAS revealing a presence of a small functional cyst in the left ovary

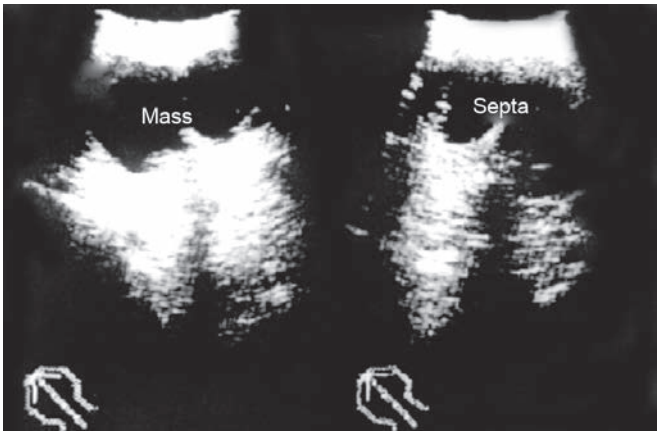


Fig. 24.6: TVS showing presence of a single cystic mass with septa arising from left adnexa

(figures 24.4 to 24.8). Discrimination between benign and malignant lesions of the ovary can be made on the basis of ultrasonic patterns. Anechoic lesions have a high likelihood of being benign. As the percentage of echogenic material in the cysts increases, the likelihood of malignancy also increases. However, there are two exceptions to this rule. The first is lesion with high echogenic foci, which are virtually always benign i.e. teratomas. Highly echogenic focus corresponds to the fat and hair, which fills many of these teratomas. The second is a group of tumors that are totally or near totally echogenic. These are less likely to be malignant in comparison to mixed density tumors that have a large percentage of anechoic component. Though sonography cannot rule out malignancy, anechoic or almost anechoic lesions have a high likelihood of being benign. In general, benign lesions

are likely to be unilateral, unilocular and thin walled with no papillae or solid areas. Septae, if present in benign masses are also thin. In contrast, malignant lesions are often multilocular with thick walls, thick septae and mixed echogenicity due to the presence of solid areas. Doppler flow studies of the ovarian artery may also help in differentiating between benign and malignant growths. Normally a high resistance pattern (resistive index >0.70) is indicative of benign growth. In malignant tumors due to increased blood supply, the resistance index is usually low (< 0.4) and there is a high peak velocity. Other signs suggestive of malignancy include presence of irregular solid parts within the mass, indefinite margins, papillary projections extending from inner wall of the cyst, presence of ascites, hydronephrosis, pleural effusion, matted bowel loops, omental implants, other evidence of peritoneal disseminated disease and lymphadenopathy. Size of tumor may also give clues regarding the nature of the mass. Larger tumors, usually greater than 8 cm in size have been thought to be associated with higher risk of malignancy in comparison to the smaller ones. Sonographic diagnosis of a malignant tumor necessitates further evaluation (e.g. computed tomography or MRI). If these investigations also suggest ovarian cancer, then the best approach is laparotomy for staging and treatment.

It takes 3–5 years after the menopause for the ovaries to atrophy. As previously mentioned, in postmenopausal women ovaries must not be palpable. There is no such thing as physiologic enlargement of the postmenopausal ovary. Since there are no follicles or corpus luteum in postmenopausal ovary, no such cysts can arise. Therefore, palpable ovary in postmenopausal women must be considered as a significant finding. The patient without delay should be subjected to an expedited examination under anesthesia. In cases of positive findings during this examination, the findings should be confirmed on laparotomy. The ovaries should be removed without a biopsy in postmenopausal woman. Until recently it was a standard practice to perform exploratory laparotomy for any ovarian mass larger than 5 to 7 cm in the reproductive age group and any palpable ovary in the postmenopausal subjects. However, now with the availability of advanced imaging technologies such as TVS, CT and MRI, diagnosis can be accurately established upon imaging in most of the instances.

In postmenopausal women, it is suggested that anechoic or near anechoic cystic lesions in postmenopausal women should be rescanned in a month. If internal echoes or increase in size is apparent, or if the lesions persist for several months, further evaluation for malignancy would appear as a wise precaution.

Evaluation of adnexal lesion observed on ultrasound imaging studies

An algorithm illustrating the use of imaging for the evaluation of ovarian masses is shown in flow chart 24.1. An ovarian mass observed on ultrasound examination, does not require further imaging characterization if it is obviously malignant, e.g. presence of concurrent omental implants, other evidence of peritoneal disseminated disease, lymphadenopathy, pleural effusion, hydronephrosis, etc. Also, simple unilocular cysts less than 5-6 cm in size, with no solid components in a premenopausal woman, are likely benign and do not require further imaging. Simple cysts that are larger may warrant additional imaging during the future follow up visit to document whether these cysts have undergone resolution. This is particularly important because such cysts can undergo torsion and may need to be removed surgically if they persist. On the other hand, lesions found in postmenopausal women and those that have solid components on ultrasound examination require further evaluation, usually within 6 weeks. The investigations which need to be done include ultrasound or MRI examination and CA 125 levels.

Computed tomography

CT scan is a useful investigation for observing the size of tumor, invasion of other organs (kidneys, bladder, intestines, peritoneum and omentum) by the tumor mass, lymph node enlargement and presence of ascites. A CT-guided biopsy may also be performed.

Barium enema

This is a test to see whether the cancer has invaded the colon or rectum. Nowadays, barium enema has been largely replaced by colonoscopy in order to assess the colonic invasion.

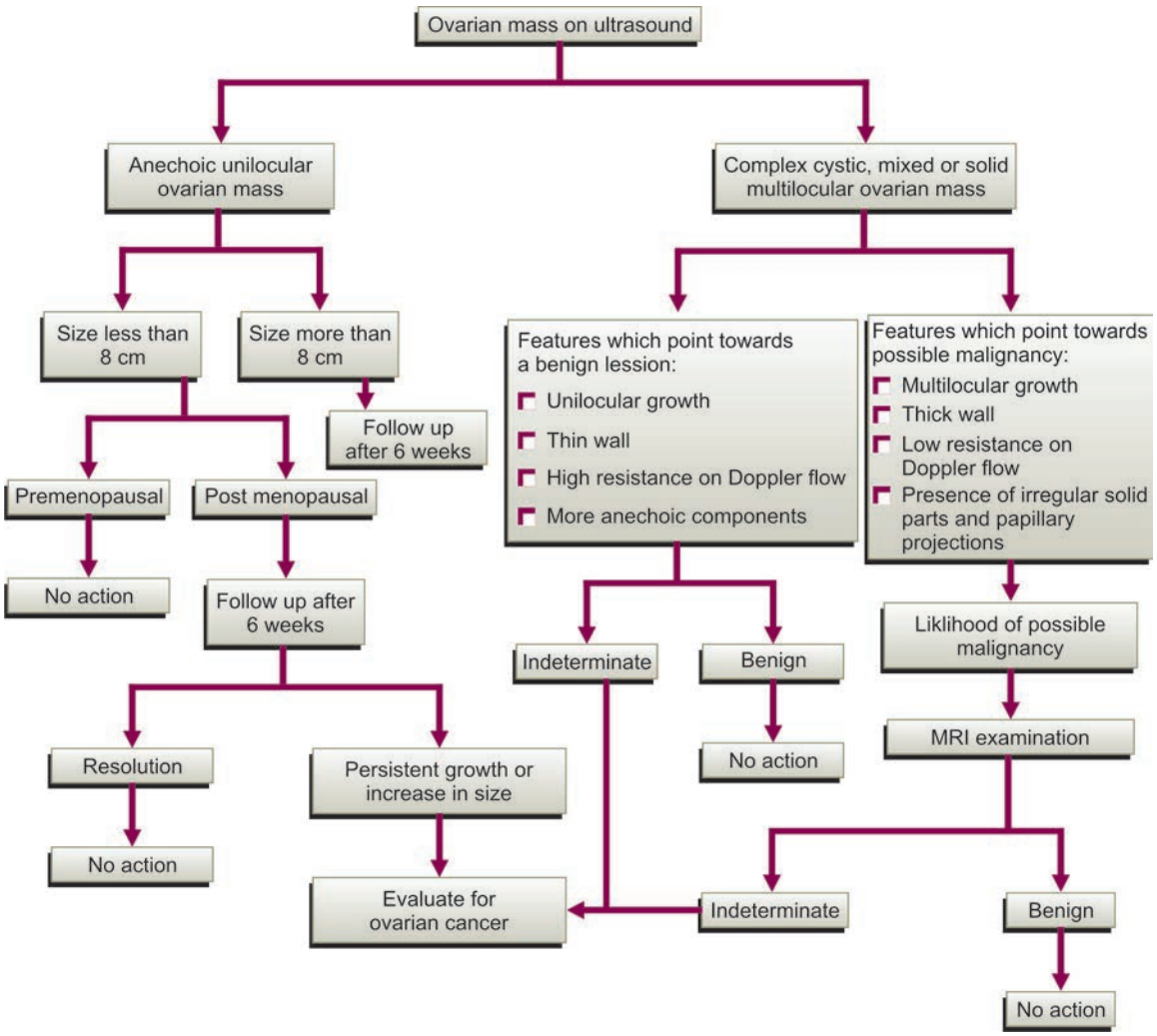
Magnetic resonance imaging

MRI scans use radio waves and magnetic energy instead of X-rays. MRI scans are not routinely used for diagnosing ovarian cancer. MRI scans help in accurate characterization of ovarian tumors (figure 24.9) and are also particularly helpful for examining metastatic spread of the cancer to the brain and spinal cord.

Positron emission tomography (PET scan)

In this test, radioactive glucose is given to detect malignancy. Since the cancers utilize glucose at a higher rate than normal tissues, the radioactivity tends to get concentrated in the area of malignancy. A scanner can spot the radioactive deposits. In some instances this test has proved useful in estimating the

Flow chart 24.1: Evaluation of adnexal lesion observed on ultrasound imaging studies



spread of ovarian cancer. However, the test is expensive and is therefore not routinely done.

Preoperative Evaluation

Once the ovarian malignancy has been diagnosed or suspected, a preoperative evaluation must be done in order to evaluate the extent of malignancy prior to undertaking surgery. The preoperative evaluation helps in excluding other primary cancers (e.g. GI malignancy), which could be metastatic to the ovary. The preoperative evaluation in case of ovarian malignancy comprises of the following investigations:

Chest X-ray

This procedure may be done to determine whether ovarian cancer has metastasized to the lungs. Chest X-rays can help in the detection of pleural effusion.

Colonoscopy and barium enema

Colonoscopy/barium enema must be performed to exclude involvement of the colon by cancerous growth. Colonoscopy is an investigation of choice for examining the interior of the colon. After prior cleaning of the large intestine with laxatives, a fiberoptic tube is inserted into the colon via the rectum. This allows the clinician to evaluate the amount of intestinal invasion by the cancerous growth. Upper gastrointestinal series or gastroscopy may also be performed if symptoms indicate gastric involvement.

Intravenous pyelography (IVP)

Intravenous pyelography is done in order to assess the urinary tract for invasion by the cancerous mass. Presence of hydronephrosis could be due to obstruction of the urinary tract by malignant growth.

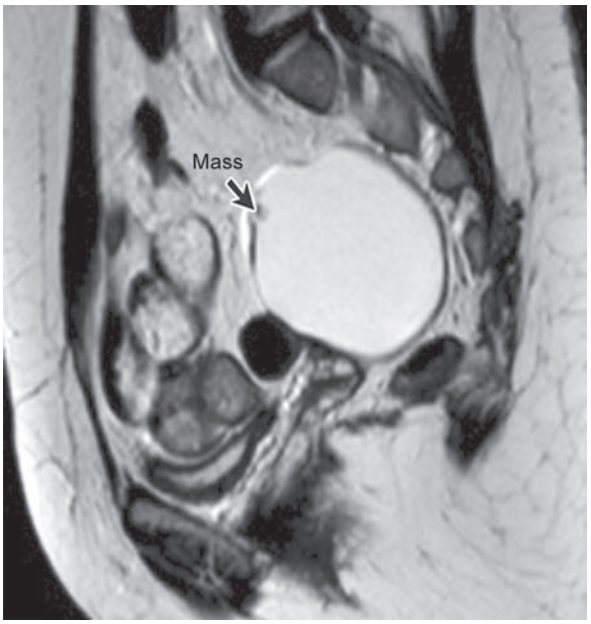


Fig. 24.9: T1-weighted image on MRI scan showing a benign serous cystadenoma. The mass is smooth walled, having homogenous consistency with no internal septae or lobulations.

Cervical cytology

Although pap test has low sensitivity for detection of ovarian malignancy, this test may help in ruling out the presence of uterine or endocervical cancer causing metastatic involvement of the ovaries.

Exploratory Laparotomy

Sometimes cancer of the ovary cannot be diagnosed before an exploratory laparotomy is carried out. The staging of ovarian cancer is done at the time of exploratory laparotomy. Surgical staging helps in estimating the spread of cancer. Staging of the ovarian cancer is particularly important because subsequent treatment depends upon the stage of the disease. Once a stage has been assigned, it doesn't change, even if the cancer later spreads to other areas of the body or comes back following surgery.

Besides estimating the stage of cancer spread, exploratory laparotomy also helps in removing most of the cancerous tissue larger than about ½ inch and helps in taking out the tissue samples. These tissue samples help the clinician in deciding the stage of the tumor. The steps of surgical staging are described below:

- A midline or a paramedian abdominal incision is given in order to allow adequate access to the upper abdominal cavity especially in cases where there is a possibility of malignancy.
- At the time of surgery, the ovarian tumor must be removed intact and a frozen histological section should be obtained.
- Any intraabdominal free fluid or that present in the pouch of Douglas must be submitted for the cytological analysis.
- If no free fluid is present, peritoneal washings should be performed by instilling and recovering 50–100 ml of saline from the pelvic cul-de-sac, each paracolic gutter and beneath each hemidiaphragm.
- A systematic exploration of all intraabdominal surfaces and viscera must be performed. The gynecologist must proceed in a clock-wise fashion from the cecum, moving cephalad along the paracolic gutter and the ascending colon to the right kidney, the liver and gall bladder, the right hemidiaphragm, transverse colon and then down to the left gutter, descending colon and the rectosigmoid.
- Biopsy must be taken from any suspicious areas and peritoneal adhesions. If there is no evidence of the disease but the disease is nevertheless suspected, multiple intraperitoneal biopsies must be performed.
- The diaphragm must be sampled.
- Ovarian tumor must be resected out. Frozen section of the tumor must be obtained and sent immediately for histopathological analysis. In case of positive histological evidence of malignancy, total abdominal hysterectomy along with bilateral salpingoophorectomy (TAH + BSO) must be performed.
- Infracolic omentectomy, which involves resection of omentum from the transverse colon needs to be performed.
- Exploration of retroperitoneal spaces to evaluate the pelvic and paraotic lymph nodes also needs to be done.

Cancer staging and grading

The FIGO (Federation International of Gynecology and Obstetrics) system is used for cancer staging based on the findings of exploratory laparotomy. This system of surgical staging is described below:

Stage 1: Cancer growth is limited to the ovaries. This stage is divided into three subgroups:

Stage 1A: The growth is limited to one ovary. There is no ascites containing malignant cells; no tumor is present on the external surface; and capsule is intact.

Stage 1B: The growth is limited to both the ovaries. There is no ascites containing malignant cells; no tumor is present on the external surface; and capsule is intact.

Stage 1C: The cancer is either at stage 1A or 1B, but with tumor on the surface of one or both the ovaries; or with capsule ruptured or with ascites present containing malignant cells or with positive peritoneal washings.

Stage 2: Growth involves one or both ovaries with pelvic extension. There are three subgroups:
Stage 2A: The cancer has spread to the uterus and/or fallopian tubes.
Stage 2B: There is extension to other pelvic tissues, such as the rectum or bladder.
Stage 2C: The cancer is either at stage 2A or 2B, with tumor on the surface of one or both ovaries; or with capsule ruptured; or with ascites present, containing malignant cells or with positive peritoneal washings.
Stage 3: Tumor involves one or both the ovaries, with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equals stage 3. Tumor is limited to the true pelvis, but with histologically proven extension to small bowel or omentum.
Stage 3A: Tumor grossly limited to true pelvis with negative nodes but with histologically confirmed seeding of abdominal/peritoneal surfaces.
Stage 3B: Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Nodes are negative.
Stage 3C: Abdominal implants > 2 cm in diameter and/or positive retroperitoneal or inguinal lymph nodes.
Stage 4: Growth involving one or both ovaries with distant metastasis. If pleural effusion is present, there must be positive cytological test results to allot a case to stage IV. Parenchymal liver metastasis equals stage IV.

The above mentioned categories are based on the findings of clinical examination and/or surgical exploration. If the cancer comes back after initial treatment, this is known as recurrent cancer.

Grading

Grading of ovarian cancer is done by evaluating the histopathological appearance of cells on the basis of microscopic examination. The tumor grading gives an idea about the degree of malignancy and how quickly the cancer is likely to progress. There are three cancer grades: Grade 1 (low grade); grade 2 (moderate grade) and grade 3 (high grade).
Low grade cancer: The cancer cells are well differentiated and look very much like the normal cells of the ovary. They usually grow slowly and are less likely to spread.
Moderate grade cancer: The cancer cells are less well differentiated and appear more abnormal in comparison to the low grade cells.
High grade cancer: The cells look very abnormal and may show a high grade of anaplasia. These cancers are highly malignant, which tend to grow very quickly and are highly likely to spread.

Rx *Treatment/Gynecological Management*

PREVENTION

Screening for Ovarian Cancer

Presently research studies are being carried out to assess whether ovarian cancers can be detected at an early stage so that they can be treated more effectively. Some of the tests which are being considered in various research trials include estimation of CA125 levels or performing a transvaginal ultrasound. The aim of these research trials is to evaluate if either of these tests might help in the diagnosis of women with early stage ovarian cancer. Since presently it is not known whether these screening tests could help in detection of ovarian cancers at an earlier stage, currently there exists no national screening programme for ovarian cancer.

DEFINITIVE THERAPY

The treatment of a patient with ovarian cancer must be planned by a multidisciplinary team comprising of a gynecological oncologist, a clinical or medical oncologist, radiologist, pathologist, a gynecological oncology nurse specialist, dietician, physiotherapist, occupational therapist, clinical psychologist or counselor. The issues which need to be discussed with the patient before undertaking therapy include: The type and extent of the treatment the patient would receive, the advantages and disadvantages of the treatment, any other treatment options that may be available and any significant risks or side effects of the treatment.

Stage 1 A (grade I disease)

Primary treatment for stage 1 epithelial ovarian cancer is surgical i.e. a total abdominal hysterectomy and a bilateral salpingoophorectomy and surgical staging .The uterus and contralateral ovary can be preserved in woman with stage IA, grade I disease who desire to preserve their fertility. However such women must be periodically monitored with routine pelvic examinations and determination of serum CA 125 levels.

Stage 1A and 1B (grade 2 and 3) and stage 1C

Treatment options in this case include additional chemotherapy or radiotherapy besides surgery as described above. Chemotherapy is the more commonly used option and comprises of either single agent or multiagent chemotherapy. The most commonly used single agent chemotherapy is melphalan which is administered orally on a “pulse” basis

for 5 consecutive days, every 28 days. Radiotherapy could be administered either in the form of intraperitoneal radiocolloids (P32) or whole abdominal radiation.

According to the current treatment recommendations, the treatment must be in form of either cisplatin or carboplatin or combination therapy of either of these drugs with paclitaxel for 3–4 cycles. Short course of melphalan (4–6 cycles) may be preferable in the older women.

Stage II, III and IV

Debulking surgery or cytoreductive surgery is performed in these cases. This involves an initial exploratory procedure with the removal of as much disease as possible, (both tumor and the associated metastatic disease). Cytoreductive surgery includes abdominal hysterectomy and bilateral salpingoophorectomy, complete omentectomy and resection of metastatic lesions from the peritoneal surface. The gynecologist also takes the biopsies or removes some of the lymph nodes in the abdomen and pelvis. They may also have to remove the omentum, the appendix and part of the peritoneum. This operation can be complicated and should ideally be done by a specialist gynecological oncologist. The goal of cytoreductive surgery is resection of the primary tumor and all the metastatic disease. If this is not possible, the goal must be to reduce the tumor burden by resection of the tumor to an "optimal status". The study by the Gynecologic Oncology Group (2004) has defined optimum debulking as residual tumor diameter of ≤1 cm^3.

Many patients are given a few cycles of chemotherapy following the surgery. For some patients with completely resected disease, whole abdominal radiation therapy may be used. For patients with no clinical evidence of disease and negative tumor markers at the completion of chemotherapy, a reassessment laparotomy or "second-look" surgery may be performed. The treatment plan for advanced stage ovarian cancer has been demonstrated in the flow chart 24.2.

Second Look Laparoscopy

Many patients who undergo cytoreductive surgery and chemotherapy may have no evidence of disease at the completion of the treatment. In order to detect the presence of subclinical disease, a second look surgery is often performed. This is usually in form of laparotomy, though laparascopy is sometimes performed. The technique of second look laparotomy is essentially identical to that for the staging laparotomy. Multiple cytological specimens and biopsies of the peritoneal surface must be performed, particularly in any areas of previously documented tumor. Additionally any adhesions or surface irregularities must also be sampled. Biopsy specimen must be taken from the pelvic side walls, cul-de-sac, bladder, the paracotic gutters, residual omentum and the diaphragm. A pelvic and para-arotic lymph node dissection should be performed for those patients whose nodal tissues have not been previously removed. Second look laparotomies have not been shown to influence patient's survival. Therefore, these should be performed only in research settings where second line or salvage therapies are undergoing clinical trials. Various second line therapies include secondary cytoreduction, whole abdominal irradiation, secondary chemotherapy and intraperitonel instillation of radiocolloids.

Radiation Therapy

Radiation therapy is not commonly used for the treatment of ovarian cancer. Whole abdominal radiation therapy appears to be a useful option for patients with metastatic disease that is microscopic or completely resected. The current evidence suggests that the whole abdominal radiation is inappropriate for the patients with macroscopic residual disease. Radiotherapy may be rarely used to treat an area of cancer that has come back after surgery and chemotherapy, when other treatment options are no longer appropriate. Radiotherapy can also be used as palliative therapy in order to reduce bleeding or symptoms of pain and discomfort. Radiotherapy has been successfully used in the treatment of recurrent germ cell tumors which are very radiosensitive. Radioactive isotopes of gold (Au 198) or phosphorus (P 32) have been used intraperitoneally in combination with external radiotherapy.

Chemotherapy

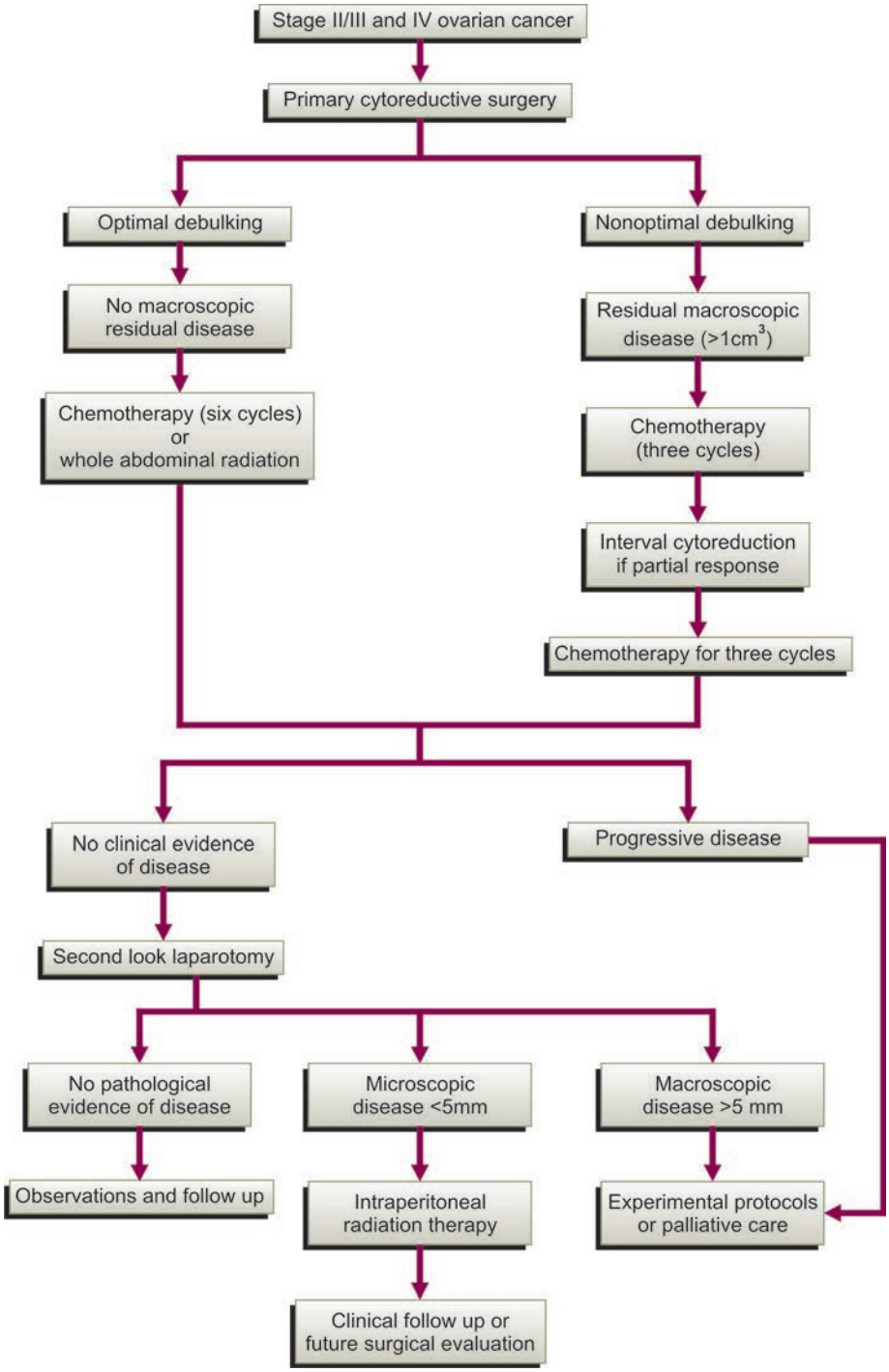
Indications

Various indications for chemotherapy are enumerated in table 24.3. Chemotherapy is often recommended after surgery for women with moderate or high grade ovarian cancer or those with stage 1B or 1C cancer. Generally six sessions of chemotherapy are given, over 5 to 6 months. In advanced-stage ovarian cancer, chemotherapy is sometimes given before surgery (neoadjuvant chemotherapy), to shrink any residual tumor. Women who are given neoadjuvant chemotherapy are given three cycles of chemotherapy before the surgery, followed by three further cycles. In case of stage

Table 24.3: Indications for chemotherapy

Early stage ovarian (stage 1B or 1C) cancer (after surgery in order to reduce the chance of the cancer recurrence): Adjuvant chemotherapy
Moderate or high grade ovarian cancer (after surgery)
Neoadjuvant chemotherapy before surgery in advanced stage ovarian cancer
Stage IV cancer with distant metastasis

Flow chart 24.2: Treatment plan for advanced stage epithelial ovarian cancer



IV cancer with distant metastasis, chemotherapy is the main treatment modality, which is used. In women with early stage ovarian cancer, chemotherapy is given after surgery to reduce the chance of the cancer recurrence. Though chemotherapy cannot guarantee that the cancer will not come back, it does help in reducing the risk of disease recurrence.

Types of chemotherapy

Intraperitoneal chemotherapy: Chemotherapy can be instilled directly into the abdomen and pelvis through a thin tube. The drugs destroy the cancer cells in the abdomen and pelvis.

Systemic chemotherapy: Systemic chemotherapy may be either taken in orally or injected intravenously. The

drugs enter the bloodstream and destroy or control cancer throughout the body. Intravenous chemotherapy is given as a session of treatment, usually over several hours. This is followed by a rest period of a few weeks, which allows the patient's body to recover from any side effects of the treatment. Together, the treatment and the rest period are known as a cycle of chemotherapy. Most women are given six cycles of chemotherapy.

Chemotherapy regimens

After surgery, the most commonly used drug to treat ovarian cancer is carboplatin, which is often given with paclitaxel (Taxol®). Other chemotherapy drugs that are less commonly used, or may be used if the cancer comes back, are topotecan (Hycamtin®), doxorubicin and cisplatin.

Previously, cisplatin based chemotherapy had been most frequently used. However, recently paclitaxel has become part of the standard therapy for the advanced ovarian cancer. If chemotherapy is necessary, it is usually given every three to four weeks, for four or more sessions of treatment. After surgery, women with ovarian cancer are offered chemotherapy to destroy the remaining cancer cells, which couldn't be completely removed by surgery. The various types of chemotherapy regimens which can be used are described below:

Single agent chemotherapy

Melphalan: Previously, the single agent chemotherapy usually involved the use of a chemotherapy drug melphalan which acts as an alkylating agent. The standard dose of the Melphalan was 0.2 mg/kg/day given for five consecutive days after every 28 days.

Platinum based chemotherapy

Platinum based drugs which are used as single agent chemotherapy include ciplatin, carboplatin and paclitaxel. These drugs are believed to be more effective than alkylating agents.

Combination Chemotherapy

Combination chemotherapy has been shown to be superior to single agent therapy for the most patients with advanced epithelial ovarian cancer.

PAC regimen

The PAC regimen has been extensively used for the advanced ovarian cancer. The drugs used in this regimen are as follows:

- Cisplatin: 50 mg/m^2 for 3–4 weeks.
- Doxorubicin: 50 mg/m^2
- Cyclophosphamide: 500 mg/m^2

CHAP regimen

- Hexamethylmelamine: 150 mg/m^2 orally for 1–14 days
- Cyclophosphamide: 350 mg/m^2 IV on day 1 and day 8
- Doxorubicin: 20 mg/m^2 IV on day 1 and day 8
- Cisplatin: 60 mg/m^2 IV on day 1

Two drug regimen

The main drugs used in this regimen are cisplatin in combination with either paclitaxel or cyclophosphamide. The principal toxicities of this regimen are renal, gastrointestinal, hematological and neurological. These toxicities limit the duration of the treatment to no more than 6–9 cycles. The recent trend is to replace cisplatin with carboplatin. Since the renal and gastrointestinal toxicities of carboplatin are modest compared to those with cisplatin, the patients being treated with carboplatin do not require prehydration as that required by cisplatin.

Administration of cisplatin requires appropriate hydration prior to therapy. Hydration is administered with one half normal saline given intravenously at the rate of 300–500 ml/hour for 2–4 hours until the urine output becomes greater than 100 ml/hour. Also immediately prior to chemotherapy, 12.5 grams of mannitol in 50 ml of normal saline is infused. When satisfactory urinary output is obtained, cisplatin is infused in normal saline; the IV fluid rate is decreased to 150–200 ml/hour for 6 hours and then is discontinued if the patient is stable.

The acute gastrointestinal toxicity of cisplatin (nausea and vomiting) can be minimized by using a strong antiemetic like ondancetron, given as a 32 mg IV bolus dose, followed by 10 mg IV every 4–6 hourly.

PT (Cisplatin and Paclitaxel): Combination chemotherapy with cisplatin and paclitaxel is the treatment of the choice for the patients with advanced epithelial ovarian cancer. Cisplatin is given in the dose of 75 mg/m^2 and paclitaxel in the dose of 175–210 mg/m^2.

CT (carboplatin and paclitaxel): Starting dose of carboplatin is AUC = 5; paclitaxel is administered in the dose of 175–210 mg/m^2.

PC (Cisplatin and cyclophosphamide): Cisplatin is administered in the dose of 75–100 mg/m^2 and cyclophosphamide in the dose of 650–1000 mg/m^2. Cisplatin combination therapy with cyclophosphamide must be administered over 3–4 weeks by intravenous injection over 1–1.5 hours. It can be administered either on inpatient or outpatient basis.

CC (carboplatin and cyclophosphamide): Starting dose of carboplatin is AUC = 5–7, while cyclophosphamide is administered in the dose of 600 mg/m^2.

Table 24.4: Different types of tumor markers being tried to detect cancer recurrence

Epithelial tumors	*Germ cell tumors*	*Stromal tumors*
CA 125 antigen	Alpha-feto protein	Inhibin
BRCA-1 and BRCA-2	Human chorionic gonadotropin	
Carcinoembryonic antigen		
Galactosyltransferase		
Tissue polypeptide antigen (TPA)		

Follow up after treatment for ovarian cancer

Follow up is usually in form of regular tests to check the level of CA125 in the patient's blood. Often the CA125 level will begin to rise before any symptoms suggestive of cancer recurrence develop. However, presently the measurement of CA 125 levels has limited role in deciding the management of cancer recurrence. As a result, presently the treatment for cancer recurrence is delayed until she starts showing symptoms, or the results of an examination or scan make it is clear that the cancer has come back. Different types of tumor markers (table 24.4), based on the histological pattern of the tumor are being tried under research settings.

If the cancer comes back, treatment is usually given with chemotherapy. Many different types of chemotherapy can be used for women in this situation. The same chemotherapy drugs that were given initially can be used or different ones may be tried. Occasionally it may be possible to remove tumors using surgery. Radiotherapy may be used to treat particular areas or to relieve symptoms.

Important Questions and Answers

Q.1. What are the features suggestive of malignant ovarian growth from the above mentioned case history?

Ans. The features suggestive of malignancy in the above mentioned case study are as follows:

Rapidity of growth

A rapidly growing tumor is highly suggestive of malignancy, while a slow growing tumor is more likely to be benign. A tumor which has been rapidly increasing in size over the past six months is suggestive of malignancy.

Consistency of the mass

In this case, the growth appeared solid, nodular and irregularly shaped on vaginal examination. This is more likely to be malignant. On the other hand, growths which are smooth, cystic and have regular margins are more likely to be benign.

Fixation of the tumors

Malignant tumors are more likely to be adherent to the underlying structures and have a restricted mobility in comparison to the benign masses which are not adherent to the underlying structures and have a greater mobility.

Presence of ascites

Presence of free fluid in the abdominal cavity is usually indicative of peritoneal metastasis or atleast the fact that the tumor has perforated the ovarian capsule. However in this case no ascitic fluid was present on per abdominal examination.

Cancer cachexia

Cachexia, associated with severe degrees of weight loss, muscle wasting, weakness and fatigue typically occurs with malignant growths. A benign tumor is usually not painful unless there is an underlying complication. A malignant tumor on the other hand, is associated with pain in the abdomen.

Q.2. What would be the most appropriate management in the above described case study?

Ans. In the above mentioned case study, after taking into consideration the patient's age and findings of ultrasound examination, the suspicion of malignancy must be definitely ruled out by the clinician. The best modality of diagnosis in patient with suspected ovarian cancer is surgical staging on exploratory laparotomy.

Q.3. What investigations must be performed prior to performing an exploratory laparotomy in this case?

Ans. Due to strong suspicion of malignancy in this case, an MRI examination was performed. MRI confirmed the diagnosis of malignancy. There was no pelvic extension of malignant growth and lymph nodes were negative. A chest X-ray and blood investigations (CBC with ESR; KFT and LFT) were also performed prior to undertaking exploratory laparotomy.

Q.4. The surgical staging revealed palpillary cystadenocarcinoma stage 1 A (grade I). What would be the next step of management?

Ans. Total abdominal hysterectomy with bilateral salpingoophorectomy was performed in this case. Removal of both the ovaries is unlikely to cause any problem in this case as she has completed her family and is postmenopausal. However she needs to be periodically monitored with routine pelvic examinations and determination of serum CA 125 levels every three four months for the first two years and then six-monthly for five years.

Q.5. What are the factors which may affect prognosis in cases of ovarian cancer?

Ans. Factors which may affect prognosis in cases of ovarian cancer include:

- The stage of the cancer
- The type and size of the tumor
- The patient's age and general health.
- Whether the cancer has been diagnosed for the first time or there has been cancer recurrence.

Q.6. What is the rationale behind cytoreductive surgery?

Ans. Cytoreductive surgery aims at removal of large tumor mass. The goal of cytoreductive surgery is to remove the primary tumor and all metastatic disease. If this is not possible, the goal is to reduce the tumor burden by resection of the tumor to an "optimal status". Removal of the large tumor mass helps in improving the patient's quality of life and nutritional status by achieving the following:

- Reduction in the volume of ascites.
- Restoration of adequate intestinal function which may lead to an improvement in the overall nutritional status of the patient.
- Improving the patient's ability to withstand subsequent chemotherapy.
- Removal of cancer invading bowl, lessens sepsis.
- Removal of a large tumor reduces pain.
- Cytoreductive surgery is also believed to increase chemosensitivity due to resection of areas with poor blood supply and necrosis.

Certain areas in the abdomen may not be easily accessible or may be unresectable, e.g., large tumor plaques on the diaphragm or liver, tumor involving the mesentery etc. In these cases other therapeutic options like CO_2 laser, ultrasonic aspirator, argon beam coagulator or loop electrosurgical excision may be used.

Q.7. What are the likely effects of surgery for ovarian cancer on the life of the patient who has yet not attained menopause?

Ans. Total abdominal hysterectomy with bilateral salpingoophorectomy in a patient who has yet not attained menopause is likely to result in premature menopause. This is unlikely to be a problem in the above mentioned cases study because she is already menopausal since last ten years. However in a women who has not attained menopause, premature menopause can produce symptoms such as hot flushes, dry skin, reduced sexual desire and dryness of the vagina, which can make sexual intercourse uncomfortable. Such women should be prescribed hormone replacement therapy (HRT) following treatment for ovarian cancer. This could help in reducing some of the problems caused by premature menopause.

Q.8. What is the pattern of spread of an ovarian malignancy?

Ans. The most common pattern of spread of epithelial ovarian cancer is through the exfoliation of the cancer cells that implant along the surfaces of the peritoneal cavity. Exfoliation of the cancer cells that implant along the surfaces of the peritoneal cavity tends to follow the circulatory path of the peritoneal fluid. As a result, metastases are typically seen on the posterior cul-de-sac, paracolic gutters, right hemidiaphragm, liver capsule and peritoneal surfaces of the intestine, their mesenteries and the omentum. Though the lumen of the intestines is rarely invaded by the malignant cells, progressive agglutination of the bowel loops often takes place, resulting in functional intestinal obstruction. This condition is known as carcinomatous ileus.

Other less common modes of spread of ovarian cancer include lymphatic and hematogeneous spread. Lymphatic spread can result in the involvement of pelvic and paraaortic group of lymph nodes. Lymphatic spread above the diaphragm can result in the involvement of supraclavicular lymph nodes. Hematogeneous spread can occur to organs like lungs and liver.

Bibliography

1. ACOG Committee on Gynecologic Practice. The role of the generalist obstetrician-gynecologist in the early detection of ovarian cancer. Gynecol Oncol. 2002;87: 237-39.
2. Cancer and its Management (5th edition). Eds Souhami and Tobias. Oxford Blackwell Scientific Publications. 2005.
3. Chemotherapy for advanced ovarian cancer. Advanced ovarian cancer triallists group. The Cochrane Database of Systematic Reviews. 2006. Issue 1.
4. Fishman DA, Cohen L, Blank SV, Shulman, L Singh, D Bozorgi, K Tamura R, Timor-Tritsch, I and Schwartz, PE. The role of ultrasound evaluation in the detection of early stage epithelial ovarian cancer. Am J Obstet Gynecol. 2005;192:1219-21.
5. Improving Outcomes in Gynaecological Cancers: Guidance on Commissioning Cancer Services. Department of Health. London 1999.
6. Improving Supportive and Palliative Care for Adults with Cancer – The Manual. National Institute for Clinical Excellence (NICE). March 2004.
7. McDonald JM and Modesitt SC. The incidental postmenopausal adnexal mass. Clin Obstet Gynecol. 2006;49:506-16.
8. Review of the clinical effectiveness and cost effectiveness of paclitaxel for ovarian cancer. National Institute for Clinical Excellence. January 2003.
9. Scully RE. Classification, pathology and biologic behavior of ovarian tumors. Meadowbrook Staff Journal. 1968;1: 148-163.

10. Scully RE. Germ cell tumors of the ovary and fallopian tube. In Progress in Gynecology, Vol. 4 (JV Meigs and SH Sturgis, Eds.), Grune and Stratton, New York. 1963.
11. Scully RE. Tumors of the ovary and maldeveloped gonads. Atlas of Tumor Pathology, Second Series, Fascicle 16, Armed Forces Institute of Pathology, Washington, DC. 1979.
12. Serov, SF, Scully, RE, and Sobin, LH. Histological typing of ovarian tumours. International Histological Classification of Tumours, No. 9, World Health Organization, Geneva. 1973.
13. Sohaib SA, Mills TD, Sahdev A, Webb JA, Vantrappen PO, Jacobs IJ and Reznek RH. The role of magnetic resonance imaging and ultrasound in patients with adnexal masses. Clin Radiol. 2005;60:340-48.
14. Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second line or subsequent treatment of advanced ovarian cancer (review). Assessment report. National Institute for Clinical Excellence. December 2004.
15. Yamashita Y, Torashima M, Hatanaka Y, Harada M, Higashida Y, Takahashi M, Mizutani H, Tashiro H, Iwamasa J and Miyazaki K. Adnexal masses: Accuracy of characterization with transvaginal US and precontrast and postcontrast MR imaging. Radiology. 1995;197:557-65.

Chapter

25

Ectopic Pregnancy

Case Study

A 24-year-old nulliparous woman married since last one year, presented with 3 months amenorrhea to the A&E department with vaginal bleeding and severe abdominal pain particularly confined to the left iliac fossa. She had done a home pregnancy test, which was positive. Vaginal examination revealed cervical motion tenderness and a normal-sized uterus. An ultrasound examination and urine hCG levels were ordered. Urine hCG levels were found to be raised and TVS examination revealed an adnexal mass (about 1 cm in size) and an empty uterus.

Introduction

Ectopic means "out of place." In an ectopic pregnancy, the fertilized ovum gets implanted outside the uterus as a result of which the pregnancy occurs outside the uterine cavity (figure 25.1). Ectopic pregnancy usually occurs as a result of delay or prevention in passage of the blastocyst to the uterine cavity resulting in its premature implantation in the extrauterine tissues.

Most commonly, i.e. in nearly 95% of cases, the fertilized ovum gets implanted inside the fallopian tube. The ovum buries into the tube and induces a decidual reaction in the cells of the endosalpinx. However, this reaction is feeble. Also, there occurs invasion of the trophoblastic cells into the wall of the fallopian tube. As a result, there is a high risk of choriodecidual hemorrhage and of erosion or rupture of the tube wall.

Since the uterus itself is under the influence of the hormones of the corpus luteum and of the trophoblast, there occurs generalized enlargement, increased vascularity, tissue hypertrophy and decidual reaction in the endometrium.

Other extrauterine locations where an ectopic pregnancy can get implanted include the ovary, abdomen or the cervix. Average incidence for occurrence of pregnancy at various locations is enumerated in table 25.1 and shown in figure 25.2.

The extrauterine locations do not have sufficient space or nurturing tissues to support a growing pregnancy. Since none of these areas have been equipped by nature to support a growing pregnancy, with the continuing growth of the fetus,

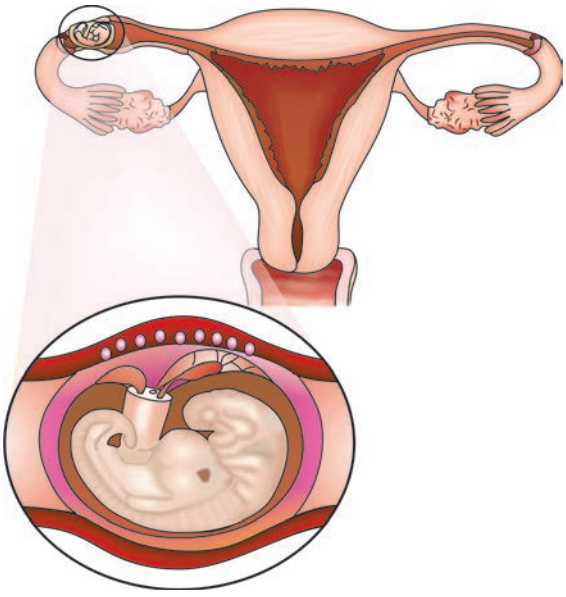


Fig. 25.1: Ectopic pregnancy

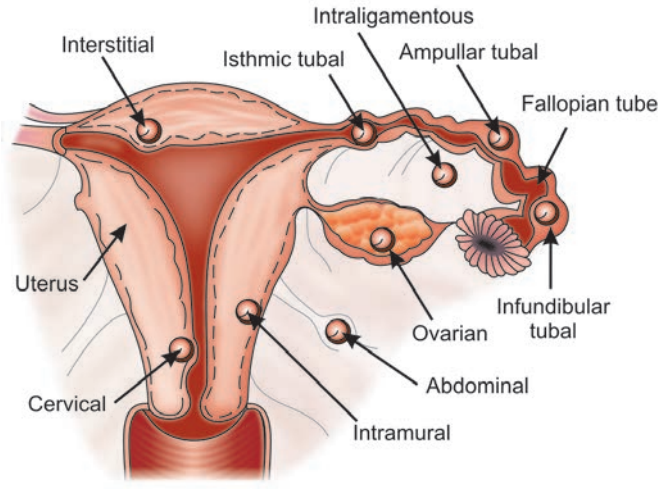


Fig. 25.2: Common sites of occurrence of ectopic pregnancy

Table 25.1: Average incidence for occurrence of ectopic pregnancy at various locations

Location of extra uterine pregnancy	*Incidence of occurrence*
Fallopian tube	97%
Ampulla	80%
Isthmus	11%
Fimbria	4%
Cornua	2%
Interstitium	3%
Abdominal cavity, ovary, and cervix	3%

the gestational sac and the organ containing it burst open. This can result in severe bleeding, sometimes even endangering the woman's life. A classical ectopic pregnancy normally does not develop into a live birth. Although spontaneous resolution of ectopic pregnancy can sometimes occur, patients are at risk of tubal rupture and catastrophic hemorrhage. Ectopic pregnancy is estimated to occur in 2% of all pregnancies. It remains a major cause of maternal morbidity and mortality when misdiagnosed or left untreated.

Course of Ectopic Pregnancy

The implanted tubal pregnancy can take the following course:

Tubal abortion: The pregnancy gets aborted out through the tube. It may either get completely absorbed or there may be complete or incomplete abortion. If the internal bleeding continues to occur, the condition may become symptomatic.

Tubal mole: The embryo dies due to faulty environment and gets converted into a carneous mole.

Tubal rupture: The fallopian tube may rupture due to its thin lumen at the isthmus and ampulla. The lumen is incapable of distension due to burrowing in and erosion by the blastocyst.

Tubal rupture is usually intraperitoneal and may result in severe bleeding and partial or complete extrusion of chorionic villi resulting in hemodynamic instability and shock like features. Rarely, the rupture may be extra-peritoneal. If the rupture occurs in the broad ligament, this may result in the development of of a broad ligament hematoma.

Chronic ectopic adnexal mass: The products of conception are partially extruded out through the fimbriae or partial rupture. After a slight or moderate bleeding, the hemorrhage may get arrested and result in the formation of an adnexal mass involving the tube and ovaries.

Fetal survival to term: This usually does not occur as the fetus is commonly unable to develop beyond 6 weeks of gestation.

History

RISK FACTORS

The risk factors for ectopic pregnancy are described below and need to be elicited at the time of taking history:

- Prior history of an ectopic pregnancy: The risk of future ectopic pregnancy is about 15% after the first ectopic pregnancy, and 30% after the second.
- History of pelvic infections, including infections such as PID, STD, salpingitis and tuberculosis: Infection in the pelvis is an important cause for ectopic pregnancy. Pelvic infections may be caused by sexually transmitted organisms, such as chlamydia or gonorrhea. However, non-sexually transmitted bacteria can also cause pelvic infection and increase the risk of an ectopic pregnancy. Infection causes an ectopic pregnancy by damaging the tubal ciliary epithelium or obstructing the fallopian tubes. Damage to the ciliated epithelium of the fallopian tubes is likely to delay the transport of the fertilized ovum along the fallopian tube. Additionally, infection-related scarring and partial blockage of the fallopian tubes are likely to further prevent the movement of fertilized ovum into the uterine cavity.
- Prior surgeries to the fallopian tubes, including tubal reconstructive surgery, tubectomy, etc.
- Endometriosis and pelvic scar tissue (pelvic adhesions): This can further narrow the fallopian tubes and disrupt the transportation of egg, thereby increasing the chances of an ectopic pregnancy.
- Fibroid tumor of the uterus,
- Pelvic scar tissue and adhesions may commonly occur in cases of previous abdominal surgeries.
- Intrauterine devices and hormonal contraception: Use of progesterone only hormonal contraceptive devices are likely to cause altered tubal mobility resulting in the development of ectopic pregnancy. The use of an intrauterine device per se does not increase the risk of ectopic pregnancy. However, a normal pregnancy is unlikely with an IUD in place, so if a woman becomes pregnant while using an IUD, it is more likely the pregnancy is not inside the uterus.
- Congenital abnormalities of tubes
- Tuberculosis of the tubes
- ART procedures
- Smoking is a risk factor in about one third of ectopic pregnancies and may contribute to decreased tubal motility by causing damage to the ciliated cells in the fallopian tubes.

- Altered tubal motility can also occur as the result of hormonal contraception. Both progesterone only contraception and progesterone intrauterine devices (IUDs) have been associated with an increased risk of ectopic pregnancy.
- Patients who are 35–44 years of age.
- Patients who have had several induced abortions.
- One third of ectopic pregnancies occur in women with no known risk factors.
- Infertility problems and use of ovulation induction drugs and techniques for assisted conception.
- The risk is highest for women who are over 35 and have had used some birth control methods for pregnancy control such as progesterone-only oral contraceptives, progesterone intrauterine devices (IUDs), or the morning-after pill. The pregnancy occuring even after the use of contraception is more likely to be ectopic in nature.
- Smoking and having multiple sexual partners also increases the risk of an ectopic pregnancy.

SYMPTOMS

Ectopic pregnancy can be difficult to diagnose in the beginning because symptoms are often very much similar to those of a normal early pregnancy. These can include missed periods, breast tenderness, nausea, vomiting, or frequent urination. The typical triad on history for ectopic pregnancy includes bleeding and abdominal pain and a positive pregnancy test result. However, while these symptoms are typical for an ectopic pregnancy, they do not imply that an ectopic pregnancy is necessarily present and could also represent other conditions. In fact, these symptoms may also be associated with a threatened abortion in non-ectopic pregnancies. The symptoms of an ectopic pregnancy typically occur 6 to 8 weeks after the last normal menstrual period, but they may occur later, if the ectopic pregnancy is not located in the fallopian tube.

When bleeding occurs, the clinical presentation can be suggestive of miscarriage. Many women with ectopic pregnancy may show no signs and symptoms. As a result, almost half of the cases are not diagnosed at the first prenatal visit. Pain may be felt in the pelvis, abdomen, lower back or, sometimes may even be referred to the patient's shoulder or neck, especially in cases of hematoperitoneum. Most women describe the pain as sharp and stabbing in nature. It may be confined to one side of the pelvis and may come and go or vary in intensity. Acute blood loss in some cases may result in the development of dizziness or fainting and hypotension. Malaise, weakness, dizziness, and a sense of passing out on standing can represent serious internal bleeding, and mandates immediate laparotomy.

General Physical Examination

The following signs may be observed on GPE:

- Normal signs of early pregnancy (e.g. uterine softening).
- Abdominal pain and tenderness.
- Evidence of hemodynamic instability (hypotension, collapse, signs and symptoms of shock).
- Hypotension: Low blood pressure could be related to significant amount of intra-peritoneal bleeding. In severe cases even shock may be present.
- Signs of peritoneal irritation (abdominal rigidity and guarding).

Specific Systemic Examination

ABDOMINAL EXAMINATION

Significant abdominal tenderness suggests ruptured ectopic pregnancy, especially in a patient with hypotension who presents with guarding and rebound tenderness.

The signs of unruptured ectopic pregnancy on examination include lower abdominal tenderness with or without rebound and pelvic tenderness, usually much worse on the affected side.

PELVIC EXAMINATION

The following findings may be observed on the vaginal examination.

- Vaginal bleeding may be observed on per speculum examination.
- Uterine or cervical motion tenderness on vaginal examination may suggest peritoneal inflammation.
- The uterus may be slightly enlarged and soft.
- An adnexal mass may be palpated (with or without tenderness).

Presence of a normal or slightly enlarged uterus and a palpable adnexal mass on vaginal examination and symptoms such as vaginal bleeding, and pelvic pain with manipulation of the cervix, significantly increase the likelihood of an ectopic pregnancy. Clinical examinations are not diagnostic because up to 30% of patients with ectopic pregnancies may have no vaginal bleeding, 90% may have a palpable adnexal mass, and up to 10% have negative pelvic examinations. The overall likelihood of ectopic pregnancy is nearly 39% in a patient with abdominal pain and vaginal bleeding but no other risk factors. The probability of ectopic pregnancy increases to 54% if the patient has other risk factors (e.g., history of tubal surgery, ectopic pregnancy, or pelvic inflammatory disease, in utero DES exposure, or an intrauterine device

in situ at the time of conception). Gynecologists should therefore remember that no combination of physical examination findings can reliably exclude ectopic pregnancy. Abdominal rigidity, involuntary guarding, and severe tenderness as well as evidence of hypovolemic shock, such as orthostatic blood pressure changes and tachycardia, should alert the clinician to a surgical emergency; this may occur in up to 20% of cases.

Differential Diagnosis

Obstetric Causes

- Threatened or incomplete miscarriage.
- Early pregnancy with pelvic tumors.
- Septic abortion.

Gynecological Causes

- Pelvic inflammatory disease.
- Ruptured or hemorrhagic corpus luteum.
- Salpingitis.
- Adnexal torsion.
- Degenerating fibroids.
- DUB.
- Endometriosis.
- Ovarian torsion.
- Tubo-ovarian abscess.

Non-gynecological Diseases

- Appendicitis.
- Urinary calculi.
- Gastroentritis.
- Intraperitoneal hemorrhage.
- Perforated peptic ulcer.

Management

By the early 20th century, the standard treatment for ectopic pregnancy included laparotomy and ligation of the bleeding vessels with removal of the affected tube (salpingectomy). Since the 1980s and 1990s, medical therapy of ectopic pregnancy had been implemented and had replaced surgical treatment in many cases. However, now in the 21st century, the treatment modality has shifted towards minimal invasive surgery (operative laparoscopy), and salpingostomy, which have largely replaced laparotomy and salpingectomy. Whenever the tubal ectopic pregnancy is diagnosed or suspected, the patient should be admitted immediately to the hospital. If the patient is in a state of shock, it needs to be treated first. Transfusion with blood, plasma or substitutes needs to be arranged as soon as possible. If in shock, resuscitation and surgery at the same time can be life saving. Immediate laparotomy and clamping of the bleeding vesssels may be the only way of saving the life of a moribund patient. Management plan for a patient with suspected ectopic pregnancy has been summarized in flow chart 25.1.

Investigations

Blood (ABO and Rh type)

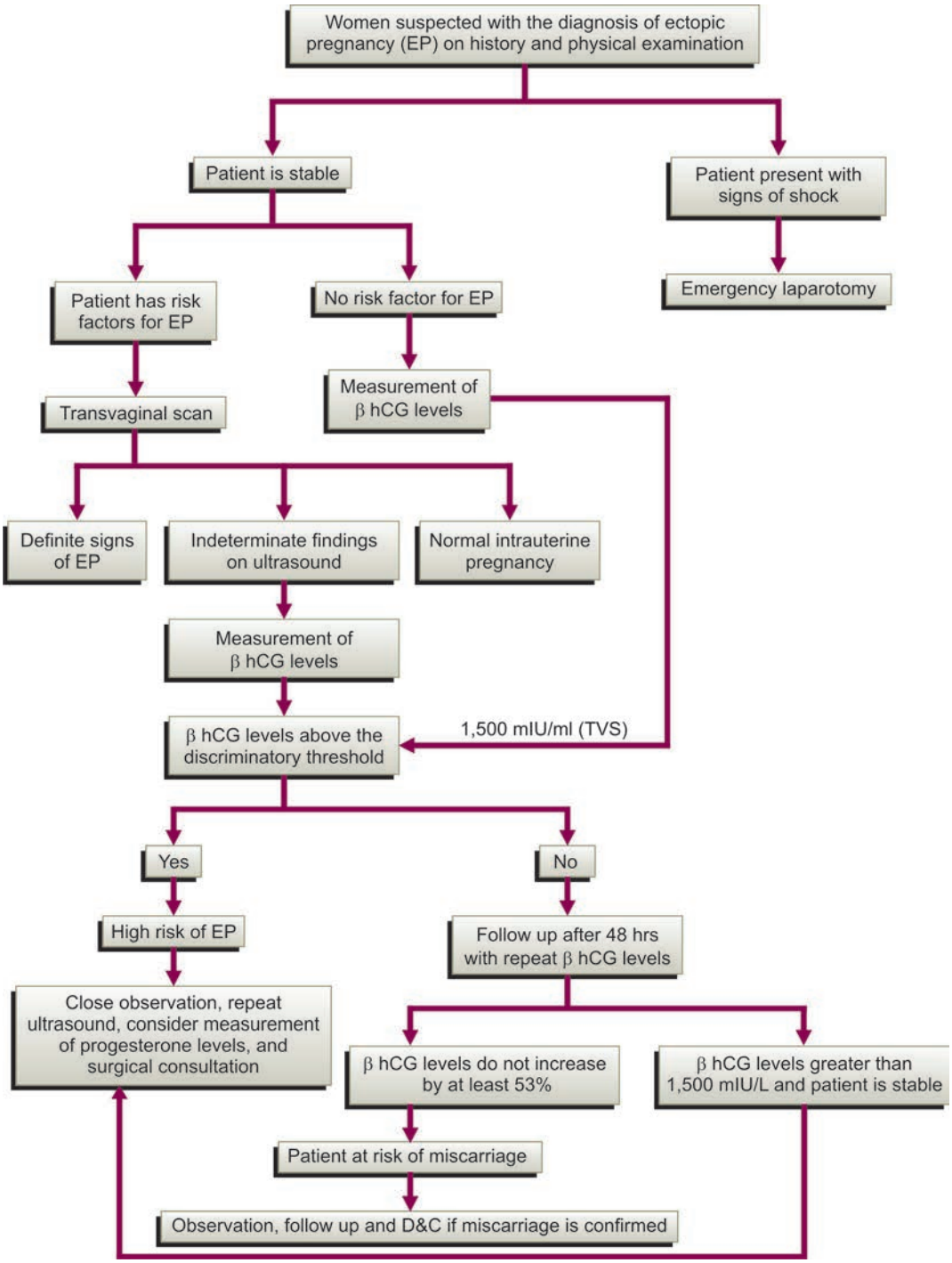
Blood typing (ABO and Rh), and antibody screen should be done in all pregnant patients with bleeding to identify Rh negative pregnant patients in whom bleeding would be associated with an increased risk of Rh isoimmunization. Such patients require to be injected with 50 μg of anti-D immune globulins (Rhogam) to prevent the occurrence of hemolytic disease of the newborn. Blood must be typed and crossed in order to ensure availability of blood products in case of excessive blood loss. Hemoglobin or hematocrit levels must be measured serially in order to quantify blood loss.

Urine or Serum β hCG Levels

In the emergency department, pregnancy is diagnosed by determining the levels of β human chorionic gonadotropin (β hCG) levels in the urine or serum. This hormone may be detected in the urine and blood as early as 1 week before an expected menstrual period. While urine testing may detect levels up to 20–50 IU/L, serum testing may detect levels as low as 5 IU/L. In most cases of suspected ectopic pregnancy, screening is initially done with urine pregnancy test. Determination of serum β hCG levels is a time consuming procedure and may not be a practical option at the time of emergency. However, if pregnancy is strongly suspected, even when the urine pregnancy test has a negative result, serum testing becomes necessary. The quantitative level of β hCG found in ectopic pregnancy varies. In a normal pregnancy, the β hCG level doubles every 48–72 hours until it reaches 10,000–20,000 mIU/mL. Normal intrauterine pregnancies are associated with a doubling time of 1.4–2.1 days. According to the ACOG recommendations (2008), an increase in serum human chorionic gonadotropin of less than 53% in 48 hours confirms an abnormal pregnancy. With ectopic pregnancies, β hCG levels usually increase at a reduced rate. Therefore, rising, falling or plateauing of β hCG levels are indicative of ectopic pregnancy.

A single serum measurement of the β hCG concentration, however, cannot definitely identify the presence of an intrauterine gestational sac. Although women with an ectopic pregnancy tend to have lower β hCG levels than those with an intrauterine pregnancy, there is considerable overlap.

Flow chart 25.1: Management of patients with suspected diagnosis of ectopic pregnancy



Therefore serial β hCG measurement is often used for women with first-trimester bleeding or pain, or both. However, similar to a single measurement, serial measurement of β hCG levels also cannot confirm the intrauterine location of the gestational sac. In a patient with a subnormal increase in β hCG concentration, nonviability is assumed, and more invasive investigations must be used for differentiating between miscarriage and ectopic pregnancy. Though the falling β hCG levels confirm nonviability, at the same time they do not rule out ectopic pregnancy. The lack of an IUP when the β hCG

level is above the discriminatory zone represents an ectopic pregnancy or a recent abortion.

Discriminatory zone of β hCG

The discriminatory zone of β hCG is the level above which a normal intrauterine pregnancy (IUP) is reliably visualized in nearly 100% cases. Ectopic pregnancy is suspected if transabdominal ultrasonography does not show an intrauterine gestational sac and the patient's β hCG level is greater than 6,500 mIU per mL (6,500 IU per L) or if transvaginal ultrasonography does not show an intrauterine gestational sac and the patient's β hCG level is 1,500 mIU per mL (1,500 IU per L) or greater.

Imaging Studies

Ultrasonography, especially transvaginal sonography or endovaginal ultrasonography should be the initial investigation of choice for symptomatic women in their first trimester. TVS can be performed either in the outpatient clinic or emergency department to diagnose intrauterine pregnancy. Transvaginal ultrasonography has been reported to have sensitivity of 90%, specificity of 99.8%, with positive and negative predictive values of 93% and 99.8% respectively. Not only is this highly accurate in identifying ectopic pregnancy, but it also helps in determining the health and viability of the patient's intrauterine pregnancy.

Signs of an IUP on TVS

Presence of a gestational sac with a sonolucent center (>5 mm in diameter) is indicative of an intrauterine pregnancy. Gestational sac is surrounded by a thick, concentric, echogenic ring located within the endometrium and contains a fetal pole, yolk sac, or both. A normal gestational sac, an ovoid collection of fluid adjacent to the endometrial stripe, can be visualized by means of the transvaginal probe at a gestational age of about 5 weeks. It can often be seen when it is 2 or 3 mm in diameter and should be consistently seen at 5 mm. Since a pseudogestational sac is often associated with an ectopic pregnncy, presence of a sac alone cannot confirm intrauterine pregnancy. The earliest embryonic landmark, the yolk sac, appears when the sac is 8 mm or more in diameter, usually during the fifth week of gestation. Cardiac activity can be seen with endovaginal scanning when the embryo reaches 4 to 5 mm in diameter, at a gestational age of 6–6.5 weeks.

Probably abnormal IUP

The gestational sac is larger than 10 mm in diameter without a fetal pole or with a definite fetal pole but without cardiac activity. In these cases, the gestational sac frequently has an irregular or crenated border.

Definite ectopic pregnancy

Signs of a definite ectopic pregnancy on TVS examination are as follows:

- A thick, bright echogenic, ring-like structure, which is located outside the uterus, having a gestational sac containing an obvious fetal pole, yolk sac or both. This usually appears as an intact, well defined tubal ring (Doughnut or Bagel sign). Though this finding confirms the diagnosis of ectopic pregnancy, it may not always be present.
- An empty uterus or presence of a pseudogestational sac. Pseduogestational sac is typically formed due to endometrial changes and fluid collection on the endometrial cavity occurring with implantation of extrauterine pregnancy. The gestational sac of a normal intrauterine pregnancy is placed eccentrically, where as a psedugestational sac is centrally placed. An empty uterus on TVS images in patients with a serum β hCG level greater than the discriminatory cut-off value is considered to be an ectopic pregnancy until proven otherwise. An empty uterus also may represent a recent abortion. However, in that case, serum β hCG levels would not be greater than the discriminatory cut-off value.
- Cystic or solid adnexal or tubal masses (including the tubal-ring sign, representing a tubal gestational sac) (figures 25.3 and 25.4) and severe adnexal tenderness with probe palpation are also suggestive of ectopic pregnancy.
- Hematosalpinx (presence of free fluid or blood in the fallopian tubes) and echogenic or sonolucent cul-de-sac fluid.
- Ruptured ectopic pregnancy: In case of a ruptured ectopic pregnancy, the ultrasonographic findings include presence of free fluid or clotted blood in the cul-de-sac or in the intraperitoneal gutters (Morrison pouch).

The criteria for TVS diagnosis of ectopic pregnancy, given by Rottem et al (1991), are described in table 25.2.

If a low-risk patient's ultrasonography is negative for intrauterine pregnancy, she is hemodynamically stable and

Table 25.2: The criteria for TVS diagnosis of ectopic pregnancy

Stage	*TVS finding*
Type 1A	Well defined tubal ring displaying fetal heart.
Type 1B	Well defined tubal ring displaying no fetal heart.
Type 2	Ill defined tubal mass.
Type 3	Free pelvic fluid, empty uterus, displaying no adnexal mass.

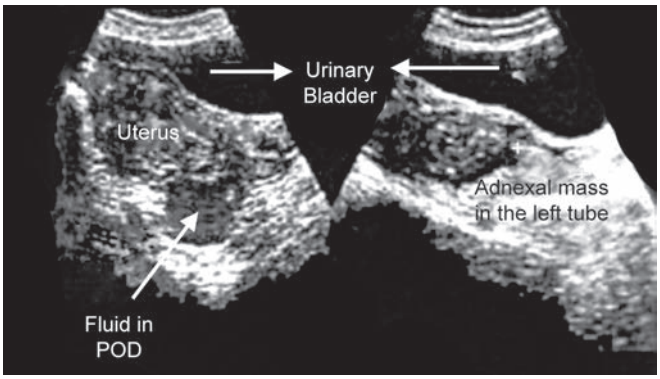


Fig. 25.3: Ultrasound showing an ectopic pregnancy of the left tube

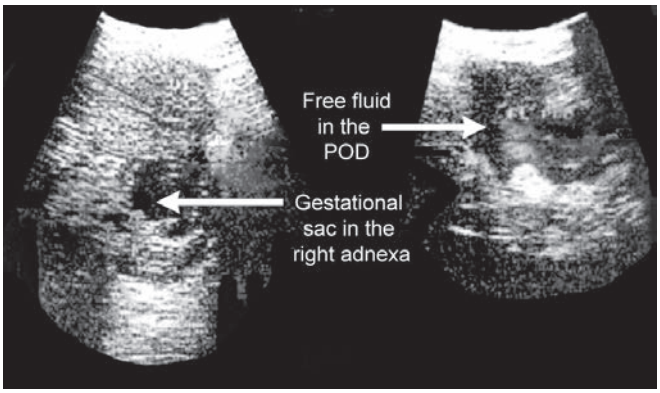


Fig. 25.4: Ultrasound showing an ectopic pregnancy in the right tube

has a β hCG level less than 1,500 mIU per mL, the physician should take another β hCG measurement after 48 hours. Patients with a nondiagnostic transvaginal ultrasonography results and a β hCG level of 1,500 mIU per mL or greater are at an increased risk for ectopic pregnancy and may require a surgical consultation and must remain under vigilance. Serial measurement of β hCG and progesterone concentrations may also be useful when the diagnosis remains unclear.

Other Tests

Progesterone has been used by some in assessment of an ectopic pregnancy. While a value of 25 ng/mL is associated with normal pregnancies in 98% of cases, a value of less than 5 ng/mL identifies a nonviable pregnancy without regard to location of the pregnancy. Most women with an ectopic pregnancy would show serum progesterone levels somewhere in between these two values, limiting the clinical usefulness of progesterone in diagnosing an ectopic pregnancy. Measurement of the serum concentration of progesterone has been investigated as a potentially useful adjunct to serum β

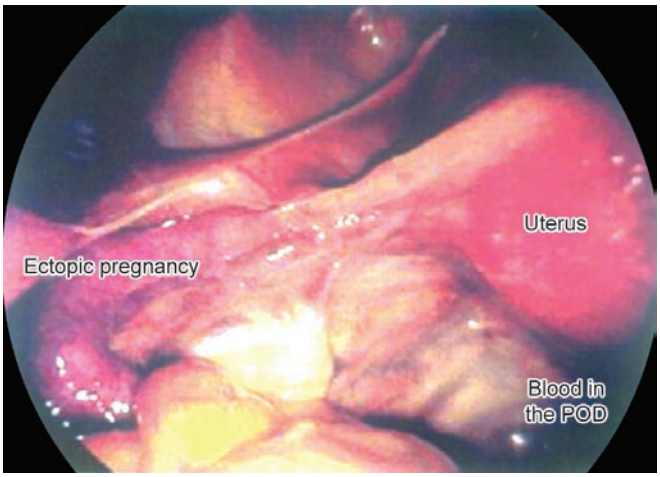


Fig. 25.5: Unruptured ectopic pregnancy in the ampulla of right tube

hCG measurement, since progesterone levels are stable and independent of gestational age in the first trimester. Rapid progesterone analysis can identify two important subgroups of patients in the emergency department with symptomatic first-trimester bleeding or pain, or both: Stable patients with progesterone levels above 22 ng/mL, who have a high (but not certain) likelihood of viable intrauterine pregnancy; and patients with levels of 5 ng/mL or less, who almost certainly have a nonviable pregnancy. Invasive diagnostic testing (e.g., D&C) could be offered to the latter, as could treatment with methotrexate, without fear of interrupting a potentially viable intrauterine pregnancy. Serum progesterone levels can detect pregnancy failure and identify patients at risk for ectopic pregnancy, but they are not diagnostic of ectopic pregnancy. Sensitivity for diagnosis of ectopic pregnancy is very low (15%); therefore, 85% of patients with ectopic pregnancy will have normal serum progesterone levels.

Diagnostic Procedures

Laparoscopic examination

Sometimes in case of doubt, laproscopic examination may be performed to diagnose an ectopic pregnancy. In case, the diagnosis of ectopic pregnancy is confirmed on laparoscopic examination (figures 25.5 and 25.6), definitive treatment (salpingectomy or salpingostomy) may be carried out.

Culdocentesis

Culdocentesis can be performed to help diagnose blood in the cul-de-sac (figure 25.7). Presence of non-clotted blood in the pouch of Douglas is diagnostic of chronic hemorrhage in the abdomen and is suggestive of a ruptured ectopic pregnancy.

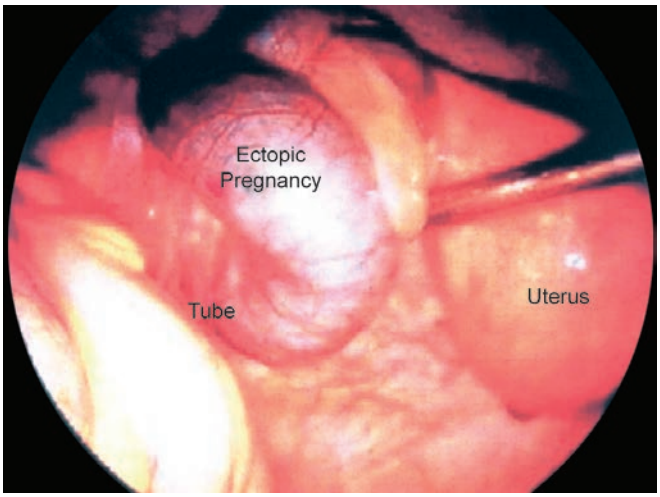
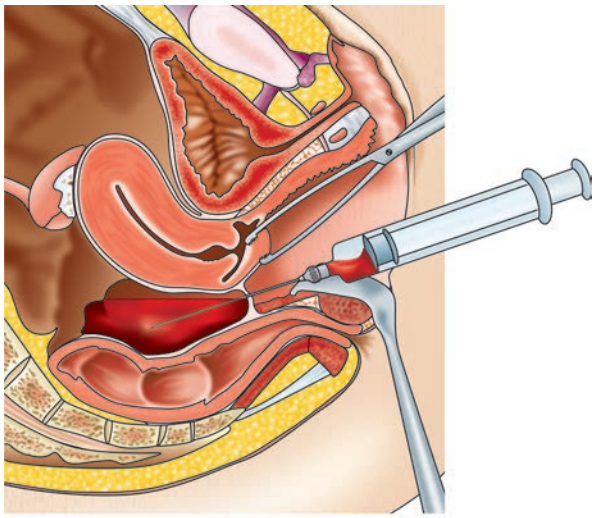


Fig. 25.6: Unruptured tubal ectopic pregnancy on the right side



The process of culdocentesis showing extraction of blood from the pouch of Douglas. It is used as a diagnostic test for identifying ectopic pregnancy

Fig. 25.7: Procedure of culdocentesis

Rx *Treatment/Gynecological Management*

Various treatment options for ectopic pregnancy include expectant, medical and surgical management (flow chart 25.2). Before deciding the treatment option in a woman with ectopic pregnancy, she and her partner must be fully involved in deciding the relevant management. They must be provided with the written information regarding the various treatment options and carefully explained about the advantages and disadvantages associated with each approach. Before deciding the appropriate surgical management, the opposite tube and ovary must definitely be examined. The procedure must then be performed after taking into consideration the patient's age, future reproductive capacity as well as the nature of lesion. Decisions regarding management should be based on the following inclusion criteria. Some of these are as follows:

- Patient's hemodynamic stability: Treatment of an ectopic pregnancy varies, depending on how medically stable the woman is. Surgery is the only treatment option which must be used in hemodynamically unstable patients.
- The size of ectopic pregnancy.
- Location of the pregnancy.

The various treatment options for ectopic pregnancy are described below in details:

Expectant Management

Expectant management of ectopic pregnancy is based on the assumption that a certain proportion of all ectopic pregnancies will regress spontaneously and be slowly absorbed. Such pregnancies will not progress to tubal rupture. This may be a possibility in cases where the hCG levels appear to be falling and the woman appears clinically well. If the initial hCG level is less than 200 mIU/mL, 88% of patients may experience spontaneous resolution. Expectant management should be offered only when transvaginal ultrasonography fails to show the location of the gestational sac and the serum levels of β hCG and progesterone are low and declining, and the patient desires future fertility. The criteria for expectant management of ectopic pregnancy are as follows:

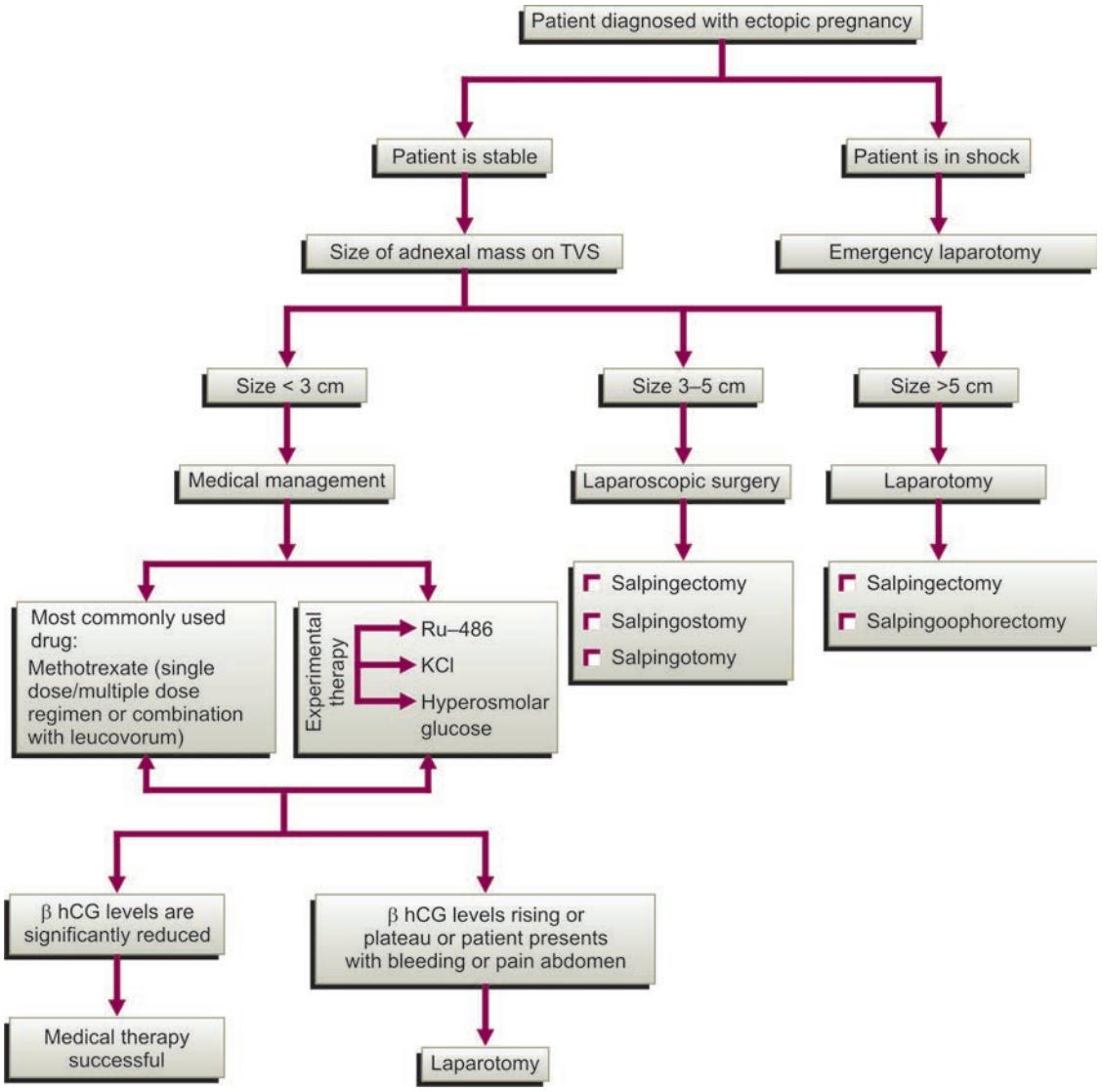
- Serum hCG levels < 200 mIU/ml.
- Ectopic pregnancy is suspected, but TVS fails to reveal suggestive extrauterine findings.
- Size of ectopic pregnancy is less than 2 cm.
- Hemoperitoneum is less than 50 ml.

In certain cases which appear to be candidates for expectant management, imaging and laboratory assessment may not be able to clearly distinguish between a failed intrauterine pregnancy and a resolving ectopic pregnancy. Expectant treatment should be abandoned if a patient experiences significant increase in abdominal pain, serum hCG starts to increase or fails to decrease, or a patient shows signs of tubal rupture. Due to the possibility of tubal rupture, these patients must be carefully monitored until the serum β hCG concentration falls below 15 IU/L; and serum progesterone levels < 5 ng/ml. At this point almost all ectopic pregnancies resolve spontaneously, without rupture.

Medical Management (Methotrexate)

Medical management is nowadays being sometimes employed in stable patient with a medically treatable ectopic pregnancy

Flow chart 25.2: Treatment plan for patients with ectopic pregnancy



or in presence of other medical conditions which would make the risk of surgery unacceptable. An early ectopic pregnancy can sometimes be treated with an injection of methotrexate, which stops the growth of the embryo. Initial protocols for medical treatment of ectopic pregnancy required long-term hospitalization and multiple doses of methotrexate. This was associated with significant side effects. With the advancement in science and technology over the years, modification and refinements of the protocols for medical therapy of ectopic pregnancy have now allowed for single-dose outpatient therapy. While methotrexate presently remains the most effective and commonly used drug in medical therapy for treatment of an ectopic pregnancy, other protocols, using drugs such as potassium chloride, hyperosmolar glucose, RU 486, and prostaglandins, have also been used. These drugs may be administered orally, systemically, and locally into the ectopic pregnancy under direct vision. However, these therapies are largely experimental at present since there is limited experience in using them and the efficacy of such treatment modalities over standard methotrexate protocol has not been established. Presently, the focus is mainly on the use of methotrexate therapy for treatment of ectopic pregnancy. Methotrexate therapy can be offered to the women who show abnormal doubling rate of the β hCG levels and an extrauterine gestational sac has been identified on sonographic examination. Before administration of methotrexate, the prerequisites mentioned in table 25.3 must be fulfilled.

Table 25.3: Prerequisites for starting medical treatment of ectopic pregnancy

Patient is hemodynamically stable and does not have pelvic pain.
Patient desires future fertility.
Patient appears to be reliable and compliant who will return for post-treatment follow up care.
Ectopic pregnancy smaller than 4 cm in diameter and no fetal heart activity on TVS or smaller than 3.5 cm with presence of cardiac activity and absence of any free fluid in the pouch of Douglas.
There is no evidence of tubal rupture.
Serum hCG is below 3000 IU/L, with minimal symptoms.
Availability of facilities for follow up care following the use of methotrexate.
Patient agrees to use reliable contraception for 3-4 months post treatment.
Patient has no underlying severe medical condition or disorder.
There is no underlying abnormality of LFT, KFT or FBC suggestive of liver, renal or bone marrow impairment.
Patient does not have any known contraindications to methotrexate.
Patient is not currently taking non-steroidal antiinflammatory drugs (NSAID), diuretics, penicillin and tetracycline group of drugs.
Patient does not have a co-existing intrauterine pregnancy.
Patient is not breastfeeding.

Table 25.4: Contraindications to methotrexate therapy

Absolute contraindications
Pregnancy and lactation.
Hepatic, renal, or hematologic dysfunction e.g., liver disease with a transaminase level two times greater than normal, renal disease with a creatinine level greater than 1.5 mg per dL (133 µmol per L).
Overt or laboratory evidence of immunodeficiency with a white blood cell count less than 1,500 per mm^3 (1.5 x 10^9 per L).
Peptic ulcer disease.
Alcoholism, alcoholic liver disease, or other chronic liver disease.
Active pulmonary disease.
Preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia [platelet count less than 100,000 per mm^3 (100×10^9 per L), or significant anemia.
Known sensitivity to methotrexate.
Relative contraindications
Gestational sac larger than 3.5 cm.
Presence of embryonic cardiac activity.

Methotrexate (MTX) is a folic acid antagonist, which inhibits DNA synthesis in actively dividing cells, including trophoblasts. When administered to properly selected patients, it has been found to be associated with a success rate of up to 94%. Side effects of methotrexate therapy include bone marrow suppression, elevated liver enzymes, rash, alopecia, stomatitis, nausea, and diarrhea. The time to resolution of the ectopic pregnancy is usually between 3 to 7 weeks following methotrexate therapy.

One of the best predictors of success of medical therapy is the initial serum β hCG levels. Success rates of more than 90% can be achieved with single-dose methotrexate when hCG levels are less than 5000 mIU/mL. Success rates with single-dose methotrexate have been observed to progressively decrease as serum hCG levels increase. The overall success rate with multiple-dose MTX therapy has been found to be greater than that associated with single-dose methotrexate therapy. However, single-dose therapy is less expensive, has a lower rate of side effects (29% vs. 48%), requires less intensive monitoring, and does not require rescue with folinic acid. Absolute and relative contraindications to methotrexate therapy have been described in table 25.4.

Protocol for single-dose methotrexate

The protocol for single-dose methotrexate is described in table 25.5. Patients treated with MTX should be followed closely. The serum β hCG concentration should be measured weekly.

On discharge from oncology unit, the women should be advised that she may experience some pain in the abdomen as the pregnancy resolves. Mild abdominal pain could be due to tubal abortion or tubal distention because of hematoma formation. Severe abdominal pain, however, can be a sign of actual or impending tubal rupture.

Protocol for multi-dose methotrexate regimen

Multi-dose regime of methotrexate may be considered for women with cervical or cornual ectopic pregnancies, after discussion with gynecology consultant (table 25.6). In this regimen, methotrexate is administered in the dose of 1 mg/kg body weight via intramuscular route every other day alternately along with leucovorin in the dose of 0.1 mg per kg body weight. Follow up with LFTs, CBC, KFT and serum β hCG levels is required at baseline, day 1, day 3, day 5 and day 7 until the serum β hCG levels decrease. Weekly follow-up must be with serum β hCG levels until serum β hCG are no longer detected.

Surgical Treatment

Surgical treatment in form of open surgery (laparotomy) or minimal invasive surgery (laparoscopy) is the most commonly used treatment option. The procedures which can be performed at the time of both laparotomy and laparoscopy include salpingectomy or salpingotomy. In a

Table 25.5: Protocol for single-dose methotrexate

Pretreatment investigations

Complete blood count.

Blood group typing (ABO & Rh) and antibody testing.

Liver function and kidney function tests.

Measurement of serum β hCG levels.

Transvaginal sonography.

Pretreatment prerequisites

Written informed consent must be obtained from the patient and her partner.

Woman's weight and height must be obtained and her body surface area must be calculated.

Day 0 (day of treatment)

Methotrexate needs to be injected in the dosge of 50 mg/m^2 intramuscular injection.

RhoGAM (300 µgms) intramuscular if the patient is Rh negative.

Advise patients not to take vitamins with folic acid until complete resolution of the ectopic pregnancy occurs.

Folinic acid supplements to be discontinued.

They should also refrain from strenuous exercises, alcohol consumption and intercourse for the same period.

Day 4

Measurement of the β hCG levels must be performed, and serve as the baseline level against which subsequent levels are measured.

Day 7

Serum β hCG levels are measured on day 7. If the β hCG level has dropped by 15% or more since day 4, weekly hCG levels must be obtained until they have reached the negative level. If the weekly levels plateau or increase, a second course of methotrexate may be administered. Second dose of methotrexate may also be required if decline in β hCG levels is less than 25% on day 7. If no drop has occurred by day 14, surgical therapy is indicated.

If the patient develops increasing abdominal pain after methotrexate therapy, repeat a transvaginal scan to evaluate for possible rupture.

AST levels, CBC and TVS also need to be done

Weekly

Measure serum β hCG concentrations, until levels become < 15 IU/L.

Perform TVS.

Anytime

Perform laparoscopy if the patient has severe abdominal pain, acute abdomen or if the ultrasound reveals blood in the abdomen.

Table 25.6: Methotrexate multi-dose regime

Methotrexate Regime
Methotrexate to be administered in the dose of 1 mg/kg IM, on alternate days (days 1, 3, 5 and 7) for total of 4 doses.
Leucovorin calcium must be administered in the dosage of 0.1 mg per kg body weight IM on alternate days (30 hours after previous methotrexate injection) – days 2, 4, 6, 8.
Srum β hCG levels must be measured at weekly intervals until <5 IU/L.

Table 25.7: Indications for surgical therapy

Candidate not suitable for medical therapy.

Failed medical therapy.

Heterotopic pregnancy with a viable intrauterine pregnancy.

Patient is hemodynamically unstable and requires immediate treatment.

Preoperative preparation.

hemodynamically stable patient, a laparoscopic approach is preferable to laparotomy. If the woman is not hemodynamically stable, the most expedient method of surgical management should be chosen, i.e. laparotomy. Some indications for surgical therapy are described in table 25.7.

- Treatment needs to be explained to the women and her partner and written informed consent must be obtained.
- Patient's blood sample needs to be typed and cross-matched (ABO and Rh) and blood needs to be arranged.

Anti-D immunoglobulins need to be administered to the women who are Rhesus negative.

The following steps need to be taken in women who are hemodynamically unstable:

- Immediate resuscitation.
- Securing immediate IV access by inserting large bore venous cannula.
- Sending blood for full blood count and cross matching and arranging at least four units of blood.
- Informing the theater staff; anesthetist; and on-call gynecology consultant.
- Foley's catheter must be inserted prior to starting the procedure.

The urgency of the situation must be stressed to all concerned. The surgery must not be delayed and should be performed even before blood and fluid losses have been replaced.

Type of surgical approach

Surgical therapy may be either in form of open laparotomy or via the laparoscopic route. Nowadays, the trend is towards using a conservative approach for surgery. Numerous factors need to be considered before deciding the type of surgical approach to be used. Some of these factors include history of multiple prior surgeries, pelvic adhesions, skill of the surgeon and surgical staff, availability of the equipment, condition of the patient and size and location of ectopic pregnancy. As previously described, a laparoscopic approach to the surgical management of tubal pregnancy must be used in the hemodynamically stable patients. On the other hand, management of tubal pregnancy in the presence of hemodynamic instability should be by laparotomy. There

Table 25.8: Advantages of laparoscopic surgery

Less postoperative pain.
Faster recovery.
Short hospital stay.
Lower rate of postoperative complications like wound infection.
Cost-effectiveness.
Reduced postoperative analgesic requirement.
Reduced adhesion formation.

Table 25.9: Complications due to laparoscopic surgery

Missed diagnosis.
Bleeding.
Incomplete removal of ectopic pregnancy.
Visceral Injury.
Leakage of purulent exudates.
Intraabdominal abscess.
Hernia.

is no role for medical management in the treatment of tubal pregnancy or suspected tubal pregnancy when a patient is showing signs of hypovolemic shock.

Laparoscopic Surgery

Benefits of laparoscopic management of tubal pregnancy

Laparoscopic management is associated with considerably reduced postoperative morbidity, duration of hospital stay, complication rate and time duration of return to normal activity level. Most cases of ruptured as well as unruptured tubal pregnancy can be treated laparoscopically. Laparoscopic management is a useful method for reducing hospital stay, complications and return to normal activity. The main advantages of laparoscopic surgery are enumerated in table 25.8.

Complications due to laparoscopic management of ectopic pregnancy

In experienced hands there is no specific complication directly related to laparoscopic procedure, but if the surgeon is not trained enough in laparoscopy then the chance of following complications as described in table 25.9 are there. However, in experienced hands, the chances of these complications are extremely rare. Altogether, laparoscopic procedure has a much lower complication rate in comparison to the conventional surgery.

Laparotomy

There are times when laparotomy is favored over the laparoscopic approach. Some of these indications are described in table 25.10.

Laparotomy is usually preferred in cases of hemodynamic instability or when ectopic pregnancy is cervical, interstitial, abdominal, etc. Laparotomy is also preferred in patients having large hematoma due to large ruptured ectopic pregnancy or in case of presence of more than 1500 cc hemoperitoneum. Patient with cardiac diseases and COPD should not be considered a good candidate for laparoscopic management.

Table 25.10: Indications for laparotomy

Patient is hemodynamically unstable.
Cervical, interstitial or abdominal ectopic pregnancy.
Patients having large hematoma due to large ruptured ectopic pregnancy.
Presence of more than 1500 cc hemoperitoneum.
Patients with underlying cardiac diseases and chronic obstructive pulmonary disease.
History of abdominal surgery in the past.
Patients at increased risk of complications with general anesthesia.

Laparoscopic management of ectopic pregnancy may also be more difficult in patients who have had previous lower abdominal surgery or those who may also be at an increased risk for complications with general anesthesia combined with pneumoperitoneum, e.g. the elderly patients.

The surgical procedure performed during laparotomy is usually sapingectomy, which is described below:

Surgical Procedures at the Time of Laparotomy

Salpingectomy

Salpingectomy involves removal of the ectopic pregnancy along with the fallopian tube of affected side. Milking of pregnancy through abdominal ostium (transfimbrial extraction) has been advocated in the past if the hemorrhage is easy to control and pregnancy is fimbrial. However, the risk of recurrent ectopic pregnancy in these cases is twice as high. Therefore, this procedure is no longer recommended.

Regardless of the route of approach (whether laparotomy and laparoscopy), salpingectomy is indicated in the situations enumerated in table 25.11.

Procedure of salpingectomy

The procedure of salpingectomy involves the following steps:

- The tube between the uterus and the ectopic pregnancy is clamped using a clamp. The pedicle is then cut and ligated.
- The tubo-ovarian artery is also clamped, cut and ligated, while preserving the utero-ovarian artery and ligament.

Table 25.11: Indications for salpingectomy
The tube is severely damaged.
There is uncontrolled bleeding.
There is a recurrent ectopic pregnancy in the same tube.
There is a large tubal pregnancy of size >5 cm.
The ectopic pregnancy has ruptured.
The woman has completed her family and future fertility is not desired.
Ectopic pregnancy has resulted due to sterilization failure.
Ectopic pregnancy has occurred in a previously reconstructed tube.
Patient requests sterilization.
Hemorrhage continues to occur even after salpingotomy.
Cases of chronic tubal pregnancy.

- The mesosalpinx must be continued to be clamped, cut and ligated until the tube is free and can be removed.

Partial salpingectomy

Partial salpingectomy may be sometimes performed instead of complete salpingectomy if the pregnancy is in the mid portion of the tube, none of the indications for salpingectomy are present, and the patient appears to be a candidate for tubal reanastomosis in future. In these cases, a clamp is placed through an avascular area in the mesosalpinx under the ectopic pregnancy. This creates spaces through which two free ties are placed, which are tied around the tube on each side of the ectopic pregnancy. The isolated portion of the tube containing the ectopic pregnancy is then cut and removed.

Follow up

All patients who have not had the entire ectopic pregnancy removed by salpingectomy need to have their weekly hCG levels observed until these levels return to non-pregnant values. If, during this time span the hCG level either plateaus or rises, the patient must be treated with methotrexate. Patients should be advised to use some form of effective contraception until their hCG levels have returned to non-pregnant levels.

Salpingotomy

Tube-sparing salpingostomy or salpingotomy is a procedure in which the gestational sac is removed, without the removal of tube, through a 1-cm-long incision on the tubal wall. This surgery is preferred over salpingectomy because not only is salpingotomy less invasive, but it is also associated with comparable rates of subsequent fertility and ectopic pregnancy. Laparoscopic salpingotomy should especially be considered as the primary modality of treatment if the woman has contralateral tube disease and desires future fertility.

When salpingotomy is used for the management of tubal pregnancy, follow-up protocols (weekly serum β hCG levels) are necessary for the identification and treatment of women with persistent trophoblastic disease. Persistent trophoblast is detected by the failure of serum hCG levels to fall as expected after initial treatment.

Procedure

After infiltrating the mesosalpinx with vasopressin (20 IU in 50 mL NS), 1- to 2-cm incision is made on the antimesenteric side of the tube. A syringe filled with saline is inserted deep into the incision and the fluid is injected forcefully in such a way so as to dislodge the ectopic pregnancy and clots. The contents of ectopic pregnancy and clots are aspirated out. Following this, the bed of the ectopic pregnancy must be irrigated well. In case some trophoblastic tissue remains, the prior injection of vasopressin may lead to anoxia and death of the trophoblasts, preventing postoperative growth. Bleeding may be controlled by applying pressure with blunt tissue forceps for 5 minutes.

Postoperative follow up

- Regular follow up must be done following surgery in order to ensure that the patient's hCG levels have returned to zero. This may take several weeks. Elevated hCG levels could mean that some ectopic trophoblastic tissue which was missed at the time of removal is still remaining inside. This tissue may have to be removed using methotrexate or additional surgery.
- The patient must be instructed to visit the clinician after one week for removal of sutures.
- The patient must be counseled that she may experience mild bleeding or pain during the first postoperative week. In case of mild pain, she can use simple analgesic drugs available over the counter. In case of pain or bleeding of severe intensity, she must be instructed to report to the clinician immediately.

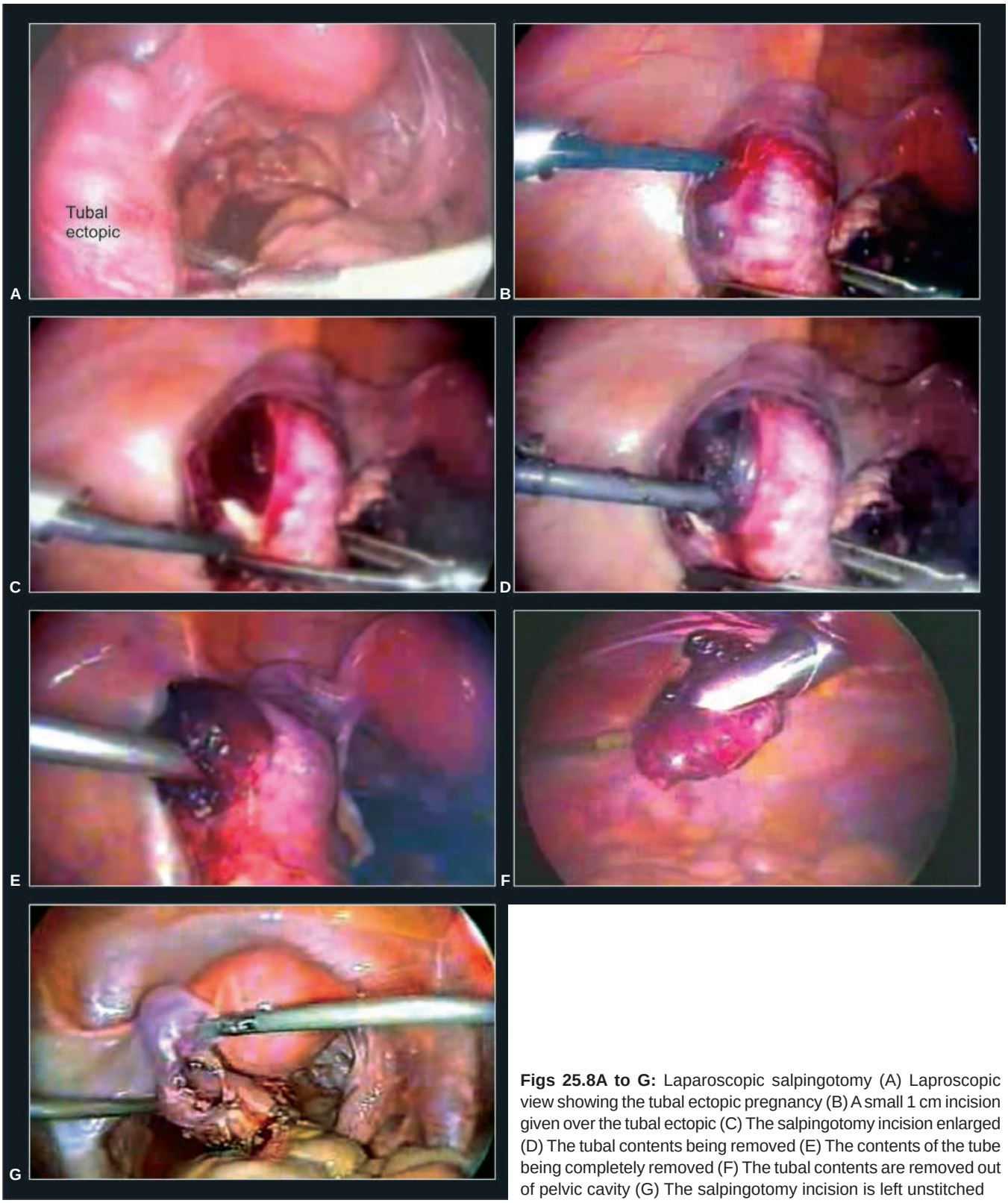
Laparoscopic Surgery

Laparoscopic Salpingectomy

Laparoscopic salpingectomy involves the use of bipolar cautery for desiccation of tube. The rest of the procedure is same as that performed during laparotomy.

Tube-sparing Salpingotomy

- The procedure of laparoscopic salpingotomy (figures 25.8A to G) is same as that described with laparotomy before.



Figs 25.8A to G: Laparoscopic salpingotomy (A) Laproscopic view showing the tubal ectopic pregnancy (B) A small 1 cm incision given over the tubal ectopic (C) The salpingotomy incision enlarged (D) The tubal contents being removed (E) The contents of the tube being completely removed (F) The tubal contents are removed out of pelvic cavity (G) The salpingotomy incision is left unstitched

Important Questions and Answers

Q.1. What is the most likely diagnosis in the previously mentioned case study?

Ans. Based on the findings of the clinical presentation (history of amenorrhea, pelvic pain and abnormal bleeding in the first trimester); positive urine pregnancy test and transvaginal ultrasound examination (empty uterus, and an adnexal mass), the most likely diagnosis appears to be that of ectopic pregnancy.

Q.2. What would be the best treatment option in this case?

Ans. The patient is young and desires future pregnancy. Since the patient is hemodynamically stable and no cardiac activity was observed on ultrasound examination, the two most commonly used treatment modalities which can be considered in this case include medical and surgical options (laparoscopic salpingostomy). Both these treatment options have been described in details in the text. Medical therapy in form of a single intramuscular injection of MTX can be offered to this patient because she is hemodynamically stable and appears willing to come for regular follow up visits. Furthermore, the serum β hCG levels were less than 5000 mIU/L and there was no ultrasound evidence of fetal cardiac activity. In this patient, medical treatment with single dose methotrexate was ultimately chosen as the treatment option. The choice of medical treatment in this case was guided by the patient's preference, after having a detailed discussion with both her and her partner regarding monitoring, outcome, risks, and benefits of the two approaches.

Q.3. What are the prospects of future pregnancies in this patient?

Ans. Some women who have had ectopic pregnancies in past may have difficulty becoming pregnant in future. This difficulty is more common in women who also had fertility problems before developing ectopic pregnancy. The likelihood of a repeat ectopic pregnancy increases with each subsequent ectopic pregnancy. If the patient has had one ectopic pregnancy, there is an approximate 15% chance of developing another one in future. This risk increases to 32% in women who have had two consecutive ectopic pregnancies in the past. Approximately 30% of women treated for ectopic pregnancy are expected to have future difficulty in conceiving. The overall future conception rate in this case can be expected to vary between 70–85%.

Q.4. What is a heterotopic pregnancy?

Ans. Hetrotopic pregnancy is combined occurence of intrauterine pregnancy and ectopic pregnancy. It may occur in approximately 1 in 30,000 pregnancies and is more common in patients taking fertility inducing agents.

Bibliography

1. Abbott J, Emmans LS, Lowenstein SR. Ectopic pregnancy: Ten common pitfalls in diagnosis. Am J Emerg Med. 1990;8(6): 515-22.
2. Al-Sunaidi M, Tulandi T. Surgical treatment of ectopic pregnancy. Semin Reprod Med. 2007;25(2): 117-22.
3. American College of Obstetricians and Gynecologists (ACOG). Medical management of ectopic pregnancy. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2008 Jun. 7 p. (ACOG practice bulletin; no. 94).
4. Ankum WM. Mol BW. Van der Veen F. Bossuyt PM. Risk factors for ectopic pregnancy: A meta-analysis. Fertility & Sterility. 1996;65(6):1093-99.
5. Anonymous. Risk factor for ectopic pregnancy. Canadian Family Physician 1999;45:300,309-10.
6. Banerjee, S, Aslam, N, Zosmer, N, et al. The expectant management of women with early pregnancy of unknown location. Ultrasound Obstet Gynecol 1999;14:231.
7. Bangsgaard N, Lund CO, Ottesen B, Nilas L. Improved fertility following conservative surgical treatment of ectopic pregnancy. BJOG. 2003;110(8):765-70.
8. Condous G, Kirk E, Lu C, Van Huffel S, Gevaert O, De Moor B. Diagnostic accuracy of varying discriminatory zones for the prediction of ectopic pregnancy in women with a pregnancy of unknown location. Ultrasound Obstet Gynecol. 2005;26(7): 770-75.
9. Elson, J, Tailor, A, Banerjee, S, et al. Expectant management of tubal ectopic pregnancy: Prediction of successful outcome using decision tree analysis. Ultrasound Obstet Gynecol. 2004;23:552.
10. Farquhar CM. Ectopic pregnancy. Lancet. 2005;366(9485): 583-91.
11. Hajenius PJ, Mol F, Mol BW, Bossuyt PM, Ankum WM, van der Veen F. Interventions for tubal ectopic pregnancy. Cochrane Database Syst rev. 2007;(1):CD000324.
12. Hsu S, Mitwally MF, Aly A, et al. Laparoscopic management of tubal ectopic pregnancy in obese women. Fertil Steril. 2004; 81(1):198-202.
13. Jafri SZ, Loginsky SJ, Bouffard JA, Selis JE. Sonographic detection of interstitial pregnancy. J Clin Ultrasound. 1987;15(4): 253-57.
14. Kadar N, DeVore G, Romero R. Discriminatory hCG zone: Its use in the sonographic evaluation for ectopic pregnancy. Obstet Gynecol. 1981;58(2):156-61.
15. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: A systematic review. Lancet. 2006;367(9516):1066-74.
16. Kirk, E, Condous, G, Bourne, T. The non-surgical management of ectopic pregnancy. Ultrasound Obstet Gynecol 2006;27:91.
17. Korhonen, J, Stenman, UH, Ylostalo, P. Low-dose oral methotrexate with expectant management of ectopic pregnancy. Obstet Gynecol 1996;88:775.
18. Leach RE, Ory SJ. Modern management of ectopic pregnancy. J Reprod Med. 1989;34(5):324-38.
19. Lipscomb GH. Medical therapy for ectopic pregnancy. Semin Reprod Med. 2007;25(2):93-98.

20. Luciano DE, Jain A, Roy G, Solima E, Luciano AA. Ectopic pregnancy—from surgical emergency to medical management. J Am Assoc Gynecol Laparosc. 2004;11(1):107-21.
21. Lund, J. Early ectopic pregnancy; comments on conservative treatment. J Obstet Gynaecol Br Emp. 1955;62:70.
22. Mateer JR, Valley VT, Aiman EJ, et al. Outcome analysis of a protocol including bedside endovaginal sonography in patients at risk for ectopic pregnancy. Ann Emerg Med. 1996;27(3): 283-89.
23. Rantala, M, Makinen, J. Tubal patency and fertility outcome after expectant management of ectopic pregnancy. Fertil Steril. 1997;68:1043.
24. Raughley MJ, Frishman GN. Local treatment of ectopic pregnancy. Semin Reprod Med. 2007;25(2):99-115.
25. RCOG (2004). The management of tubal pregnancy. Guideline No. 21.
26. Sowter MC, Farquhar CM. Ectopic pregnancy: An update. Curr Opin Obstet Gynecol. 2004;16(4):289-93.
27. Stovall TG, Kellerman AL, Ling FW, Buster JE. Emergency department diagnosis of ectopic pregnancy. Ann Emerg Med. 1990;19(10):1098-103.
28. Stovall TG, Ling FW, Gray LA. Single-dose methotrexate for treatment of ectopic pregnancy. Obstet Gynecol. 1991;77(5): 754-57.
29. Zohav E, Gemer O, Segal S. Reproductive outcome after expectant management of ectopic pregnancy. Eur J Obstet Gynecol Reprod Biol. 1996;66:1.

Section 7

Abnormalities in Conception

- Infertility
- Amenorrhea

Chapter

26

Infertility

Case Study

A 28-year-old woman married since last 5 years presented to the Gynecology OPD along with her husband with the complaint of infertility. The couple has been practicing regular sexual intercourse since last 2 years. On general physical examination, there was no significant finding except that the patient's BMI was 27. There were no signs of hyperandrogenism (hirsuitism), galactorrhea or thyroid dysfunction. The woman's menstrual history revealed that she has been having irregular menstrual cycles since last 3 years. The cycle duration ranges within 30–35 days. The cycles last for approximately 4–5 days. However, the woman has been observing a progressive decrease in the amount of menstrual blood flow over the past few months. The couple had previously visited an infertility specialist 6 months back who had ordered a semen analysis. The result of this investigation was within normal limits.

Introduction

Infertility is defined as the inability to conceive even after trying with unprotected intercourse for a period of one year for couples in which the woman is under 35 years and six months of trying for couples in which the woman is over 35 years of age. Infertility commonly results due to the disease of the reproductive system, in either a male or a female, which inhibits the ability to conceive and deliver a child. Approximately 6.1 million people in the United States, or roughly 10–15% of the individuals belonging to the reproductive-age group are affected by infertility. Approximately one in six couples are affected by infertility and there are a number of factors (table 26.1), both male and female, that can cause the condition. In fact, in nearly 30% of cases the cause is attributed to the female, in 30% to the male, in 30% the cause is attributed to both and in remaining 10% of cases the causes are unknown. Though both male and female factors are responsible for producing infertility, female factor infertility would primarily be discussed in this chapter. Among the female causes of infertility, ovulatory dysfunction and tubal obstruction are each responsible for 35% cases of infertility. Endometriosis may be responsible for nearly 20% cases whereas idiopathic causes may be responsible for the remainder 10% cases (figure 26.1). Causes of male factor infertility and its treatment are largely beyond the scope of this chapter. Nevertheless, the evaluation for infertility must focus on the couple as a whole and not on one or the other partner. Both the partners must be encouraged to attend the clinic at the time of each appointment.

Table 26.1: Causes of infertility

Causes of infertility	*Percentage of cases*
Female causes	30%
Male causes	30%
Both male and female partner	30%
Unexplained causes	10%

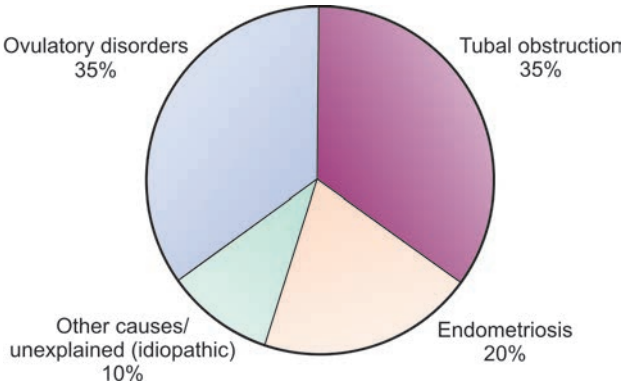


Fig. 26.1: Female causes of infertility

History

Infertility is a problem that may involve both male and female partners; therefore the initial assessment must involve both the partners. The intial evaluation must include a detailed reproductive history and at least two semen analyses at a laboratory that is qualified to perform the testing. The consultation is grossly incomplete, if only the woman is evaluated. Anxiety is very common in couples desiring

pregnancy and many couples may seek consultation only after a few months of unprotected intercourse. Diagnostic testing must not be performed if the couple has not attempted to conceive for at least 1 year, unless the woman is 35 years old or older, or there is a history of male factor infertility, endometriosis, tubal factor, exposure to DES, pelvic inflammatory disease, or pelvic surgery. In many cases, attempts at alleviation of anxiety through reassurance and briefly explaining the physiology of reproduction are usually enough to lessen the couple's anxiety.

History from the Female Partner

During the consultation, the following history should be taken from the woman:

History of presenting complaints

- A detailed medical history regarding the type of infertility (primary or secondary), its duration and if any treatment for this had been sought in the past. Primary infertility implies that woman had never been able to conceive in the past. Secondary infertility implies that the woman had conceived in the past, (irrespective of the outcome of pregnancy, whether she progressed till term or had a miscarriage) but is presently not being able to conceive.
- *Patient's age*: It is important to know the woman's age because increasing age of the women (greater than 35 years) is associated with reduced fertility. The present evidence indicates that age-related decline in female fertility is largely due to progressive follicular depletion and a high rate of abnormalities (particularly aneuploidy) in the aging oocytes.
- *Duration of infertility*: Duration of the couple's attempts for becoming pregnant, whether or not they have ever had children or a positive pregnancy test together with same or a different partner in the past needs to be asked.
- *Thyroid dysfunction or galactorrhea*: Symptoms suggestive of thyroid disease, pelvic or abdominal pain and galactorrhea must be asked. Thyroid dysfunction is commonly associated with menstrual abnormalities and reduced fertility. Galactorrhea or milk secretion from the breasts is often a manifestation of pineal gland tumor and may be associated with amenorrhea.
- *Previous history of Pap smears:* Previous history of abnormal Pap smears or undergoing treatment for CIN could be responsible for producing cervical stenosis.
- *History of vaginal or cervical discharge:* This must be enquired. The infections could be at times responsible for producing infertility, for eg. infection with Chlamydia can cause PID and tubal blockage resulting in subsequent infertility.

Sexual history

Sexual history must be taken in details in order to enquire about the frequency of sexual intercourse, use of lubricants (e.g., K-Y gel) that could be spermicidal, use of vaginal douches after intercourse and history of any sexual dysfunction. History of sexual dysfunctioning such as absence of orgasm or painful intercourse (dyspareunia) must be enquired. Use of any form of contraception including natural methods, medical methods and surgical form of contraception (e.g, vasectomy, tubal ligation) needs to be asked. Overall pattern of sexual activity during the period of time the couple has been trying to conceive, specifically in relation to ovulation needs to be asked. The patient should also be asked if she had ever used ovulation-predictor kits or has been prescribed ovulation-promoting medications such as clomiphene citrate.

The patient should be explained about the period of fertility. The optimal chances for pregnancy occurs if the patient has intercourse in the six days before ovulation, with day six being the actual day of ovulation. Sometimes, simply advising the patients to adjust the timing of their intercourse can result in a significantly increased chance for pregnancy.

Patient's lifestyle

Detailed history regarding the patient's lifestyle; consumption of alcohol, tobacco, use of recreational drugs of abuse (amount and frequency); occupation; and physical activities must be asked.

Menstrual history

The age of attaining menarche and puberty must be asked. The woman should be questioned in details about her menstrual history and asked about the frequency, cycle length, patterns since menarche and history of dysmenorrhea. Regular menstrual cycles are usually ovulatory in nature, while irregular cycles may be anovulatory in nature. A history of weight changes, hirsutism, frontal balding, and acne should also be addressed. History of progressively worsening dysmenorrhea, newly developed dyspareunia and physical findings of focal tenderness or nodularity of cul-de-sac point towards endometriosis. Irregular or infrequent menstrual cycles are usually indicative of ovulatory dysfunction.

Obstetric history

The patient should be enquired about details regarding previous pregnancies (including miscarriages or medical terminations of pregnancy and previous history of live births), dead babies or stillborn children. She should also be asked if she has ever undergone evaluation regarding infertility issues and any medical or surgical management

that had been instituted. The patient should be asked about outcome of each of the previous pregnancies; interval between successive pregnancies and presence of any other complications associated with any pregnancy. If the patient has ever experienced pregnancy losses, she should be asked about the duration of pregnancy at the time of miscarriage, human chorionic gonadotropin (hCG) levels, if they were done, ultrasonographic data, if available, and the presence or absence of fetal heartbeat as documented on the ultrasound report. History of previous pregnancy is particularly important because couples who have conceived before usually have a better prognosis in comparison to those who have never conceived. A history of past obstetric hemorrhage suggesting postpartum pituitary necrosis (i.e., Sheehan syndrome) must be asked.

Past history

A previous history of pelvic infection, septic abortion, ruptured appendix, ectopic pregnancy, abdominal myomectomy or adnexal surgery raises the suspicion for tubal or peritoneal disease. Past or current episodes of sexually transmitted diseases or pelvic inflammatory diseases must also be enquired. The patient must be asked if she is currently receiving any medical treatment, the reason for treatment and if she has any history of allergies.

Family history

Family history of birth defects, mental retardation, early menopause or reproductive failure needs to be taken.

History from the Male Partner

- The history should include several points specific to the patient's sexual functioning including history of impotence, erectile dysfunction, premature ejaculation, change in libido, etc. The history should include several points specific to the patient's sexual functioning such as the precise nature of the dysfunction, for example, whether the problem is in attaining or sustaining an erection, or whether there is difficulty with penetration due to insufficient rigidity. The presence or absence of nocturnal and morning erections and their quality must be asked. The patient must be enquired if he is taking any treatment, both pharmacologic and nonpharmacologic for treatment of his problem. Complaints of reduced libido may also be associated with depresssion, loss of interest in daily activities, a decline in erectile function, fatigue, etc. Thus, history related to these symptoms must also be elicited. Additionally, the time period since which these complaints have been present must be enquired from the patient.
- History of pain both during time of ejaculation and erection must be enquired. The time of pain onset, its localization to any specific organ and the quality of pain must also be asked.
- History of testicular trauma, previous sexual relationships, history of any previous pregnancy and the existence of offspring from previous partners must also be asked.
- History of undergoing previous treatment for infertility including semen analysis must also be asked.
- Any complaints specific to the genitourinary structures, such as complaints of a dull ache or fullness in the scrotum, or non-radiating pain on one side, dysuria, dyspareunia, etc must also be asked.
- History of exposure to environmental toxins, such as excessive heat, radiation, and chemicals such as heavy metals, and glycol ethers or other organic solvents needs to be asked.

Medical history

- History of treatment for malignancy (especially chemotherapy or radiotherapy), regardless of site, should be documented.
- History of medical disorders such as diabetes, chronic obstructive pulmonary disease, renal insufficiency, hemochromatosis, hepatic insufficiency, etc which may contribute to male subfertility must be asked.
- History of systemic illness, particularly, a febrile illness, and any recent weight gain or loss in last 6 months must be asked.

Surgical history

History of any surgery related to genitourinary organs such as orchidopexy, repair of inguinal hernia, epispadias or hypospadias repair, prostate surgery, bladder reconstructions, bladder or testicular surgeries needs to be asked. The patient should be asked specifically if there is a history of a vasectomy.

Treatment history

The dose and duration of use of certain prescription drugs which can affect sperm count, motility, and morphology must be documented. Some of the drugs which can commonly affect semen parameters by reducing spermatogenesis include calcium channel blockers, spironolactone, chemotherapy drugs, anabolic steroids, etc. The patient must also be asked about the ingestion of herbal drugs or drugs belonging to other alternative systems of medicine and other over-the-counter medications. Many times the patient may not disclose this history unless specifically enquired. Any of these substances may be responsible for affecting spermatogenesis.

Social history

Cigarette smoking, excessive alcohol consumption and consistent marijuana use are all known to be gonadotoxins. A careful history of the use of these agents and other illicit drug use must be part of the complete male infertility evaluation. Cigarette smoking has been thought to cause changes in sperm morphology, production and motility while chronic alcohol use may contribute to infertility by causing erectile dysfunction, and hypogonadism. Simply eliminating these agents can improve semen parameters in the absence of other physical findings.

Patients should be asked about recreational activities, as some activities, such as long-distance cycling, may put pressure on the perineal area and result in possible impairment of erectile function. Certain occupations which result in exposure of male genital organs to high temperatures such as men working in blast furnaces may be the reason behind the patient's infertility.

Family history

The family history must include a discussion regarding the presence of testicular or other genitourinary malignancies specifically related to prostate or bladder in other family members. The patient should be queried regarding siblings or extended family members who may have had similar fertility problems. It is especially important to ask about the family history of cystic fibrosis because this genetic disease could be responsible for infertility by causing congenital absence of vas deferens. According to the ACOG recommendations, screening for cystic fibrosis should be made available to all the couples seeking preconceptional care and not just to those with a personal or family history of cystic fibrosis. The screening should be specifically offered to couples belonging to racial or ethnic groups with a high risk for cystic fibrosis (e.g., Caucasians, particularly those of Ashkenazi Jewish descent).

General Physical Examination

General physical examination requires routine measurement of the patient's vital signs including pulse rate, blood pressure and temperature. Other important aspects of the general physical examination include measurement of the following parameters:

BMI: Measurement of the patient's height and weight to calculate the body mass index.

Thyroid examination: Note for thyroid enlargement, nodule or tenderness.

Eye examination: Eye examination must be performed in order to establish the presence of exophthalmos, which may be associated with hyperthyroidism.

Stigmata of Turner's syndrome: The presence of epicanthus, lower implantation of the ears and hairline, and webbed neck can be associated with chromosomal abnormalities.

Breast examination: A breast examination must be performed in order to evaluate breast development and to assess the breasts for the presence of abnormal masses or secretions, especially galactorrhea. This opportunity must be taken by the gynecologist to educate patients about breast self-examination during the early days of their menstrual cycles.

Signs of androgen excesss: Signs of androgen excess such as hirsuitism, acne, deepening of the voice, hypertrichosis, etc must be looked for.

Examination of extremities: The extremities must be examined in order to rule out malformation, such as shortness of the fourth finger or cubitus valgus, which can be associated with chromosomal abnormalities and other congenital defects.

Examination of the skin: The skin must be examined for the presence of acne, hypertrichosis, and hirsutism.

Examination of the secondary sexual characteristics: Failure of development of secondary sexual characteristics must always prompt a workup for hypopituitarism. Loss of axillary and pubic hair and atrophy of the external genitalia should lead the physician to suspect hypopituitarism in a previously menstruating young woman who develops amenorrhea.

Specific Systemic Examination

ABDOMINAL EXAMINATION OF FEMALE PARTNER

The abdominal examination should be done to detect the presence of abnormal masses in the abdomen. Masses felt in the hypogastrium could be arising from the pelvic region.

PELVIC EXAMINATION OF FEMALE PARTNER

Per Speculum Examination

A thorough gynecologic examination has already been described in chapter 16. The distribution of hair pattern on the external genitalia should be particularly noted. The inspection of the vaginal mucosa may indicate a deficiency of estrogens or the presence of infection. Cervical stenosis can be diagnosed during a speculum examination. Complete cervical stenosis is confirmed by the inability to pass a 1–2 mm probe into the uterine cavity.

Bimanual Examination

Bimanual examination should be performed to establish the direction of the cervix and the size and position of the uterus.

The gynecologist should look for presence of any mass, tenderness or nodularity in adnexa or cul-de-sac. Various pelvic pathologies such as fibroids, adnexal masses, tenderness or pelvic nodules indicative of infection or endometriosis can be detected on bimanual examination. Many uterine defects related to infertility such as absence of the vagina and uterus, presence of vaginal septum, etc can be detected during the pelvic examination.

EXAMINATION OF MALE PARTNER

The patient should be examined for age-appropriate development of male secondary sex characteristics, gynecomastia, or hirsutism. The structures of male external genitalia structures which must be evaluated include the penis, scrotum, testes, epididymis, spermatic cord and vas deferens. The clinician must examine the external genitalia for the presence of following abnormalities:

- The scrotum must be carefully and thoroughly palpated, and the presence of all scrotal structures should be confirmed, along with their size and consistency.
- Presence of congenital abnormalities of the genital tract, e.g., hypospadias, cryptorchidism (undescended testes), absence of the vas deferens (unilateral or bilateral), etc must be assessed.
- Testicular size, presence of tenderness on palpation of testicle and presence of any associated mass must be assessed. If any mass is palpated, it must be verified whether the mass is arising from the testicles or is separate from it.
- Urethra must be assessed for presence of any stenosis, diverticulum, etc.
- Presence of an inguinal hernia or varicocele: A varicocele can be exaggerated during physical examination by asking the patient to perform the Valsalva maneuver while standing. The varicocele normally disappears when the patient lies down. A long-standing varicocele may result in testicular atrophy. If the varicocele is large, it may be visible during inspection resulting in "bag of worms" appearance.
- The complete physical examination should also include a digital rectal examination.

Differential Diagnosis

The process of human reproduction begins with the deposition of spermatozoa, during sexual intercourse, into the vagina. The spermatozoa migrate through the cervix and uterine cavity to the fallopian tubes where they meet the egg and fertilization takes place. The embryo then travels back down the fallopian tube and enters the uterine cavity where implantation takes place. As a result, female factor infertility can result from various causes including cervical factors, uterine factors, ovarian factors or tubal factors. Infertility due to each of these causes would be described in details:

Cervical Factor Infertility

The uterine cervix plays an important role in capturing, nurturing and then transportation and capacitation of the sperms after intercourse. The cervix ultimately releases the mature sperms into uterus and fallopian tube. Cervical factors account for 5–10% cases of infertility. Cervical factor infertility can most commonly result due to abnormalities of the mucus-sperm interaction and narrowing of the cervical canal due to cervical stenosis. Both these causes of cervical infertility would now be discussed.

Mucus-sperm interaction

In normal women, at the beginning of the menstrual cycle, cervical mucus is scanty, viscous, and very cellular. This mucus does not allow the sperms to pass into the uterine cavity. Mucus secretion from the cervix increases during the mid follicular phase and reaches its maximum approximately 24–48 hours before ovulation. Just prior to ovulation, the mucus becomes thin, watery, alkaline, stretchable, acellular, and elastic in appearance due to increase in the concentration of salt and water in the mucus under the influence of estrogen. In this type of cervical mucus pattern, multiple microchannels are formed so that the spermatozoa can travel through the mucus into the uterine cavity and the mucus also acts as a filter for abnormal spermatozoa and cellular debris present in the semen. Furthermore, during this phase, the mucus assumes a fern-like pattern (figure 26.2) when allowed to dry on a slide under the microscope. Following ovulation,

Fig. 26.2: Ferning pattern of the cervical mucus

under the effect of progesterone, the cervical mucus changes its character. During this stage, the mucus becomes opaque, viscid and may become hostile, resistant and impenetrable to sperms.

Cervical stenosis

Cervical stenosis can cause infertility by blocking the passage of sperm from the cervix to the intrauterine cavity. Cervical stenosis can be congenital or acquired in etiology, resulting from surgical procedures, infections, hypoestrogenism and radiation therapy.

Uterine Factor Infertility

The uterus is the ultimate destination for the fertilized egg and the site for embryo implantation and fetal growth. Therefore, uterine factors may be associated with primary infertility or with recurrent pregnancy wastage and premature delivery. Uterine factors may affect either the endometrium or myometrium and are responsible for nearly 2% to 5% cases of infertility. Uterine factors can be congenital or acquired and would be discussed below.

Congenital defects

Abnormalities in the development of the müllerian ducts may result in a spectrum of congenital/müllerian duct abnormalities varying from total absence of the uterus and vagina (Rokitansky-Küster-Hauser syndrome) to minor defects such as arcuate uterus and vaginal septa (transverse or longitudinal). The classification of müllerian anomalies by the American Fertility Society (AFS, 1988) has been described in chapter 9. The relationship between müllerian anomalies and infertility is not entirely clear except when there is absolute absence of the uterus, cervix, or vagina.

Acquired causes

Drug induced uterine malformations: The drug diethylstilbestrol (DES), used for treating patients with a history of recurrent miscarriages during 1950s was found to be responsible for producing numerous defects such as malformations of the uterine cervix, irregularities of the endometrial cavity (e.g., T-shaped uterus), malfunction of the fallopian tubes, menstrual irregularities, and development of clear cell carcinoma of the vagina.

Asherman's syndrome: Development of adhesions or synechiae within the endometrial cavity may result in its partial or total obliteration. This could be due to Asherman's syndrome, which may develop following a vigorous dilatation and curettage procedure (chapter 9). Development of adhesions or synechiae within the endometrial cavity may result in its partial or total obliteration.

Endometritis: Endometritis or inflammation of the uterine cavity due to infections such as tuberculosis could be associated with an increased risk of infertility.

Leiomyomas: The impact of fibroids on fertility presently remains controversial and has been a subject of extensive debate. Uterine fibroids have been covered in details in chapter 18. As a sole factor, fibroids probably account for only 2% to 3% of infertility cases.

Leiomyomas are more common in nulliparous or relatively infertile women but it is not known whether infertility causes myomas or vice versa or whether both the conditions have a common cause? The general view is that the uterus which is deprived of pregnancy consoles itself with myomas. This has been aptly summed up by the saying, "Fibroids are rewards of virtue, babies the fruit of sin." Postponement of pregnancy results in uninterrupted estrogenic stimulation of the uterus, which can act as a predisposing factor for development of myoma. Presence of myomas may then discourage the development of pregnancy. However, mere presence of myomas in an infertile patient should not be considered as a cause of her infertility. Firstly, she should be investigated for all the common causes of infertility (including the tubal factor, the ovarian factor, male factor, etc). Only after all the other common causes of infertility in a woman have been ruled out, presence of myomas may be considered as a cause for infertility in a woman. The extent to which presence of myomas can influence fertility in a woman depends upon the position of fibroids inside the uterus, the number of fibroids and their size.

Myomas can cause infertility through the following mechanisms:

Distortion of the endometrial cavity: Presence of submucous myomas may distort the endometrial cavity thereby interfering with normal implantation. Thus, submucous myomas are most likely to affect the woman's fertility followed by interstitial myomas and lastly the subserosal myomas. Subserosal myomas are located farthest from the endometrial cavity; as a result they are associated with minimum affect on fertility. Removal of fibroids that distort the uterine cavity may be indicated in infertile women, where no other factors have been identified, and in women about to undergo in vitro fertilization. Besides causing distortion of the uterine cavity, myomas may also cause dysfunctional uterine contractions, which may interfere with sperm migration, ovum transport or nidation. Furthermore, the growth of myoma is dependent on estrogen production. Thus, uterine myomas in a woman are often associated with anovulation, which may play a role in producing infertility. Also menorrhagia and dyspareunia associated with uterine myomas can cause infertility to some extent.

Anatomical location of the fibroid: The anatomical location of myoma inside the uterus can affect fertility. For example, presence of large submucous fibroids in the vicinity of cervix may result in displacement of cervix, which can prevent normal deposition of sperms at the cervical os or a submucosal myoma impinging on the intramural portion of the fallopian tube can interfere with the proper transportation of ovum.

Inflammation: Biological factors like infiltration of inflammatory cells (macrophages) and production of inflammatory mediators [cytokines, monocyte chemoattractant protein-1 (MCP-1), prostaglandin F 2α, etc] due to presence of fibroids may be responsible for producing infertility.

Indirect evidence: Since there is very limited direct evidence in form of prospective randomized controlled trials regarding the role of myoma in producing infertility, we have to depend on indirect evidence. The indirect evidence is mainly available in two forms: The first one is studying the effect of fibroids based on the outcomes of assisted reproductive techniques (IVF, GIFT etc). The second is assessing the outcome of fertility following removal of myomas. Various studies have indicated pregnancy rates of 44% to 62% following myomectomy.

Ovarian Factor Infertility

Oogenesis occurs in the ovary from the first trimester of embryonic life and is completed by 28–30 weeks of gestation. By then, approximately 6–7 million oogonia are present. This can be considered as the maximal oogonial content of the gonad. They are arrested at the prophase stage of the first meiosis division. Subsequently, the number of oocytes irretrievably decrease until the menopause is attained because of a continuous process of atresia. At birth, the pool of oocytes is reduced to approximately 2 million. By menarche, approximately 500,000 oocytes are present. These oocytes are used throughout the reproductive years until menopause.

The ovulatory process begins after the maturation of hypothalamus-pituitary-ovarian axis and there occurs production of gonadotropins such as follicle stimulating hormone (FSH) and luteinizing hormone (LH), under the regulation of gonadotropin releasing hormone (GnRH). Though a cohort of follicles gets recruited every month, only a single oocyte ultimately gets selected, develops to the preovulatory stage and is known as the dominant follicle. LH surge occurring during the midpoint of the menstrual cycle triggers the ovulatory process, and stimulates the formation of the corpus luteum. Following ovulation, the luteal phase begins under the influence of progesterone secreted by corpus luteum. Furthermore, ovulation induces the resumption of meiosis by the oocyte, which had been arrested at the prophase stage.

Causes of ovulatory dysfunction

Ovulatory dysfunction results in an alteration in the frequency and duration of the menstrual cycle. Anovulation or failure to ovulate is one of the most common causes for infertility. Absence of ovulation can also be associated with primary or secondary amenorrhea, or oligomenorrhea. Amenorrhea as a cause of infertility has been discussed in details in chapter 27. The rise in prevalence of infertility with increase in woman's age could be related to reduction in the ovarian reservoir. Polycystic ovary syndrome (PCOS), a common endocrine disorder in women, frequently results in infertility by causing ovulatory dysfunction.

PCOS

Polycystic ovary syndrome (PCOS) is the most common cause of hyperandrogenic chronic anovulation. For diagnosis of PCOS, at least two of the three following criteria must be present:

- Anovulation: About 50% of women with PCOS have amenorrhea, about 30% have irregular bleeding and about 12% have "cyclic menses." No particular pattern of menstrual bleeding is characteristic of women with PCOS, although a history of oligomenorrhea is probably most common.
- Hirsuitism.
- Ultrasound findings suggestive of PCOS: Presence of multiple small cysts of the size 0.5–1mm, (usually more than ten in number) along the periphery of the ovary, giving rise to the "necklace appearance" on the ultrasound. Hyperplasia of the stroma results in an increase in the ovarian volume to more than 8 ml or 9 cm^3.

The diagnostic criteria for PCOS developed by National Institute for Health is as follows:

1. Clinical evidence of hyperandrogenism (e.g., hirsutism, acne, etc) and/or hyperandrogenemia (e.g., elevated total or free testosterone levels). PCOS is associated with mild-to-moderate hyperandrogenism and/or hyperandrogenemia. On the other hand, signs of markedly elevated androgen levels, such as clitoromegaly, temporal balding, and deepening of the voice are suggestive of an androgen-producing tumor.
2. Oligoovulation (i.e., cycle duration >35 days or <8 cycles per year).
3. Exclusion of related disorders (e.g., hyperprolactinemia, thyroid dysfunction, androgen-secreting tumors, 21-hydroxylase-deficient nonclassical congenital adrenal hyperplasia).

Grossly, the ovaries of most women with PCOS are bilaterally enlarged and globular and have a thickened capsule. Due to the presence of a smooth glistening capsule,

the ovaries often have an "oyster shell" appearance. The tunica albuginea is often thickened diffusely and many cysts 3 to 7 mm in diameter are present in the periphery on cut section. Corpora lutea are rarely present due to absence of ovulation. The clinical syndrome accompanying this pathologic finding is typically characterized by massive obesity, severe hirsutism due to excessive ovarian production of androgens, glucose intolerance with insulin resistance and hyperuricemia.

Women with PCOS invariably are well estrogenized, with normal breast development and abundant cervical mucus on examination. Patients with PCOS often have excess unopposed circulating estrogen, increasing their risk of developing endometrial cancer. The insulin resistance associated with PCOS increases a patient's risk of diabetes mellitus by two- to five-folds. Therefore, testing for glucose intolerance should be considered. The diagnosis of PCOS is primarily clinical, although laboratory studies may be needed to rule out other causes of hyperandrogenism. The following laboratory investigations must be done:

- Androgen levels: Increased levels of androgens such as testosterone, epiandrostenedione and dehydroepiandrosterone. Significantly elevated testosterone levels (> 200 ng/ml) or dehydroepiandrosterone sulfate levels (> 700 mg/ml) indicate a possible androgen-secreting tumor (ovarian or adrenal). On the other hand, slightly raised testosterone >80 ng/ml ≤ 200 ng/ml) or dehydroepiandrosterone sulfate levels (>300 ng/ml ≤ 700 mg/ml) are associated with PCOS.
- Raised serum concentrations of luteinizing hormone (LH) with normal follicle stimulating hormone (FSH) levels often result in an increased LH: FSH ratio of greater than two.
- Increased levels of 17-alpha hydroxyprogesterone (> 800 ng/dl).
- Increased fasting insulin levels (>10 mIU/L); and increased fasting glucose/insulin ratio >4.5 (normal 2.4–4.5).

Two important biochemical features associated with PCOS include insulin resistance to a standard glucose challenge and compensatory hyperinsulinemia and obesity. Weight loss in patients with PCOS helps in reducing the levels of insulin and androgens. The androgen is converted to estrogen, primarily estrone, in the periphery. The estrogen feedbacks on the central nervous system hypothalamic-pituitary unit to induce inappropriate gonadotropin secretion with an increased LH to FSH ratio. The estrogen stimulates GnRH synthesis and secretion in the hypothalamus, causing preferential LH release by the pituitary gland. Selective inhibition of FSH secretion by increased ovarian inhibin levels may also occur in PCOS. The increased LH secretion stimulates theca cells in the ovary to produce excessive androgen. The androgen also inhibits production of sex hormone binding globulins (SHBG), resulting in increased free androgen levels and predisposing affected women to hirsutism. The absence of follicular maturation in the ovaries is related to the reduced estradiol production by the ovaries apparently resulting from combination of inadequate FSH stimulation and inhibition by the increased concentrations of intraovarian androgens. The low levels of SHBG probably facilitate tissue uptake of free androgen, leading to increased peripheral formation of estrogen and perpetuating the acyclic chronic anovulation. The androgenic basis for the inappropriate estrogen feedback is partly shifted to the ovaries. The increased estrogens (and perhaps androgens) may also stimulate fat cell proliferation, leading to obesity. The current data suggest that there is no defect in the hypothalamic-pituitary axis in PCOS but rather that peripheral alterations result in abnormal gonadotropin secretion.

Tubal Factors

The fallopian tubes play an important role in reproduction. After ovulation, the fimbriae pick up the oocyte from the peritoneal fluid which has accumulated in the cul-de-sac. The epithelial cilia in the tubal epithelium then transport the oocyte up to the ampulla. The capacitated spermatozoa are transported from the cervix through the endometrial cavity into the ampulla of fallopian tube, where ultimately fertilization occurs. Fallopian tube abnormalities or tubal damage or obstruction may either result in infertility or abnormal implantation or ectopic pregnancy.

Causes of tubal obstruction

Pelvic inflammatory disease: Pelvic inflammatory disease (PID) is typically associated with gonorrheal and chlamydial infection (figures 26.3A and B and 26.4A and B). Formation of peritoneal adhesions secondary to PID can compromise the motility of the fallopian tubes. Furthermore, obstruction of the distal end of the fallopian tubes results in accumulation of the normally secreted tubal fluid, creating distention of the tube. This subsequently causes damage to the epithelial cilia and may result in development of hydrosalpinx.

Other causes of tubal obstruction

Tubal obstruction can commonly result due to formation of scar tissue and adhesions due to infections (especially Chlamydia and gonorrhea), endometriosis or abdominal or gynecological surgery. Tubal obsrtruction prevents the ovum from entering or traveling down the fallopian tube and meeting the sperm. Damage to the ciliary epithelial of the fallopian tube as a result of infection can result in the development of abnormal implantation or an ectopic pregnancy. Ectopic pregnancy has been discussed in details in chapter 25.

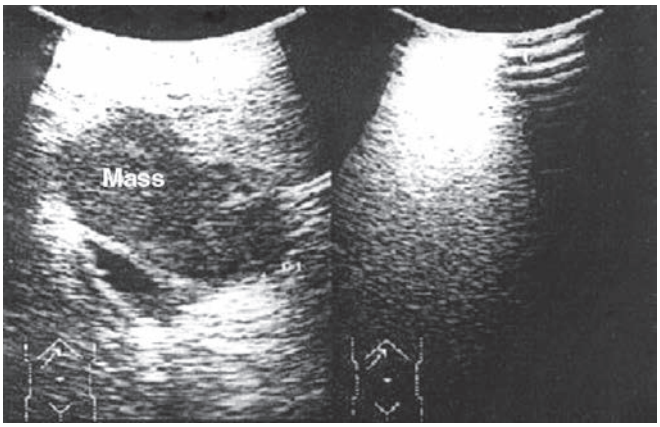


Fig. 26.3A: USG showing a mass of variable echogenicity arising from left adnexa suggestive of a tubo-ovarian mass

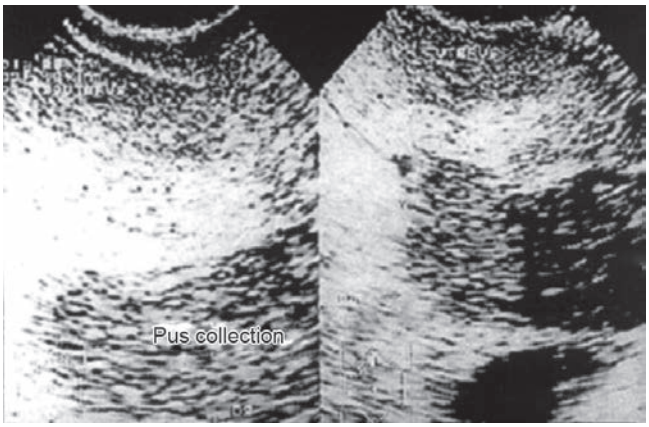


Fig. 26.4A: Presence of loculated collection with variable echogenicity present in the Pouch of Douglas, suggestive of a pyosalpinx

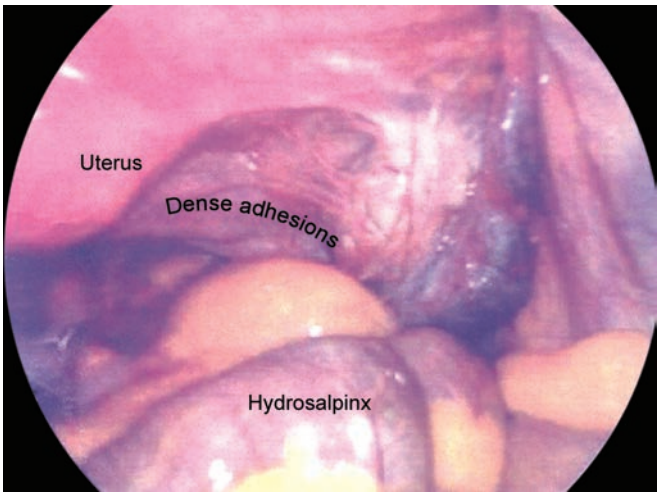


Fig. 26.3B: Laparoscopic appearance of hydrosalpinx arising from left tube

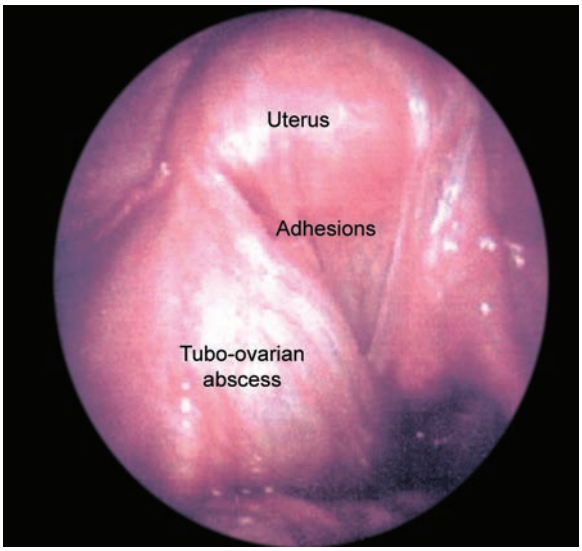


Fig. 26.4B: Laparoscopic findings in the same patient showing the presence of a tubo-ovarian mass

Peritoneal Factors

The uterus, ovaries, and fallopian tubes are all present in the same space within the peritoneal cavity. The released ovum from the ovary often gets extruded into the peritoneal cavity into the cul-de-sac from where it is picked up by the fimbriae. Anatomical defects or physiologic dysfunctions of the peritoneal cavity, including infection, adhesions and adnexal masses, may cause infertility.

Peritoneal defects

Endometriosis: Endometriosis is an enigmatic disease characterized by the growth of endometrial tissue outside the uterus, which may affect a woman's fertility. Detailed description of endometriosis has been done in chapter 23.

Endometriotic lesions vary from microscopic to macroscopic size. Classic endometriosis appears as bluish-black pigments, (i.e., "powder-burn lesions") that affect the peritoneal surfaces of the bladder, ovary, fallopian tubes, cul-de-sac and bowel. Nonclassic endometriosis may appear as red, tan or white colored lesions and vesicles. Medical treatment of minimal or mild endometriosis has not been shown to increase pregnancy rates. Moderate-to-severe endometriosis should be treated surgically. Different mechanisms through which endometriosis results in infertility are described below in table 26.2.

Factors Affecting Both Sexes

Environmental and occupational factors

Excessive radiation may damage the germinal cells. It has yet not been proven whether exposure to heavy metals such as lead, excessive heat, microwave radiation, ultrasonography, etc may be responsible for inducing infertility.

Table 26.2: Different mechanisms through which endometriosis results in infertility

Type of endometriosis	*Cause for infertility*
Severe endometriosis	Damage to the fallopian tubes due to presence of adhesions.
	Damage to the ovaries due to presence of endometriomas.
Minimal and mild endometriosis	Increased peritoneal macrophages that increase phagocytosis of the sperms, reduced sperm binding to the zona pellucida, proliferation of peritoneal lymphocytes, increased production of cytokinin and immunoglobulins and defective activity of natural killer cells.
	Ovulatory disorders such as luteal phase deficiency, oligo-ovulation, and luteinized unruptured follicle syndrome.

Toxic effects related to tobacco, marijuana and other drugs

Smoking has been associated with infertility in both males and females. Various chemical substances in tobacco such as nicotine and polycyclic aromatic hydrocarbons have been observed to block spermatogenesis and decrease testicular size. In women, various chemicals present in the tobacco smoke are thought to affect the transportation of sperm and ova across the fallopian tube by altering the cervical mucus and the cilial epithelium respectively.

Marijuana and its metabolite, delta-9-tetrahydrocannabinol, inhibit the secretion of LH and FSH in women, thereby inducing ovulatory and luteal phase dysfunction. Also, marijuana use affects male fertility by reducing the sperm count and the quality of the sperm. Use of heroin, cocaine, and crack cocaine may produce similar effects. Chronic alcoholism in women may induce ovulatory dysfunction, thereby producing infertility. Alcohol use by males interferes with the synthesis of testosterone and may reduce sperm concentration. Alcoholism may also inhibit sexual response and cause impotence.

Exercise

Exercise should be encouraged as part of normal activity. However, compulsive exercise is deleterious, especially for long-distance runners, athletes, dancers etc. In these women, excessive exercise could also result in amenorrhea. In males, exercise has been associated with oligospermia.

Inadequate diet associated with extreme weight loss or gain

Both excessive weight gain and loss may have an impact on woman's fertility. Although weight loss associated with anorexia nervosa or bulimia induces hypothalamic amenorrhea, obesity may be associated with anovulation and oligomenorrhea. In men, obesity has been associated with decreased sperm quality.

Management

Evaluation of the couple is the starting point for treatment of infertility as it may suggest specific causes and appropriate treatment modalities. Patient evaluation should begin by taking detailed history from both the partners. Sometimes simple reassurance and explanation about the physiology of menstrual cycle and importance of having regular intercourse is sufficient in achieving pregnancy. Although the history and physical examination is able to provide important information, specific diagnostic tests are also required to evaluate infertility.

Investigations

Evaluation of infertile couples should be organized and thorough. Diagnostic tests should start from the simplest (e.g., semen analysis, pelvic ultrasonography, etc) tests onto the more complex and invasive ones (e.g., laparoscopy). Also, the evaluation of fertility must first begin with tests for the assessment of male fertility. The semen analysis is the most commonly performed test of male infertility which yields tremendous amount of information as to the potential causes of male infertility.

EVALUATION OF THE MALE PARTNER

Semen Analysis

A comprehensive semen analysis must be performed in a certified andrology laboratory. Male patient should be instructed well in advance that they must provide a semen sample after a period of abstinence of 2 to 5 days. This sample is collected through masturbation, and must be collected into a container, which is non-toxic to the sperms. The semen is usually not collected from condom samples because it may be containing a spermicidal agent. The patient is discouraged from attempting to collect a sample through intercourse as coitus interruptus is not a reliable means for sample collection. Ideally, the specimen must be collected at the same andrology laboratory, which would conduct the test. If the sample is collected at home, it should be transported to the lab within 30 minutes to ensure the accuracy of the results. The primary values that are evaluated at the time of semen analysis include the volume of the ejaculate, sperm motility, total sperm concentration, sperm morphology, motility and viability. The results

Table 26.3: Normal parameters for semen analysis (World Health Organization)

Parameter	*Normal range*
Volume	2–5 mL
Liquefaction time	Within 60 minutes
pH level	7.2–7.8
Sperm concentration	20 million or greater
Total sperm number	40 million spermatozoa per ejaculate or more
Motility	50%, forward progression; 50% or more motile (grades a* and b**) or 25% or more with progressive motility (grade a) within 60 minutes of ejaculation
Morphology	Normal sperms (>4%)
Vitality	75% or more live
White blood cells	Fewer than 1 million cells/µL

*Grade a: Rapid progressive motility (sperm moving swiftly, usually in a straight line).

**Grade b: Slow or sluggish progressive motility (sperms may be less linear in their progression).

of semen analysis conducted as part of an initial assessment should be compared with World Health Organization reference values as described in table 26.3.

Spermatogenesis takes approximately 72 days. Therefore, the sperm analysis must be repeated after 3 months if any of the parameters appear abnormal or as soon as possible in case of gross sperm deficiency. Morphology has become an important parameter for evaluation of the quality of sperm and their capability for fertilization. Kruger reported a new classification based on strict sperm morphology after fixing and staining the sperm. According to this criterion, sperm morphology of greater than 14% is considered as normal. Morphology of less than 4% is associated with severe infertility and is an indication for assisted reproduction technology/intracytoplasmic sperm injection.

Strict criteria of normal sperm morphology as established by Kruger et al have been defined as spermatozoa having an oval configuration with a smooth contour, with head length varying from 5–6 µm, the width varying from 2.5–3.5 µm and the width/length ratio varying between 1/2–3/5. The acrosome must be well-defined, comprising 40–70% of the distal part of the head. No abnormalities of the neck, midpiece or tail are accepted. Borderline forms are also considered abnormal. In Kruger's practice, only the normal forms are considered and are known as the "percentage of ideal forms" (PIF). A PIF of greater than 4% is considered favorable and less than 4% is considered as unfavorable.

Interpretation of semen analysis

Abnormal semen analysis results can be attributed to various unknown reasons such as, short period of sexual abstinence, poor sexual stimulus, etc. Therefore, it is important to repeat the semen analysis at least 1 month later before making a diagnosis. Terminology associated with abnormal results of semen analysis is described in table 26.4.

Determination of serum testosterone levels

Serum testosterone levels particularly that of total testosterone, free testosterone, LH and FSH must be measured if

Table 26.4: Terminology associated with abnormal results of semen analysis

Terminology	*Interpretation*	*Causes*
Normozoospermia	Normal ejaculate as defined by the WHO reference values.	
Hypospermia	Decrease in semen volume to less than 2 mL per ejaculation.	
Hyperspermia	Increase in semen volume to more than 8 mL per ejaculation.	
Aspermia	No ejaculate.	
Azoospermia	Absence of sperms in the semen.	Congenital absence or bilateral obstruction of the vas deferens or ejaculatory ducts.
Oligozoospermia	Concentration of sperms fewer than 20 million sperms/mL.	Ejaculatory dysfunction such as retrograde ejaculation, genetic conditions, or hormonal disturbances.
Asthenozoospermia	Sperm motility of less than 50%.	Extreme temperatures.
Teratospermia	An increased number of sperms with abnormal morphology at the head, neck or tail level.	
Teratozoospermia	Sperm morphology less than the WHO reference.	
Oligoasthenoteratozoospermia	Disturbance of all three variables: Motility, morphology and sperm concentration.	
Crypotozoospermia	Few spermatozoa recovered after centrifugation.	

hypogonadism is suspected as a cause for infertility. Morning values are preferred to afternoon blood samples because testosterone is secreted in the morning. Hypogonadism is the only cause of male infertility that can successfully be treated with hormone therapy.

EVALUATION OF THE FEMALE PARTNER

A complete evaluation of the female reproductive tract must involve cervical, uterine, endometrial, tubal, peritoneal, and ovarian factors. Since thyroid disease and hyperprolactinemia can cause menstrual abnormalities and infertility, serum TSH and prolactin levels must be checked first before instituting further investigations.

Evaluation of Cervical Factor

Postcoital test (Sim's or Huhner's test)

This test aims at identifying the cervical factor infertility by testing the characteristics of the cervical mucus. The couple is advised to have intercourse in the early hours of morning and present to the clinic as soon as possible in the morning. Ideally, the male partner must have abstained from ejaculation at least 48 hours prior to the test. The mucus which is aspirated from the cervical canal is spread over the glass slide and then examined under the microscope. This test involves both a gross and microscopic examination to grade the cervical mucus. Normally, there are 10–50 motile sperms per high power field. Presence of less than 10 sperms is considered abnormal and requires the performance of a proper semen analysis. However, many researchers consider presence of a single motile sperm in most fields as a "positive" or normal test result. Normally, the sperms show progressive mobility. Presence of a jerky or rotatory mobility could be due to presence of anti-sperm antibodies. A smear must be taken from the posterior fornix which serves as a control. Physical properties of cervical mucus such as volume, pH, viscosity (length to which the cervical mucus can be stretched) and fern test are also studied. The most common cause for a "negative" postcoital test is improper timing. While of historical interest, this test is no longer routinely performed in the standard infertility workup because it has been found to be associated with poor predictive value. Furthermore, infertility due to cervical factors can be easily overcome by performing intrauterine inseminations.

Tests for Uterine Factor

The commonly used investigations include hysterosalpingogram (HSG), pelvic ultrasonography, and endometrial biopsy. Operative procedures such as laparoscopy and hysteroscopy are often necessary for confirmation of the final diagnosis.

Screening tests for Chlamydia trachomatis

Before undergoing uterine instrumentation women should be offered screening for *Chlamydia trachomatis* using an appropriately sensitive technique. In case the results for the test of *Chlamydia trachomatis* are positive, women and their sexual partners should be referred for appropriate management with antibiotic treatment and contact tracing.

Prophylactic antibiotics may be considered before uterine instrumentation if screening has not been carried out.

Hysterosalpingogram (HSG)

The HSG is the most frequently used diagnostic tool for evaluation of the endometrial cavity as well as the tubal pathology. If performed meticulously under fluoroscopic guidance, HSG helps in providing accurate information about the endocervical canal; endometrial cavity; cornual ostium; patency of the fallopian tubes; and status of the fimbriae. Tubal patency is indicated by spillage of dye into the endometrial cavity. HSG is able to accurately define the shape and size of the uterine cavity. It can help diagnose uterine developmental anomalies, (e.g., unicornuate uterus, septate uterus, bicornuate uterus and uterus didelphys), submucous myomas, adnexal masses (figures 26.5A and B), intrauterine adhesions and endometrial polyps. Furthermore, the HSG also provides indirect evidence regarding the presence of pelvic adhesions and uterine, ovarian, or adnexal masses. Normal uterine cavity is symmetrical and triangular in shape. It is widest at the level of cornual orfices near the fundus. HSG is best performed during the two to five day interval period immediately following the end of menses.

Timing

The HSG should be performed postmenstrually during the early follicular phase, usually after the end of menstrual bleeding and before the occurence of ovulation. At this time, the endometrium is thin and the HSG can help delineate the minor defects. Additionally, performance of HSG before the occurrence of ovulation eliminates the possibility of accidental irradiation to the fetus in case of an undiagnosed pregnancy.

Procedure

The procedure of HSG involves the following steps:

- The patient is made to lie on the examination table either in lithotomy position, with her feet held up with stirrups or in dorsal position with her knees bent.

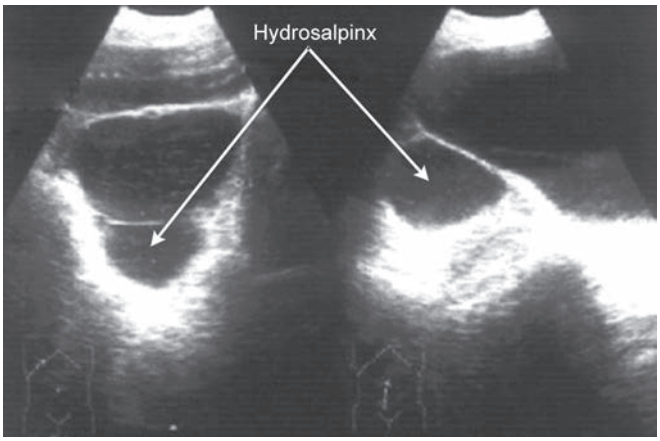


Fig. 26.5A: TAS revealing the presence of bilateral mass with multiple internal echoes suggestive of hydrosalpinx

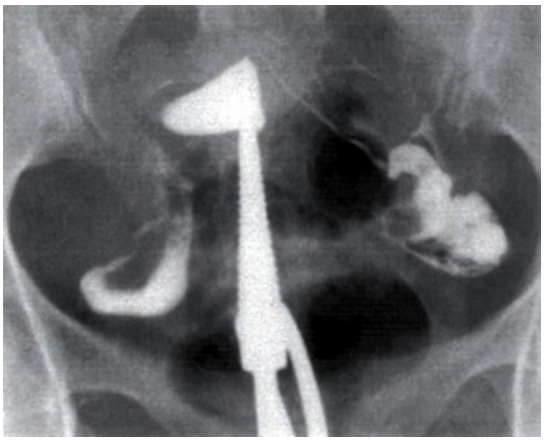


Fig. 26.5B: Hysterosalpingogram in the same patient showing the presence of mass bilaterally

- The posterior vaginal wall is retracted using a Sims speculum and the anterior lip of cervix is held with a tenaculum.
- The procedure is performed after taking strict aseptic precautions. The cervix is cleansed with a povidone-iodine solution (betadine).
- After cleaning the cervix, a catheter is inserted through the cervix inside the uterine cavity.
- The speculum and tenaculum are removed and the patient is carefully situated underneath the fluoroscopy device.
- The contrast material is inserted through the catheter into the uterine cavity, fallopian tubes and peritoneal cavity and fluoroscopic images are taken. Initially the oil based dye, lipoidal was used as the contrast media. However now, water-soluble contrast material is generally being preferred as its helps in preventing the development of possible complications such as oil embolism.
- X-ray pictures are taken as the uterine cavity begins filling. Following this, additional contrast material is injected inside the uterine cavity so that the tubes fill up and the dye begins to spill into the abdominal cavity. More X-ray pictures are taken as the spillage of dye occurs. The X-ray images can help in determining whether the fallopian tubes are patent or blocked and whether the blockage is located at the proximal or at the distal end of the fallopian tube.
- When the procedure is complete, the catheter is removed. Since the injection of dye can sometimes cause cramping, the woman is asked to remain lying on the table for a few minutes following the completion of the procedure in order to let her recover from this cramping. Normal HSG findings with bilateral spillage have been previously discussed in chapter 9. Hysterosalpingogram in the patient whose ultrasound had revealed the presence of bilateral masses suggestive of hydrosalpinx is shown in figures 26.5A and B.

Indications

Women who are not known to have comorbid disorders (such as pelvic inflammatory disease, previous ectopic pregnancy or endometriosis) should be offered hysterosalpingography as a screening test for tubal occlusion. HSG serves a reliable, noninvasive, cost-effective test for ruling out tubal occlusion. Where appropriate expertise is available, hysterosalpingo-contrast-ultrasonography can be considered as an appropriate cost-effective alternative to hysterosalpingography for women who are not known to have any comorbidities. Women who are thought to have comorbidities should be offered laparoscopy with dye instillation so that tubal and other pelvic pathology can be assessed at the same time.

Saline Infusion Sonography

Saline infusion sonography (SIS) provides a simple and inexpensive method for evaluation of the uterine cavity and for assessing tubal patency. Detailed description of the procedure has been done in chapter 17. The procedure is well-tolerated by patients and can be performed in the OPD. In comparision to HSG, SIS helps in eliminating the risks associated with the use of dye and radiation required by the HSG. SIS helps in diagnosing intracavitary uterine abnormalities and tubal patency. The SIS should be performed during days 6–12 of the menstrual cycle prior to the occurrence of ovulation. Thin uterine endometrium during this phase allows better detection of intrauterine lesions. In addition, this ensures that an undiagnosed pregnancy is not disrupted.

While the SIS can confirm tubal patency, it does not provide information about the contour of the tubes. Thus, if a

patient has a history of endometriosis or other tubal disease, laparoscopy is preferred.

Ultrasonography

Pelvic ultrasonography (both transabdominal and transvaginal) have became an important tool in the evaluation and monitoring of infertile patients, especially during ovulation induction. Pelvic ultrasonography has become an important part of the routine gynecologic evaluation because it allows precise evaluation of the uterus, endometrial cavity and adnexa (especially the ovaries). Pelvic sonograms also help in the early detection of uterine fibroids, endometrial polyps, ovarian cysts, adnexal masses and endometriomas. Ultrasonography can help in diagnosing conditions such as ectopic pregnancy, polycystic ovaries and persistent corpus luteum cysts. In the diagnostic evaluation of the infertile couple, ultrasound examination of the endometrium has no proven value. Although ultrasound examination cannot be used to evaluate endometrial receptivity, it does help in the identification of important uterine pathology in infertile women (e.g. presence of congenital malformations, septate uterus and bicornuate uterus).

Hysteroscopy

Hysteroscopy is a method for direct visualization of the endometrial cavity, which is commonly performed as an OPD procedure using local anesthesia (i.e., paracervical block). Hysteroscopy is a definitive method for both the diagnosis and treatment of intrauterine pathology, which is likely to have an affect on the fertility. While performing hysteroscopy, solutions such as hyskon (previously used) and glycine and sorbitol (used nowadays) are used for intrauterine instillation. Hysteroscopic examination helps in both the diagnosis and treatment of endometrial pathology. Hysteroscopic surgery can also be used for treatment of intrauterine pathologies such as uterine synechiae, endometrial polyps, submucous myomas, removal of foreign bodies (e.g., intrauterine devices) and lysis of intrauterine adhesions produced by Asherman's syndrome.

Endometrial Biopsy

The endometrial lining constantly changes in response to the various hormones secreted during the different phases of the menstrual cycle. Detailed description of the procedure of endometrial biopsy has been done in chapter 17. A diagnosis of luteal phase dysfunction is made on the basis on the lack of correlation between the findings on endometrial biopsy and day of the menstrual cycle. During the follicular phase of the menstrual cycle, the endometrium exhibits a proliferative pattern. The growth is stimulated by rising levels of estrogen derived from the dominant ovarian follicle. Progesterone secreted by the corpus luteum causes secretory transformation of the endometrium. The endometrium in anovulatory women is always in the follicular phase. Unopposed estrogen stimulation can cause endometrial proliferation resulting in endometrial hyperplasia. Pathologists date the endometrium by estimating the number of days that have passed since ovulation. Ovulation can be detected by measuring LH surge or by observing the signs of follicular collapse on ultrasound examination. Agreement between the histological and sampling dates by two days is considered as normal. If there is a discrepancy of more than two days, the endometrium is considered to be out of phase. This is known as luteal phase deficiency.

Tubal and Peritoneal Factors

The two most frequent tests used for diagnosis of tubal pathology are laparoscopy and hysterosalpingogram. Hysterosalpingogram has been previously described. Therefore, only laparoscopy would be described here. An endoscopic procedure known as falloscopy is sometimes used for delineating fallopian tube pathology.

Laparoscopy

The laparoscope is one of the greatest developments in gynecologic instrumentation. The laparoscope was first used to visualize the pelvic cavity. Gynecological laparoscopy is used for diagnosis as well as treatment of pelvic pathology. During laparoscopic examination, a laparoscope is used for visualizing the pelvic area, uterine surface, anterior and posterior cul-de-sacs, fallopian tubes and ovaries (figures 26.5A and B). Gynecological laparoscopy is commonly used for diagnosing and treating endometriosis, PID, ectopic pregnancy and removal of adhesions and scar tissue. Laparoscopy can be used for monitoring the effects of ovulation induction medicines on the ovaries, and taking biopsies from ovarian cysts. Diagnostic laparoscopy may be performed under deep sedation and local anesthesia, while operative laparoscopy typically requires general anesthesia. Injection of a dye solution through the cannula inserted inside the cervix permits evaluation of tubal patency (chromotubation). Indigocarmine dye is usually preferred over the dye, methylene blue due to the possible risk of acute methemoglobinemia.

Laparoscopy is contraindicated in patients with probable bowel obstruction, bowel distention, cardiopulmonary disease or shock due to internal bleeding. Laparoscopy is associated with the risk of complications such as bowel perforation, uterine and pelvic vessel injury, bladder trauma, etc. Therefore, the procedure must be preferably performed by a skilled and experienced surgeon.

Currently, laparoscopy has become the gold standard method for detection of tubal patency.

In comparison to laparoscopy, HSG is less invasive, does not require general anesthesia, is able to reveal the internal structure of the uterus and tubes and is associated with a reduced rate of complications, such as injury to the bowel or blood vessels. HSG has only moderate sensitivity, but high specificity in detection of tubal pathology. This implies that when HSG reveals obstruction, there is a high degree of probability that the tube is in fact open. On the other hand, when the HSG demonstrates patency, there is a little chance that the tube is actually occluded.

Falloposcopy

Falloposcopy is defined as transvaginal microendoscopy of the fallopian tubes and enables the gynecologist to directly visualize the entire lumen of the fallopian tube.

Ovarian Factors

Checking the ovarian reserve

The level of ovarian reserve and the age of the female partner are the most important prognostic factors in the fertility workup. The level of ovarian reserve is supposed to decrease with age. Checking for ovarian reserve is specifically indicated in patients 35 years or older. Ovarian reserve is most commonly evaluated by performing the clomiphene citrate challenge test. In this test, serum FSH and estradiol levels are measured on day 3. Then clomiphene citrate is administered in the dosage of 100 mg orally on the days 5–9 of the cycle, following which the FSH and estradiol levels are measured on day 10. Normal ovarian function is indicated when the FSH levels are less than 10 mIU/mL and the estradiol levels are less than 65 pg/mL on day 3 or day 10 of the cycle.

Serum progesterone levels

To confirm ovulation, serum progesterone levels are measured in the mid-luteal phase or 21st day of the cycle. Serum progesterone levels greater than 4 ng/mL on 21st day of a 28-day cycle or later in cycle (in case of longer cycles) is indicative of ovulation.

Ultrasound

Serial ultrasonographic examination can be performed to confirmation follicular rupture or ovulation. Ultrasound examination is also helpful in diagnosing PCOS (figure 26.6).

Basal body temperature

Basal body temperature charts can be used for predicting ovulation. In this method, the woman is asked to measure her oral temperature with an oral glass or mercury thermometer, the first thing when she wakes up in the morning or after at least three hours of uninterrupted sleep. She should measure her temperature throughtout the entire duration of her menstrual cycle for atleast three menstrual cycles. The temperatures are then plotted on a graph paper.

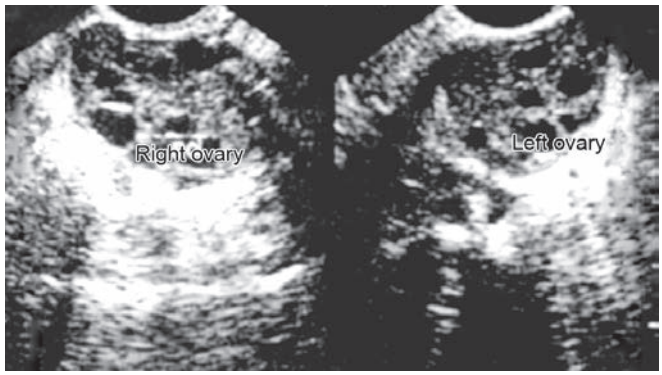


Fig. 26.6: TVS showing a row of intermediate sized subcapsular follicles present peripherally in both the ovaries suggestive of PCOD

BBT varies between 97.0 to 98.0°F during the follicular phase of the cycle and rises by 0.4–0.8°F over the average preovulatory temperature during the luteal phase. The thermogenic shift in BBT occurs when serum progesterone levels rise above 5 ng/ml, usually occurring for upto four days following ovulation. In a normal ovulating woman, there occurs a rise in body temperature by 0.5–1.0°C immediately following ovulation under the thermogenic effect of progesterone (figure 26.7). This increase in temperature remains sustained throughout the luteal phase. The temperature again falls to baseline just before or after the onset of menses. This biphasic pattern is evident in ovulatory women. Besides providing an evidence for ovulation, BBT recording can also help in determining the approximate time of ovulation. BBT recording can also reveal an abnormally long follicular phase or a short luteal phase. Treatment of these may help in improving fertility. Though an easy, noninvasive and cost-effective procedure, taking the temperature daily can become cumbersome. BBT serves as a useful method for couples who are reluctant or unable to pursue more formal and costly evaluations.

Monitoring of the LH surge

Urinary monitoring of the LH surge (e.g., with an LH predictor kit) can serve as a substitute for BBT. When accurate prediction of ovulation is required, determination of LH secretion serves as the most cost-effective and appropriate choice. The patient should start monitoring the urinary LH secretion daily starting on menstrual cycle day 12. Ovulation usually occurs within the 32–40 hours after the indicative color change in the kit.

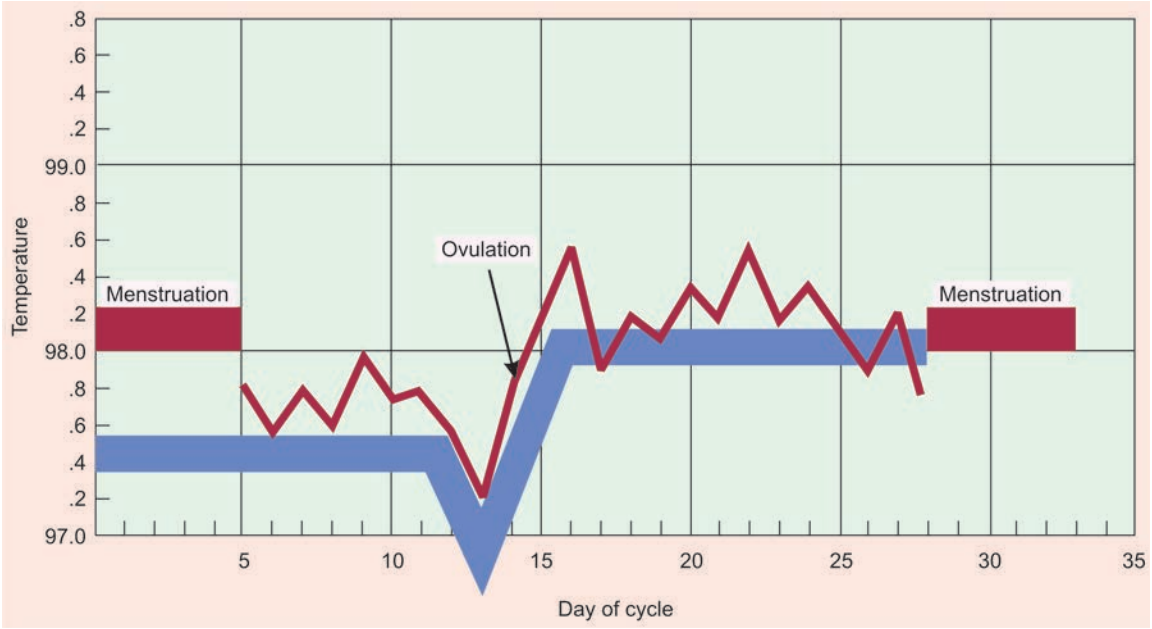


Fig. 26.7: Basal body temperature method

Rx *Treatment/Gynecological Management*

A treatment plan should be generated based on the diagnosis established through the findings of laboratory investigations, clinical history and examination, duration of infertility, and the woman's age. If pregnancy has not been established within a reasonable time, further evaluation and/or an alternative treatment plan should be considered. Initial treatment should comprise of patient counseling and lifestyle changes, especially if no obvious cause of infertility has been detected.

Patient counseling

Counseling the patients is an important aspect of management. Patients with infertility are emotionally vulnerable and require emotional support. Before deciding the final line of management, the couple's emotional, medical, financial and social requirements and concerns must be taken into consideration. The couple should be explained about the normal menstrual cycles and the time for maximum fertility. They must also be explained about the reproductive cycle and that average fecundability per cycle is on an average equal to 20%. The patient should be explained that normal sperm retains its ability to survive in the female reproductive tract for about 3–5 days, while the oocyte remains viable for about 12–24 hours following ovulation. Therefore for conception to occur, intercourse must occur while the ovum is still alive, with the highest estimated conception rates associated with intercourse two days before ovulation. However, timed intercourse is less likely to result in fertility and is supposed to further increase the patient's anxiety. Therefore for most couples, the gynecologist must recommend the couple to have intercourse every 2 to 3 days. This stategy helps in avoiding unnecessary stress and at the same time ensures high fertility rate.

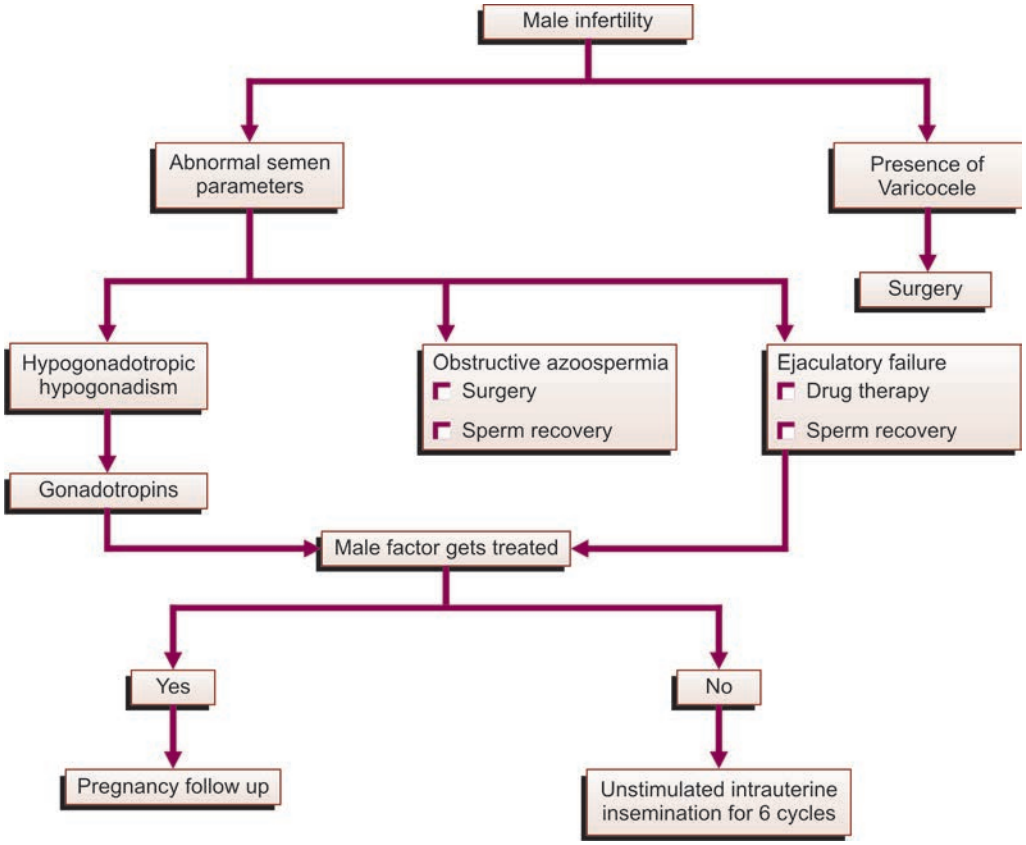
Lifestyle changes

Raised BMI and obesity have been found to be associated with infertility, polycystic ovarian disease and anovulation. For couples attempting conception, it is recommended that the BMI is achieved between 20 and 25. Alcohol consumption must be limited to four or fewer drinks per week for men and to one or two units, once or twice a week for women. Women who regularly smoke should be informed that this is likely to reduce their fertility. Women who smoke should be referred to a smoking cessation programme in order to help them quit smoking. The male partner should also be encouraged to quit smoking because passive smoking is also likely to affect their chances of conceiving. Men who smoke should be informed that there is an association between smoking and reduced semen quality. The couple should also be informed that presently there is no consistent evidence advocating any association between consumption of caffeinated beverages (tea, coffee and colas) and fertility problems.

Treatment of Male Infertility

The treatment of male factor infertility has been described in flow chart 26.1. In most cases of male factor infertility due to oligospermia, intrauterine insemination is the treatment

Flow chart 26.1: Treatment of male infertility



of choice if more than 2 million sperms are recovered after the sperm wash. Men with hypogonadotropic hypogonadism should be offered treatment with gonadotropin drugs because these are effective in improving fertility. Patients with ejaculatory sexual dysfunction may benefit from a prescription for phosphodiesterase type 5 inhibitors, e.g., sildenafil.

Use of drugs such as antiestrogens, gonadotropins, androgens, bromocriptine or kinin-enhancing drugs are not recommended. These have not been shown to be effective in improving male factor infertility. Men with leukocytes in their semen should not be offered antibiotic treatment unless the presence of infection has been confirmed because there is no evidence that use of antibiotics improves pregnancy rates.

Where appropriate expertise is available, men with obstructive azoospermia should be offered surgical correction of epididymal blockage because it is likely to restore patency of the duct and improve fertility. Other options which can be considered as an alternative to surgery include surgical sperm recovery and in vitro fertilization. Though men with varicoceles are commonly offered surgery as a form of fertility treatment, this has not been observed to improve the pregnancy rates.

Treatment of Cervical Factors

Chronic cervicitis may be treated with antibiotics. The easiest and most successful treatment option for infertility related to cervical factors is artificial intrauterine insemination (IUI). Low-dose estrogen therapy may provide some benefit in cases with reduced secretion of cervical mucus.

Artificial intrauterine insemination

Artificial insemination can be performed by depositing the sperms at the level of internal cervical os (cervical insemination) or inside the endometrial cavity (intrauterine insemination). Since cervical insemination is associated with low success rates in comparison with intrauterine insemination, the latter is more commonly used. Intrauterine insemination may be performed either during a natural cycle (unstimulated IUI) or following ovulation induction with clomiphene citrate or gonadotropins (stimulated IUI). The average pregnancy rate achieved after a natural-cycle intrauterine insemination is 8%. This rate increases by 5% to 10% in the stimulated cycles. Of all the successful pregnancies achieved by IUI, 85% are achieved within the first four cycles of intrauterine inseminations. Artificial insemination can be of two types: Homologous and heterologous. While the homologous

Table 26.5: Indications for intrauterine insemination

Unexplained infertility.
Cervical factor infertility.
Failure to conceive after ovulation induction treatment.
Immunological causes (anti-sperm antibodies).
Couples with minimal to mild endometriosis.
Mild-moderate male factor infertility and other causes of male infertility such ejaculatory failure and retrograde ejaculation.

insemination refers to the use of sperm from the patient's partner, heterologous insemination refers to the use of frozen donor sperms that have been quarantined for at least 6 months.

Indications for intrauterine insemination

Important indications for intrauterine insemination are enumerated in table 26.5.

Procedure

The procedure is performed 30–34 hours after the spontaneous LH surge or 36 hours after the administration of 10,000 U of hCG.

- Timing for the procedure is very crucial while dealing with IUI, because sperms should be injected at the precise time when ovulation has occurred or is about to occur.
- Sperm preparation: At the time of expected ovulation, a fresh semen sample is collected from the male partner and processed in the lab by washing in a culture medium or using a density gradient column. After sperm preparation, the spermatozoa are enhanced in motility and become activated and ready to fertilize an oocyte.
- Intrauterine insemination: The prepared semen sample is delivered inside the endometrial cavity using an intrauterine insemination catheter.
- Following the injection of the sperms, the patient must remain in the recumbent position for at least 10–15 minutes.

Treatment of Uterine Factors

Surgical intervention

Surgical treatment involves lysis of uterine septae and uterine synechiae, surgical treatment of uterine anomalies (e.g. bicornuate uterus, etc). Uterine synechiae and septae are corrected using operative hysteroscopy. This surgery is performed during the early follicular phase. Once the synechiae/septae have been resected, an intrauterine balloon is left for 7 days inside the uterine cavity to prevent the recurrence of adhesions. Endometrial polyps may also be removed through operative hysteroscopy associated with a dilatation and curettage, if required. Treatment of fibroids may be required if they are associated with abnormal uterine bleeding or if they are thought to be the cause of infertility. Three modalities which are commonly used for treatment of myomas i.e. medical treatment, surgical treatment (conventional laparotomy, operative laparoscopy and operative hysteroscopy), and embolization are described in chapter 18.

Treatment of Tubal Factors of Infertility

The treatment of tubal-factor infertility has undergone tremendous changes, especially during the last few decades with the widespread use of tubal microsurgery and assisted reproductive techniques.

Microsurgery

Tubal obstruction due to elective sterilization is usually repaired using microsurgical technique. Before undertaking microsurgery, it is important to determine the type of tubal ligation technique that had been employed in that particular case. This knowledge helps the clinician in predicting the success rate for surgery. For example, tubal cauterization results in the destruction of a large amount of tissue, so tubal reanastamosis if performed in the remnant part of fallopian tube may not prove to be successful.

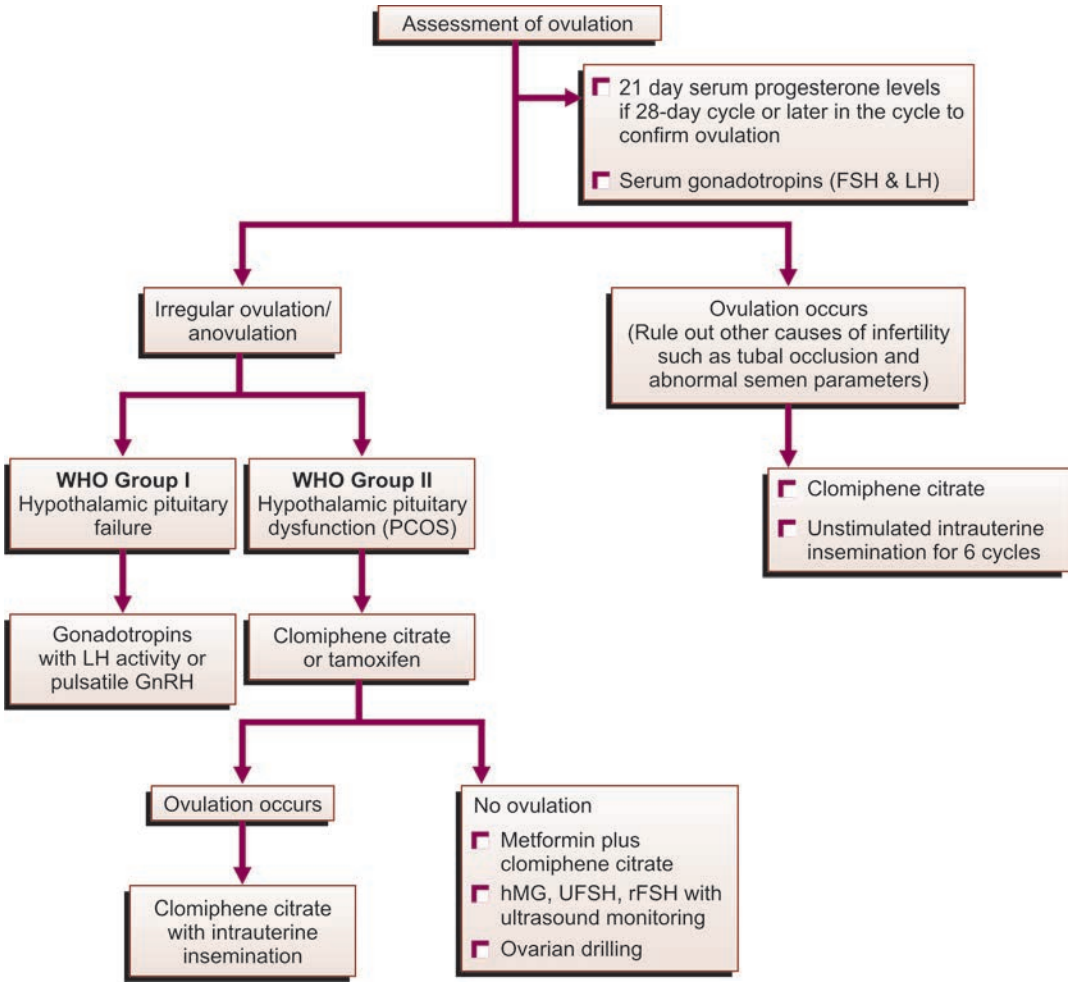
Before undertaking reanastomosis, the lengths of proximal and distal fragments of the fallopian tubes from the point of tubal ligation need to be determined. In order to achieve a successful reanastomosis, the final tube length should measure at least 4.5 cm. If previously fimbriectomy had been performed, no treatment option is available other than IVF. The best candidates for tubal reanastomosis are patients who had undergone tubal ligation by the method of fallopian ring, Filshie clip, or Pomeroy's technique. The pregnancy rate following a tubal reanastomosis performed by surgeons skilled in microsurgery varies from 70% to 80%. However, the procedure is also associated with an ectopic pregnancy rate varying between 7% to 10%.

Laparoscopy

Nowadays, laparoscopic surgical approach is widely being used for the treatment of multiple tuboperitoneal pathologies, using techniques such as electrocautery, endocoagulation, lasers and ultrasonography.

Laparoscopy for lysis of adhesions may be indicated in patients with severe pelvic adhesions that compromise the bowel, ovaries and tubes along with the obliteration of the cul-de-sac. Lysis of adhesions should be meticulous, using hydrodissection and fine instruments. Blunt dissection should be avoided. Constant irrigation with ringer lactate solution and heparin prevents fibrin formation. Meticulous hemostasis

Flow chart 26.2: Treatment of infertility due to ovarian factors



must be maintained at all times. Fimbrial phimosis and periadnexal disease can also be treated by fimbrioplasty using laparoscopy.

Treatment of hydrosalpinx (distal tubal obstruction) with salpingostomy can be performed through microsurgery or operative laparoscopy. The success of either procedure is related to the diameter of the hydrosalpinx and to the damage to the ciliated epithelium. If the ciliated epithelium has been destroyed, the outcome of the procedure is poor. In these cases, it is better to perform a salpingectomy in preparation for future IVF.

Treatment of Ovarian Factors

In case of patients with ovulatory dysfunction, the most appropriate treatment option is to begin with ovulation inducing drugs. The treatment can be begun immediately before other potential causes of infertility have been investigated. Women with ovulatory disorders due to hyperprolactinemia should be offered treatment with dopamine agonists such as bromocriptine. In cases where anovulation is the only obstacle to be overcome, most couples would conceive promptly on using ovulation induction agents. In these cases, the various ovulation induction agents which can be used include clomiphene citrate, hMG, hCG, recombinant FSH, and recombinant LH.

Treatment of infertility due to ovarian factors has been described in flow chart 26.2.

Clomiphene citrate

Clomiphene citrate (CC) is a nonsteroidal antiestrogen drug which is largely believed to act by exerting its antiestrogen effect by competing with the estrogen receptors at the level of hypothalamus, pituitary and ovaries. By blocking the estrogen receptors within the hypothalamus, CC alleviates the negative feedback effect exerted by endogenous estrogens. As a result, the GnRH release gets normalized. Therefore, the secretion of FSH and LH is able to reestablish the normal process of ovulation and is capable of normalizing follicular

recruitment, selection, and development. Clomiphene citrate can also be prescribed to the women with unexplained fertility problems.

The standard dose of CC is 50 mg PO once a day for 5 days, starting on the day 3–5 of the menstrual cycle or after progestin-induced bleeding. The response to CC is monitored using pelvic ultrasonography starting on the day 12 of the menstrual cycle. The follicle should develop to a diameter of 23–24 mm before a spontaneous LH surge occurs.

However, the women who are being prescribed CC should be informed that this drug may be associated with the risk of multiple pregnancies. Women undergoing treatment with clomiphene citrate should be offered ultrasound monitoring during at least the first cycle of treatment to ensure that they receive a dose that minimizes the risk of multiple pregnancy. Another important adverse effect associated with the use of this drug is the thickening of the cervical mucus under the antiestrogenic effect of CC. This may create an iatrogenic cervical factor which may be responsible for producing infertility in a patient who has otherwise ovulated. Other adverse effects which may be rarely associated with CC include hot flashes, scotomas, dryness of the vagina, headache and ovarian hyperstimulation. The use of CC is contraindicated in cases of ovarian cyst, pregnancy and liver disease. Its use is also controversial in patients with a history of breast cancer. Anovulatory women with polycystic ovary syndrome, having a body mass index of more than 25 who have not responded to clomiphene citrate alone, should be offered metformin in combination with clomiphene citrate. Women who are prescribed metformin should be informed about the side effects such as nausea, vomiting and other gastrointestinal disturbances associated with its use.

26

Human menopausal gonadotropins

hMG and its derivatives are indicated for ovulation induction in patients with primary amenorrhea and/or infertility, who did not respond to ovulation induction with CC. Human menopausal gonadotropins or hMG (Menopur) contains 75 U of FSH and 75 U of LH per mL, although the concentration may vary in the range of 60–90 U for FSH and for LH in the range of 60–120 U. The new generations of available gonadotropins are produced by genetically engineered mammalian cells, i.e., Chinese hamster ovary cells.

Multiple adverse effects and complications that may occur following the use of the gonadotropins, include multiple pregnancy, ectopic pregnancy, miscarriages, ovarian torsion and rupture and ovarian hyperstimulation syndrome. Due to the risk of various side effects, especially ovarian hyperstimulation syndrome, the administration of hMG and its derivatives should be directly supervised by a reproductive endocrinologist under ultrasound guidance and daily determinations of estradiol, FSH and LH levels.

Ovarian hyperstimulation syndrome

Ovarian hyperstimulation syndrome is an iatrogenic condition that occurs in patients undergoing ovulation induction with hMG or controlled ovarian hyperstimulation for assisted reproductive technologies. The incidence rate fluctuates from 0.1% to 30%. The pathophysiology of the disease is not well understood, but is associated with massive extravascular accumulation of fluid. This causes severe depletion of the intravascular volume resulting in dehydration, hemoconcentration, and electrolyte imbalance (i.e., hyponatremia, hyperkalemia). Ovarian hyperstimulation syndrome can be classified as mild, moderate, or severe (table 26.6).

Gonadotropin releasing hormone

Synthetic GnRH (e.g., Gonadorelin) has a chemical composition similar to native GnRH and is indicated for patients with hypothalamic dysfunction, especially those who do not respond to CC. This drug is administered in a pulsatile fashion every 60–120 minutes, intravenously or subcutaneously using a delivery pump in the starting dose of 5 mcg per pulse intravenously or 5–25 mcg subcutaneously. The administration of GnRH should be extended throughout the luteal phase, or this should be supplemented with the administration of exogenous hCG. Intensive monitoring of folliculogenesis is not required in these patients due to low risk of ovarian hyperstimulation. Urinary LH kit is a practical way to monitor these patients. Pelvic ultrasonography can be used once a week until the dominant follicle is detected.

Pure FSH treatment for ovulation induction is another alternative for patients with PCOS who are clomiphene resistant. Pure FSH must be started at 37.5 IU/d subcutaneously. The dosage is increased slowly (i.e., by 37.5 IU q5d) until follicle development is detectable based on an elevation of the E_2 levels and the presence of follicle development on sonograms. Using this small amount of FSH, the patient generally develops 1–2 follicles, decreasing the risk for multiple pregnancy and eliminating the risk of ovarian hyperstimulation syndrome.

Treatment of PCOS

Some commonly used treatment options for PCOS include ovulation inducing medicines such as clomiphene citrate, insulin sensitizing agents (such as glucophage, and metformin), dietary changes (low glycemic diet) and surgery (ovarian drilling). The primary treatment for PCOS is weight loss through diet and exercise. Modest weight loss helps

Table 26.6: Features of ovarian hyperstimulation syndrome

Feature	*Mild*	*Moderate*	*Severe*
Ovarian enlargement	5–12 cm	–	–
Accompanying symptoms	–	Nausea, vomiting, and abdominal discomfort	Nausea, vomiting, diarrhea, shortness of breath, hydrothorax, peripheral edema, oliguria, hemoconcentration (e.g., hematocrit level >48% and hemoglobin level >16 g), and creatinine level greater than 1.6 mg/dL.
Ascites	Mild	Moderate	Severe
Weight gain	Less than 10 pounds	Greater than 10 pounds	–
Treatment	Treatment at home with bedrest and strict control of fluid intake and output	Hospitalization, with intravenous fluids, albumin for promoting diuresis and transvaginal or abdominal paracentesis	Hospitalization

in lowering the androgen levels, improving hirsutism, normalization of menstrual cycles, resumption of ovulation and reduction of insulin resistance. However it may take months, before these results become apparent. Besides facilitating fertility, the aims of treatment in women with PCOS are to control hirsutism, to prevent endometrial hyperplasia from unopposed acyclic estrogen secretion, and to prevent the long-term consequences of insulin resistance. The treatment must be individualized according to the needs and desires of each patient. Use of oral contraceptive pills or cyclic progestational agents can help maintain a normal endometrium and also reduce the increased risk of endometrial hyperplasia and carcinoma.

For the woman with PCOS who wants to conceive, clomiphene citrate is used initially because of its high success rate and relative simplicity and inexpensiveness. Clomiphene citrate is able to induce ovulation in nearly 80% of the individuals and 40% are able to conceive. Other possible therapeutic approaches for ovulation induction include the use of insulin-sensitizing agents, gonadotropins (perhaps preceded by a GnRH analogues), FSH alone, pulsatile GnRH and wedge resection of the ovaries at laparotomy.

Clomiphene citrate

Clomiphene citrate has been described previously in the text.

Gonadotropins

Women with polycystic ovary syndrome having BMI within normal range, who have not responded to clomiphene citrate can be treated with gonadotropins. Human menopausal gonadotropin, urinary follicle stimulating hormone and recombinant follicle stimulating hormone are equally effective in achieving pregnancy.

Laparoscopic ovarian drilling

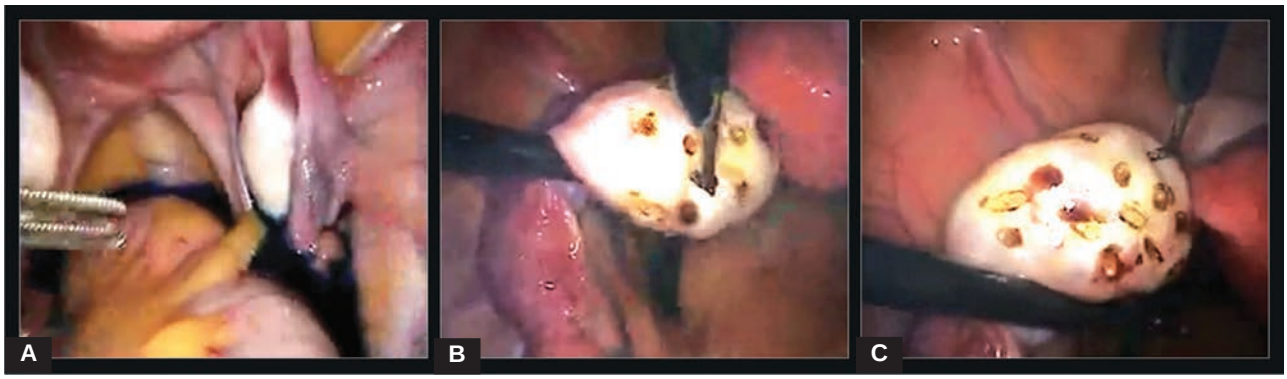
Women with polycystic ovary syndrome who have not responded to clomiphene citrate should be offered laparoscopic ovarian drilling because it is as effective as gonadotropin treatment and is not associated with an increased risk of multiple pregnancy. This procedure involves creation of approximately 4–20 holes, having a size of 3 mm diameter and 3 mm depth to be made in each ovary, preferably on the anti-mesentric side (figures 26.8A to C). Women who are unable to conceive naturally following the above mentioned therapeutic options often respond to assisted reproductive technologies, including IVF.

Aromatase inhibitors

Aromatase inhibitors such as letrozole and anastrozole inhibit the action of the enzyme aromatase, which is responsible for the process of aromatization (conversion of androgens into estrogens). As a result, estrogen levels are dramatically reduced, releasing the hypothalamic-pituitary axis from its negative feedback. Aromatase inhibitors have presently not been approved by FDA for ovulation induction in cases of PCOS.

Metformin

Patients with PCOS, having a BMI > 25 are often resistant to treatment with CC alone. These patients commonly have other problems such as hyperinsulinism and hyperandrogenism associated with acanthosis nigricans. This group is amenable to metformin treatment in combination with CC. Metformin improves insulin sensitivity and decreases hepatic gluconeogenesis and, therefore, reduces hyperinsulinism, basal and stimulated LH levels, and free testosterone concentration. Consequently, the patient with PCOS becomes



Figs 26.8A to C: (A) Laparoscopic visualization of the pelvis in an effort to locate the ovaries (B) The procedure of laparoscopic ovarian drilling (C) Appearance of the ovary following the procedure

responsive to CC ovulation induction. Metformin is used as an insulin sensitizer. It helps in treating the root cause of PCOS and improves fertility by rectifying endocrine and metabolic functions.

Adverse effects of metformin include GI intolerance, nausea, vomiting and abdominal cramps. Weight loss has also been observed. The initial dose is 500 mg PO once a day for 7 days, then 500 mg BID for another 7 days, and, finally, 500 mg TID. Since patients can ovulate while on metformin treatment, pelvic ultrasonography is required for documentation of ovulation. In case ovulation does not occur, CC is started at the initial dose of 50 mg/d for 5 days.

Treatment of Tubal Disease

Treatment of tubal factor infertility has been described in flow chart 26.3. For women with mild tubal disease, tubal surgery may be more effective than no treatment, especially in centers where appropriate expertise is available. For women with proximal tubal obstruction, selective salpingography plus tubal catheterization, or hysteroscopic tubal cannulation, may serve as effective treatment options. The following treatment options can be used in cases of endometriosis:

- Conservative laparoscopic surgery (laparoscopic ablation or adhesiolysis) when reproductive potential is to be retained.
- Semiconservative management when reproductive ability is eliminated but ovarian function is to be retained, e.g., laparoscopic cystectomy for ovarian endometriomas.
- In case of severe disease where it is impossible to achieve fertility, radical approach involving the removal of the uterus and ovaries may be required.

Treatment of Unexplained Infertility

Initially, the couples with unexplained infertility are managed expectantly. Next line of management comprises of the use of drugs such as antiestrogens (usually clomiphene citrate) and IUI. If none of these options work, the final stage of management is IVF treatment.

Assisted Reproductive Techniques

In vitro fertilization

IVF consists of retrieving a preovulatory oocyte from the ovary; fertilizing it with sperm in the laboratory, and subsequently transferring the embryo within the endometrial cavity. With increasing developments in the field of science and technology, IVF is now being recognized as an established treatment for infertility.

Factors affecting the outcome of in vitro fertilization treatment

The woman's age: Women should be informed that the chance of a live birth following in vitro fertilization treatment reduces with an increase in the woman's age and that the optimal female age range for achieving a successful in vitro fertilization treatment is 23–39 years. Chances of a live birth per treatment cycle are:

- Greater than 20% for women aged 23–35 years.
- 15% for women aged 36–38 years.
- 10% for women aged 39 years.
- 6% for women aged 40 years or older.

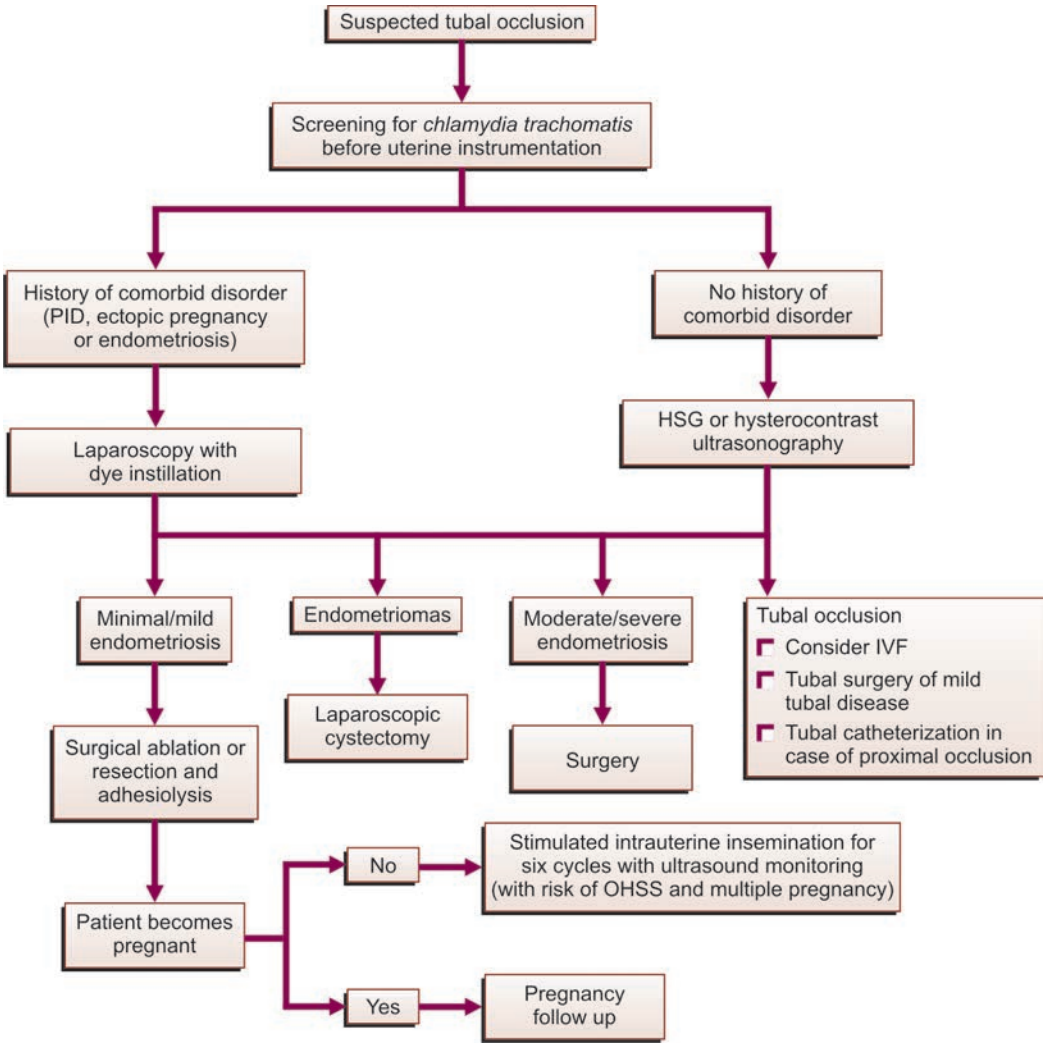
Number of embryos to be transferred: The more the number of embryos are transferred, greater would be the chances of success. However, in order to reduce the chances of multifetal gestation, number of embryos transferred have been limited to two at most of the IVF centres.

Number of previous treatment cycles: The chances of conception greatly reduce after three cycles of IVF.

Pregnancy history: Treatment is more effective in women who have previously been pregnant and/or had a live birth.

Alcohol, smoking and caffeine consumption: Couples should be informed that maternal and paternal smoking can adversely

Flow chart 26.3: Treatment of tubal disease



affect the success rates of assisted reproduction procedures, including in vitro fertilization treatment.

Body mass index: Women should be informed that a female body mass index outside the normal range (19–30) is likely to reduce the success rate of assisted reproduction procedures.

Indications

Indications for in vitro fertilization include the following:

- Uterine malformations (e.g., unicornuate uterus).
- Damage/absence of fallopian tubes.
- Severe pelvic adhesions.
- Severe endometriosis, which is unresponsive to medical or surgical treatment.
- Severe oligospermia or a history of obstructive azoospermia in the male partner.
- Premature ovarian failure.
- Gonadal dysgenesis including Turner syndrome.
- Bilateral oophorectomy.
- Ovarian failure following chemotherapy or radiotherapy.

Procedure

IVF consists of retrieving preovulatory oocytes from the ovary and fertilizing them with sperms in the laboratory, with subsequent embryo transfer within the endometrial cavity. The procedure of IVF comprises of the following steps (figures 26.9A to G):

- Ovarian stimulation.
- Follicular aspiration.
- Oocyte classification.
- Sperm preparation.
- Oocyte insemination.
- Embryo culture.
- Embryo transfer.

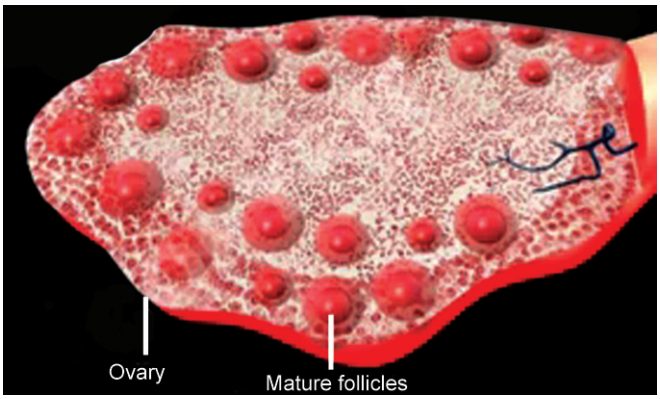


Fig. 26.9A: Follicular stimulation

Fig. 26.9D: Oocyte insemination with multiple sperms

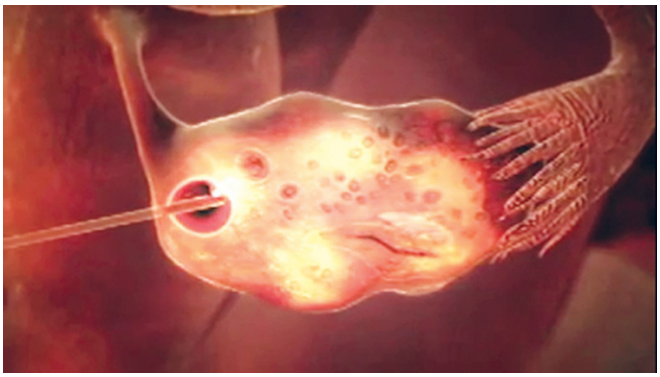


Fig. 26.9B: Follicular aspiration

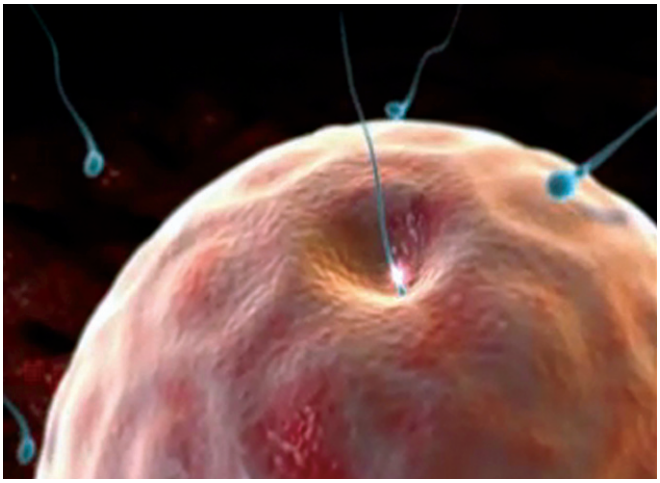


Fig. 26.9E: Fertilization of the ovum with a single sperm

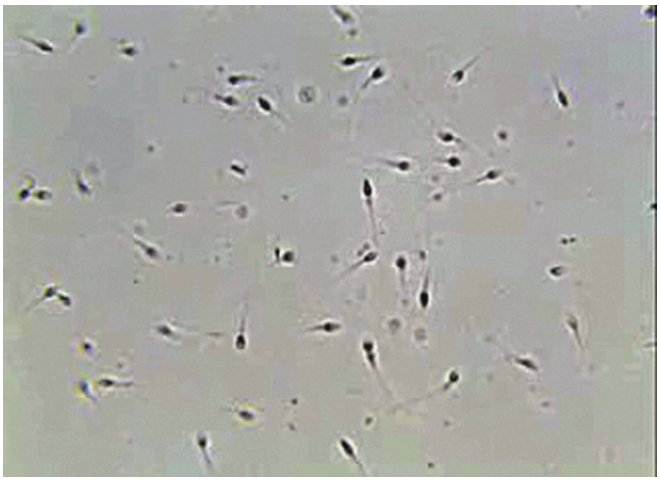


Fig. 26.9C: Sperm concentrate

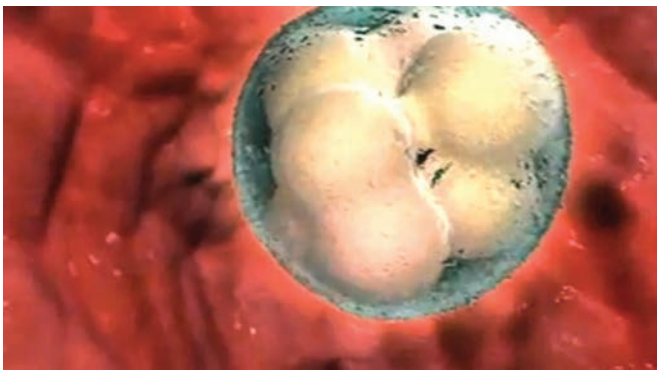


Fig. 26.9F: Embryo culture

Ovarian stimulation for IVF

The success of IVF is related to the patient's age and the number of embryos transferred into the endometrial cavity. Therefore, in order to increase the number of ovarian follicles which get recruited, selected and finally get trasnsformed into dominant follicle, several protocols may be used. These include: Clomiphene citrate protocol; use of clomiphene citrate with human menopausal gonadotropins; use of human menopausal gonadotropins only; use of GnRHa (GnRH agonists) and GnRHa antagonists.

In the clomiphene citrate-only protocol, clomiphene citrate is administered in the doses of 50–150 mg for 5–7 days,

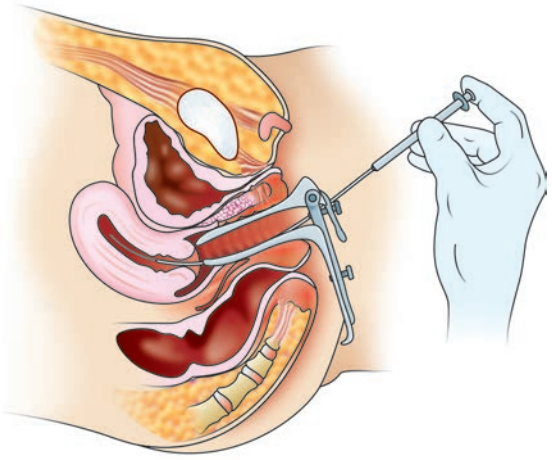


Fig. 26.9G: Transfer of embryo inside the uterine cavity

starting from the second day of the menstrual cycle. The ovarian response is monitored using pelvic ultrasonography and serial determinations of serum E_2 and LH levels. Oocyte retrieval must be performed within 24–26 hours after the LH surge. The advantages of the CC protocol include low cost and a very low risk of development of ovarian hyperstimulation syndrome. The major disadvantages associated with this protocol include low oocyte yield (1–2 per cycle), high cancellation rates (25% to 50%) and low pregnancy rates.

The combination of clomiphene citrate and human menopausal gonadotropins protocol is also sometimes used. This has an advantage of increasing the number of recruited follicles. The dose of CC is similar to that described above, while that of hMG is 150 IU, administered for a period of 2–7 days after the CC. Frequent montitoring with pelvic ultrasonography and daily determinations of E_2 and LH levels are performed. When the follicle reaches a size of 17–18 mm, hCG (10,000 IU IM) must be administered in order to complete the oocyte maturation. Oocyte aspiration should be performed 35 hours after the hCG injection. The advantage of the combined protocol is an increase in the number of recruited follicles. The disadvantages of the protocol are premature luteinization, spontaneous LH surge (20% to 50%) and high cancellation rate (15% to 50%).

The protocol comprising of human menopausal gonadotropins only involves the administration of hMG for ovarian stimulation. With the introduction of new technologies, besides the Human menopausal gonadotropins (Menopur), pure FSH gonadotropins and recombinant FSH and LH gonadotropins are also currently available. The gonadotropins are administered in the dosage varying from 150–450 IU/d, depending on the patient's age and history of previous ovulatory response. Gonadotropins are usually started on the second or third menstrual cycle day. The response is monitored using daily serum E_2 determination and later using pelvic ultrasonography. Once most of the follicles reach 17–18 mm in diameter, the gonadotropins are discontinued. hCG (10,000 IU) is administered that evening, and oocyte retrieval is performed 35 hours later.

The GnRHa can be used for ovulation induction in two protocols known as the flare-up protocol and the luteal-phase protocol. In the flare-up protocol, high doses of GnRH agonists are administered during the early follicular phase of the cycle. The flare-up protocol has the advantage of causing transitory elevation of FSH which occurs during the first four days of the follicular phase. This elevation helps in the follicular recruitment process. In the luteal-phase protocol, GnRHa is started on the 17th or 21st day of the menstrual cycle.

The GnRHa antagonists are the latest generation of GnRHa that block LH secretion without a flare-up effect. The GnRHa antagonists are administered as a single dose on the eighth day of the menstrual cycle. Use of GnRHa antagonists has the advantage of blocking the LH surge at the periovulatory period; therefore, premature luteinization or spontaneous LH surge does not occur. As a result, the pituitary gland is not down-regulated at the beginning of the menstrual cycle, due to which smaller amounts of gonadotropins are required to stimulate ovulation. Another advantage with this protocol is the prevention of ovarian hyperstimulation syndrome.

Follicular aspiration

Oocytes are aspirated from the ovary 35–36 hours following administration of hCG. Initially all aspirations were performed under laparoscopic guidance. However now, follicular aspirations are commonly performed under ultrasonographic guidance, both transabdominal as well as transvaginal. The transvaginal route for follicular aspiration has now become the preferred procedure in most IVF programs.

The procedure of follicular aspiration comprises of the following steps:

- The oocyte aspiration is usually performed under heavy sedation, while the patient has been placed in the dorsal lithotomy position.
- The vaginal wall is washed with saline, following which a 5- to 9-MHz ultrasonographic probe with a sterile cover and attached needle guide is inserted inside the vagina. This helps in localizing the ovaries and the follicles.
- A 17-gauge needle is subsequently passed via the needle guide through the vaginal fornix into the ovaries in order to aspirate the follicular fluid.
- Once the fluid has been aspirated out, it is sent to the IVF laboratory as soon as possible.

Oocyte classification

Following their aspiration, the oocytes are graded according to the appearance of the corona-cumulus complex. The presence of a polar body (metaphase II stage) and/or germinal vesicle (prophase stage) is a determining factor for the short preincubation time prior to the insemination. The degenerated oocytes are those which are atretic or have a fractured zona. The last category constitutes fewer than 15% of the total oocytes obtained.

Sperm preparation and oocyte insemination

A semen sample is obtained after a 3- to 5-day period of sexual abstinence immediately prior to the oocyte retrieval. The procedure of sperm preparation involves the removal of certain components of the ejaculate (i.e., seminal fluid, excess cellular debris, leukocytes, morphologically abnormal sperms, etc) along with the retention of the motile fraction of sperms. For most specimens, the motile portion of the sperms is separated via the process of centrifugation through a discontinuous density gradient system. The sperms are incubated for 60 minutes in an atmosphere of 5% carbon dioxide in air. Finally, the supernatant containing the motile fraction of sperm is removed. Sperm concentration and motility are determined. A final number of 200,000 motile sperms in a small volume of media with a layer of mineral oil on top is added to the oocytes.

Embryo culture

The inseminated oocytes are incubated in an atmosphere of 5% carbon dioxide in air with 98% humidity. Presence of two pronuclei and the extrusion of a second polar body are the criteria which ascertain fertilization, and should occur approximately 18 hours following insemination.

The fertilized embryos are transferred into growth media and placed in the incubator. No further evaluation is performed over the next 24 hours. A 4- to 8-cell stage, pre-embryo is observed approximately 36–48 hours after insemination.

Embryo transfer

The procedure of embryo transfer is performed within 72 hours after oocyte insemination, when the embryo has become approximately 8–16 cells in size. The transfer is usually performed transcervically under guidance of transabdominal ultrasound. The embryos should be loaded with 15–20 µL of culture media at the time of transfer. The catheter is advanced up to the fundus of the endometrial cavity, and then withdrawn slightly. The embryos are ejected into the miduterine cavity, approximately 1–2 cm away from the fundus. Subsequent to the embryo transfer, the patient must be on bed rest for 30–60 minutes. No more than two embryos must be transferred during any one cycle. Cryostorage of supernumerary embryos can be offered if there are more than two embryos.

Management of the luteal phase

Following 36–72 hours after oocyte retrieval, the endometrium must be supplemented with progesterone in order to maintain the luteal phase. Supplementation with exogenous progesterone is especially required because the superovulation and the follicular aspiration at the time of oocyte retrieval is likely to have induced an abnormal endocrine milieu. Several progesterone preparations are available for use; for example, natural progesterone in oil base for intramuscular injection; vaginal progesterone suppositories and gels and capsules of micronized progesterone to be used vaginally or sublingually. Normally, progesterone supplementation is continued for approximately 2 weeks. In case the pregnancy test result is positive, progesterone must be continued until the twelfth week of gestation.

Assisted Fertilization Techniques

Some techniques which help in facilitating fertilization include partial zona dissection (PZD), subzonal sperm injection (SUZI), intracytoplasmic sperm injection (ICSI) and assisted hatching (AH). Currently, only ICSI and AH are being used clinically. These procedures can be used on their own or as part of an IVF cycle for treatment of infertility.

Partial zona dissection (PZD)

PZD consists of creating a small opening at the zona pellucida level either mechanically or using low-pH solutions (tyrode) to digest a small portion of the zona. This enables the sperm to make contact with the oocyte membrane through the weak spot, thereby facilitating fertilization.

Subzonal sperm injection (SUZI)

The SUZI procedure consists of suspending the oocyte in a sucrose medium. By osmosis, the oocyte is dehydrated; therefore, the perivitelline space is enlarged. Next, 3–5 spermatozoa are injected into the perivitelline space using a microneedle. This procedure is supposed to be successful in individuals in whom IVF and PZD have not proved to be successful.

Intracytoplasmic sperm injection (ICSI)

PZD and SUZI are obsolete and have been replaced by the ICSI procedure. ICSI has revolutionized the treatment of severe male factor infertility because only a single live sperm is required, which is injected directly into the ovum. ICSI is commonly used in cases of male factor infertility such as obstructive azoospermia (due to congenital absence of the vas

deferens). ICSI nowadays is also commonly being used as part of an IVF cycle.

Procedure

The sperm can be obtained through masturbation, epididymal aspiration, testicular biopsy, or needle puncture of the testes. The sperm is paralyzed by stroking the distal portion of its tail.

The oocyte is stripped from the cumulus using a solution of hyaluronidase.

To inject the sperm, first the oocyte is stabilized with a micropipette, then the sperm is loaded, tail first, into a microneedle (figures 26.10A to E). The oocyte membrane is pierced with the microneedle and the oolemma is entered. The spermatozoon is released inside the oolemma, and the microinjected oocyte is kept in the incubator.

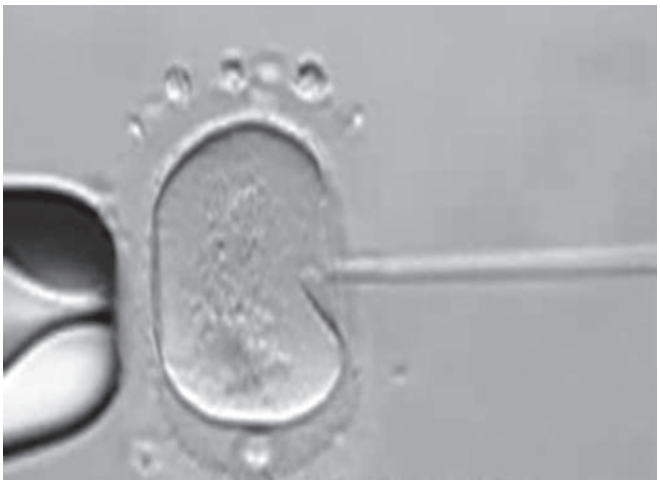


Fig. 26.10C: The microneedle pierces the oocyte membrane

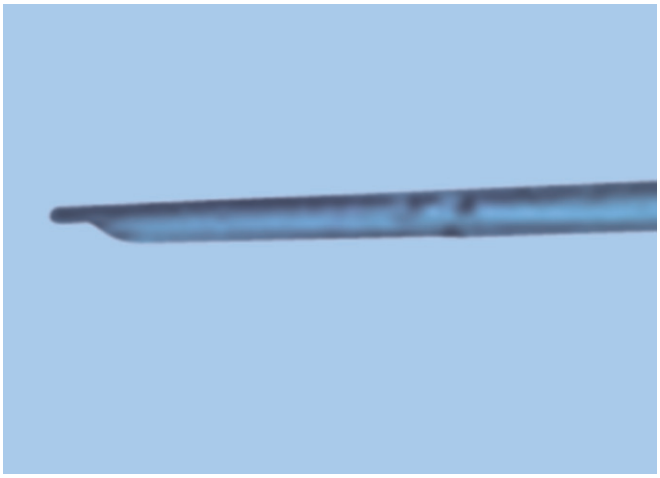


Fig. 26.10A: Microneedle is loaded with a sperm

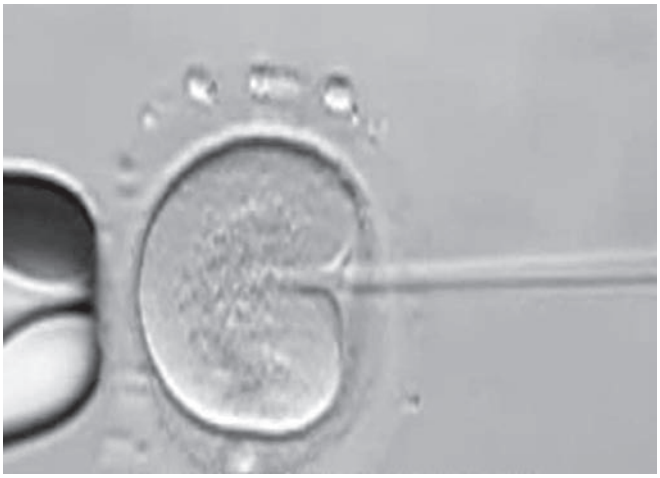


Fig. 26.10D: The microneedle is advanced deeper inside the cytoplasm

Fig. 26.10B: The microneedle approaches the oocyte

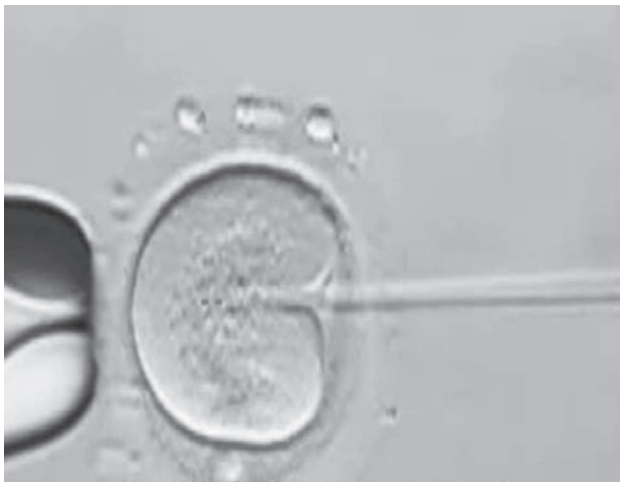


Fig. 26.10E: The spermatozoon is released inside the oocyte

Indications

Indications for intracytoplasmic sperm injection are as follows:

- Severe deficits in semen quality.
- Obstructive azoospermia.
- Non-obstructive azoospermia.
- Failure of previous in vitro fertilisation treatment cycles.

Where the indication for intracytoplasmic sperm injection is a severe deficit of semen quality or nonobstructive azoospermia, the man's karyotype should be established. Men who are undergoing karyotype testing should be offered genetic counseling regarding the genetic abnormalities that may be detected. Couples should be informed that intracytoplasmic sperm injection improves fertilization rates compared to in vitro fertilization alone, but once fertilization is achieved, the pregnancy rate is no better than with in vitro fertilization.

Assisted hatching (AH)

Embryo hatching is an obligatory step in the process of embryo implantation. It has been observed that some of the IVF embryos may have a rather thick zona pellucida. This thickened zona may represent an obstacle for the normal embryo hatching, thereby interfering with the implantation. In order to facilitate the hatching of normal embryos, the procedure of assisted hatching is sometimes used for the embryos which show a thick zona pellucida. The procedure is usually performed a couple of hours before the embryo transfer. AH can be performed mechanically, using laser beams to create a microrent, or by chemical digestion of the zona using tyrode solution (low pH). Both the procedures create a weak spot within the zona, facilitating the break of the zona and the hatching of the embryo. AH is recommended for patients undergoing IVF who are older than 38 years, patients with multiple ART failures and in all cryopreserved embryos.

IVF-Related Procedures

IVF-related procedures such as gamete intrafallopian transfer (GIFT) and zygote intrafallopian transfer (ZIFT) are sometimes used as alternatives to IVF. These would now be described in brief.

Gamete intrafallopian transfer (GIFT)

The procedure of GIFT comprises of stimulating the ovaries, monitoring follicular development, and oocyte aspiration similar to IVF. This procedure is different from IVF in the sense that in IVF, the embryo is transferred inside the endometrial cavity, while in case of GIFT, the embryo is transferred into the fallopian tube. Thus in order to qualify for this procedure, the patient must have at least one normal-appearing and patent fallopian tube.

Following the oocyte aspiration and classification of oocytes, a laparoscopy or a mini–laparotomy is performed. The oocytes, along with 150,000 sperms, are loaded into a special catheter in the laboratory under a microscope and then handed over to the surgeon in the operating room. Before the injection of the gametes into the fallopian tube, the fimbria must be gently picked up with an atraumatic grasping forceps. The ostium must be identified, following which the tip of the catheter is passed through the ostium and advanced up to the ampulla of the fallopian tube, where the gametes are eventually released. Fertilization therefore occurs inside the fallopian tube, unlike the procedure of IVF where fertilization occurs in the laboratory settings. Thus this procedure is more physiologic and mimics the normal procedure of conception more closely than IVF. Nevertheless, a major disadvantage associated with GIFT procedure is that it does not allow for visual confirmation of fertilization because it occurs inside the body. Furthermore, if pregnancy does not occur, there is no way to determine whether the cause of failure was lack of fertilization or lack of implantation. Also the procedure of GIFT requires a laparoscopy or mini–laparotomy, both of which can be performed under general anesthesia. Both these factors are likely to increase the total cost of the procedure.

Zygote intrafallopian transfer

The zygote intrafallopian transfer (ZIFT) procedure is a combination of IVF and GIFT. Fertilization occurs in the IVF laboratory. However, the pre-embryo is transferred into the fallopian tube via laparoscopy at the 2-pronuclei stage or 24 hours after oocyte retrieval.

Donor Insemination

Indications for donor insemination

The use of donor insemination is considered effective in managing fertility problems associated with the following conditions:

- Obstructive azoospermia.
- Non-obstructive azoospermia.
- Infectious disease in the male partner (such as HIV).
- Severe rhesus isoimmunization.
- Severe deficits in semen quality in couples who do not wish to undergo intracytoplasmic sperm injection.
- Cases where there is a high risk of transmitting a genetic disorder to the offspring.

Before starting treatment by donor insemination, it is important to confirm that the woman is ovulating. Women with a history that is suggestive of tubal damage should be offered tubal assessment before treatment. Couples using donor sperms should be offered intrauterine insemination in

preference to intracervical insemination because it improves pregnancy rates.

Women who are ovulating regularly should be offered a minimum of six cycles of donor insemination without ovarian stimulation to reduce the risk of multiple pregnancy and its consequences.

Oocyte Donation

Indications for oocyte donation

The use of donor oocytes is considered effective in managing fertility problems associated with the following conditions:

- Premature ovarian failure.
- Gonadal dysgenesis including turner syndrome.
- Bilateral oophorectomy.
- Ovarian failure following chemotherapy or radiotherapy.
- Certain cases of in vitro fertilisation treatment failure.
- There is a high risk of transmitting a genetic disorder to the offspring.

All people considering participation in an egg-sharing scheme should be counseled about its particular implications.

Important Questions and Answers

Q.1. What minimum investigations must be offered in the above mentioned case study?

Ans. Since the causes of infertility can be multifactorial, a systematic approach typically is used and involves testing for male factor, ovulatory factor, uterotubal factor and peritoneal factor. Since the evaluation for male factor infertility has already been done in form of semen analysis, the next step should be towards evaluation of ovulatory factors. These must include tests such as serum progesterone level, serum basal follicle-stimulating hormone level, and clomiphene citrate challenge test.

Q.2. What advice must be given in this case?

Ans. Couples concerned about their fertility should be informed that about 84% of couples in the general population will conceive within 1 year if they do not use contraception and have regular sexual intercourse. Of those who do not conceive in the first year, about half will do so in the second year (cumulative pregnancy rate of 92%). Regular sexual intercourse after every 2 to 3 days is likely to maximize the overall chances of natural conception, as spermatozoa survive in the female reproductive tract for up to 7 days after insemination. In this case, the sexual history revealed that the couple had reasonable knowledge regarding the female reproductive cycle and had been having regular unprotected sexual intercourse. The main abnormality detected on the general physical examination was an increased BMI. Also the menstrual cycles were irregular. Both these things raised suspicion towards the likely ovulatory dysfunction in this patient. Keeping in mind the diagnosis of anovulatory cycles, the woman was advised the following investigations: Pelvic ultrasound examination, serum progesterone levels on day 21, serum LH: FSH ratio, fasting insulin levels and serum testosterone levels. In view of the raised BMI, the woman was advised life style changes in order to reduce her weight. She was advised to indulge in brisk walking for 30 minutes every day. She was also referred to the nutrition specialist to help her devise a proper dietary plan in order to bring her weight under control.

Q.3. On the basis of the results of various investigations, a diagnosis of PCOS was established in this case. What should be next step of management in this case?

Ans. Since the ultrasound examination revealed findings suggestive of polycystic ovarian disease, she was started on clomiphene citrate in the dosage of 50 mg per day for first five days of the menstrual cycle. However even after a course of 6 months, there was no ovulation. Keeping in view the increased BMI and insulin resistance, she was also simultaneously administered metformin, 500 mg OD, which was soon increased to 500 mg BID. Ultrasound examination for follicular monitoring in this case revealed evidence of ovulation.

Q.4. Define the term fertility. How is it different from the terms fecundability and fecundity?

Ans. Fertility is defined as the capacity to reproduce or the state of being fertile. Fecundability is the probability of achieving a pregnancy each month, which is approximately 20% to 25%. Taking an average fecundability of 20% per cycle, the cumulative pregnancy rate over 3 months of exposure is 57%, over 6 months is 72%, over 1 year is 85% and over 2 years is 93%. On the other hand, fecundity can be defined as the ability to achieve a live birth within 1 menstrual cycle. The factors which are likely to influence fecundablity include the woman's age at time of planning pregnancy and the frequency of sexual intercourse.With regular unprotected sexual intercourse, 94% of fertile women aged 35 years or younger are likely to conceive after 3 years of trying.

Q.5. How can obesity produce infertility in both men and women?

Ans. Obesity can lead to the aromatization of testosterone in fatty tissue to estradiol, leaving less testosterone available for maintenance and virilization functions in males. This may result in a reduction in sperm production in males because the testes are not able to receive an adequate hormonal signal to produce sperms.

In women, increased BMI and truncal obesity has been found to be associated with a spectrum of disorders related to menstrual irregularities ranging from oligomenorrhea, to anovulation and polycystic ovarian syndrome (PCOS). Hyperinsulinemia and increased BMI, both have also been

found to be associated with polycystic ovarian syndrome (PCOS) and reduced fertility. It has been shown that women with PCOS may be divided into two subgroups: Those with obesity, insulin resistance, hyperinsulinemia, elevated LH levels, hyperandrogenism and infertility and those with normal body weight, normal/minimally elevated LH levels, and normoinsulinemia.

Q.6. What are the indications for cryopreservation of embryo?

Ans. The cryopreservation of embryos is usually done prior to commencing chemotherapy or radiotherapy, both of which are likely to affect the fertility of an individual.

Bibliography

1. Adamson GD. Treatment of uterine fibroids: current findings with gonadotropin-releasing hormone agonists. Am J Obstet Gynecol. 1992;166(2):746-51.
2. American Society for Reproductive Medicine (ASRM). (2004). Frequently asked questions about infertility. [online]. Available from http://www. asrm.org/Patients/faqs.html#Q2 [Accessed September 2009]
3. American Urological Association (AUA) & American Society for Reproductive Medicine (ASRM). (2001). Report on optimal evaluation of the infertile male. [online]. Available from http://www.auanet.org/timssnet/products/guidelines/main_reports/optimalevaluation.pdf [Accessed September 2009].
4. Brown JB. Gonadotropins. In: Insler V, Lunenfeld B, eds. Infertility: Male and Female. London, United Kingdom: Churchill Livingstone, 1986.
5. Clark JH, Markaverich BM. The agonistic-antagonistic properties of clomiphene: a review. Pharmacol Ther. 1981;15(3): 467-519.
6. Confino E, Friberg J, Gleicher N. Preliminary experience with transcervical balloon tuboplasty. Am J Obstet Gynecol. 1988;159(2):370-5.
7. Dodson WC, Haney AF. Controlled ovarian hyperstimulation and intrauterine insemination for treatment of infertility. Fertil Steril. 1991;55(3):457-67.
8. Garcia J, Jones GS, Wentz AC. The use of clomiphene citrate. Fertil Steril. 1977;28(7):707-17.
9. Giner J, Merino G, Luna J, Aznar R. Evaluation of the Sims-Huhner postcoital test in fertile couples. Fertil Steril. 1974; 25(2):145-8.
10. Golan A, Ron-el R, Herman A, Soffer Y, Weinraub Z, Caspi E. Ovarian hyperstimulation syndrome: an update review. Obstet Gynecol Surv. 1989;44(6): 430-40.
11. Goldzieher JW. Polycystic ovarian disease. Fertil Steril. 1981; 35(4):371-94.
12. Gomel V, Yarali H. Infertility surgery: microsurgery. Curr Opin Obstet Gynecol. 1992;4(3):390-9.
13. Goss DA. Current status of artificial insemination with donor semen. Am J Obstet Gynecol. 1975;122(2): 246-52.
14. Guidelines for gamete donation: 1993. The American Fertility Society. Fertil Steril. 1993;59(2 Suppl 1): 1S-9S.
15. Hunt RB, Siegler AM. Hysterosalpingography: Techniques and Interpretations. St. Louis, Mo: Mosby-Year Book 1990.
16. Jones GE. Some newer aspects of the management of infertility. JAMA. 1949;141:1123.
17. Jones GS. The clinical evaluation of ovulation and the luteal phase. J Reprod Med. 1977;18(3):139-42.
18. Jones HWJr, Rock JA. Reparative and constructive surgery of the female generative tract. Baltimore, Md: Lippincott Williams & Wilkins; 1983.
19. Mettler L, Giesel H, Semm K. Treatment of female infertility due to tubal obstruction by operative laparoscopy. Fertil Steril. 1979;32(4):384-8.
20. Mueller BA, Daling JR. Epidemiology of infertility. In: Soules MR, ed. Controversies in Reproductive Endocrinology and Infertility. New York, NY: Elsevier Science; 1989.
21. Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. N Engl J Med. 1998;338(26):1876-80.
22. Noyes RW, Hertig AT, Rock J. Dating the endometrial biopsy. Fertil Steril. 1950;1:3.
23. Olive DL. Conservative surgery. In: Schenken RS, ed. Endometriosis: Contemporary Concepts in Clinical Management. Philadelphia, Pa: Lippincott Williams & Wilkins 1989;213-49.
24. Palermo G, Joris H, Devroey P, Van Steirteghem AC. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. Lancet. 1992; 340(8810):17-8.
25. Phipps WR, Cramer DW, Schiff I, et al. The association between smoking and female infertility as influenced by cause of the infertility. Fertil Steril. 1987;48(3):377-82.
26. Revised guidelines for the use of semen donor insemination. The American Fertility Society. Fertil Steril. 1991;56(3):396.
27. Rowe PJ, Comhaire FH, Hargreave TB and Mahmoud AMA. WHO manual for the standardized investigation, diagnosis and management of the infertile male. Cambridge, England: Cambridge University Press, 2000.
28. Schenker JG, Ezra Y. Complications of assisted reproductive techniques. Fertil Steril, 1994;61(3): 411-22.
29. Shirai E, Iizuka R, Notake Y. Clomiphene citrate and its effects upon ovulation and estrogen. Fertil Steril. 1972; 23(5):331-8.
30. Southam AL, Janovski NA. Massive ovarian hyperstimulation with clomiphene citrate, JAMA 1962; 181:443.
31. Speroff L and Fritz M. Clinical Gynecologic Endocrinology and Infertility. 7. Lippincott Williams & Wilkins; 2004.
32. Strathy JH, Molgaard CA, Coulam CB, Melton LJ. Endometriosis and infertility: a laparoscopic study of endometriosis among fertile and infertile women. Fertil Steril. 1982; 38(6):667-72.
33. Weström L. Effect of acute pelvic inflammatory disease on fertility. Am J Obstet Gynecol. 1975;121(5): 707-13.
34. Whelan JG 3rd, Vlahos NF. The ovarian hyperstimulation syndrome. Fertil Steril. 2000;73(5):883-96.
35. Winston RM. Reversal of tubal sterilization. Clin Obstet Gynecol. 1980;23(4):1261-8.
36. World Health Organization. WHO Laboratory Manual for the Examination of Human Semen and Sperm Cervical Mucus Interaction. 4th ed. Cambridge, United Kingdom: Cambridge Unviersity Press; 1999.
37. Zacur HA. Ovulation induction with gonadotropin-releasing hormone. Fertil Steril. 1985;44(4):435-48.

Chapter

27

Amenorrhea

Case Study

A 15-years-old girl presented to the gynecology OPD with the complaint of absence of periods. The menstrual cycles had never begun, even though she had experienced normal breast and secondary sexual development at the age of about 13 years. Physical examination revealed an absent vaginal canal. A small depression was present in place of the vaginal introitus. An ultrasound examination showed absent uterus and presence of normal ovaries.

Introduction

Amenorrhea implies absence of menstrual periods. Amenorrhea can be of two types: Primary and secondary. Primary amenorrhea is absence of menstrual cycles in a woman who had never experienced menstrual cycles before. Secondary amenorrhea on the other hand is defined as the cessation of menstruation in a woman who had been previously experiencing menstrual bleeding. This cessation must last for at least 6 months or for at least 3 of the previous 3-cycle intervals. Secondary amenorrhea is more common than primary amenorrhea. Primary amenorrhea can be defined as follows:

- Absence of menses by age of 14 years with the absence of growth or development of secondary sexual characteristics.
- Or as absence of menses by the age of 16 years with normal development of secondary sexual characteristics.

Pathophysiology of Menstrual Bleeding

As previously described in chapter 16, circulating estradiol levels in the body stimulates the growth of uterine endometrium. Progesterone, which is produced by the corpus luteum, is formed after ovulation. It transforms proliferating endometrium into a secretory one. If pregnancy does not occur, this secretory endometrium breaks down and sheds in the form of menstrual bleeding. A complex interaction between the hypothalamic-pituitary-ovarian axis and the outflow tract (uterus, cervix and vagina) is required for the normal menstrual bleeding to take place. For menstrual cycles to occur normally, the following are required:

- An intact outflow tract: An intact outflow tract which connects the bleeding occurring in the internal genitalia with the outside is essential for normal menstrual flow. This requires a patent outflow tract and continuity the vaginal orifice, vaginal canal and endocervix with the uterine cavity.
- Normal endometrial development: Normal development of endometrial lining which responds cyclically to stimulation by estrogen and progesterone.
- Normal functioning ovaries: Proper functioning of the ovaries is required for secretion and synthesis of estrogens and progesterone. The entire spectrum of follicle development, ovulation and formation of corpus luteum occurs here.
- Normal functioning pituitary glands: The stimulus for the production of ovarian hormones and ovarian follicles is provided by the hormones secreted from anterior pituitary including hormones such as FSH and LH.
- Normal functioning hypothalamus: The secretion of these hormones is dependent on secretion of GnRH by the hypothalamus.

Any disruption of the interaction in above mentioned compartments can result in amenorrhea. The causes of primary amenorrhea are therefore related to defects in either of the four compartments as described below and shown in figure 27.1:

- Compartment I: Outflow tract and the uterus.
- Compartment II: Defect in ovulation.
- Compartment III: Defect at the level of pituitary gland.
- Compartment IV: Defect at the level of hypothalamus and central nervous system.

History

A good history can reveal the etiologic diagnosis in up to 85% of cases of amenorrhea. Physicians should take a comprehensive patient history including the following points:

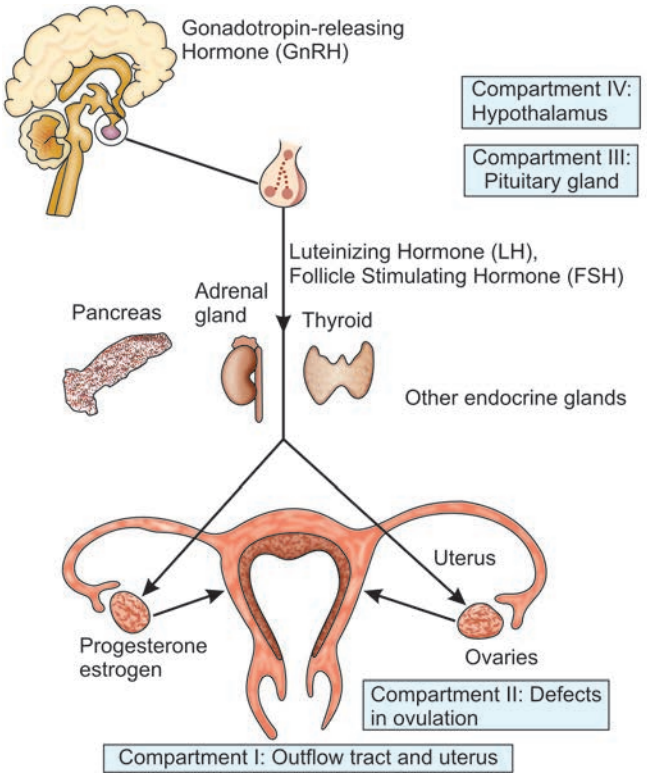


Fig. 27.1: Causes of primary amenorrhea related to defects in either of four compartments

- History of exercise, excessive weight loss, current or previous chronic illness and illicit drug use could be suggestive of hypothalamic amenorrhea. History of psychosocial stressors (recent emotional upsets and psychological dysfunction); and extreme dieting (anorexia or bulimia nervosa) can also be the cause for amenorrhea.
- History of irradiation or chemotherapy to the central nervous system could be another cause for hypothalamic amenorrhea.
- History of previous pelvic/abdominal radiation could result in premature ovarian failure. Presence of vasomotor symptoms such as hot flashes, dryness of vagina etc could be suggestive of premature ovarian failure.
- History of galactorrhea, headache and visual disturbances could be related to the presence of pituitary tumors.
- History of infertility needs to be specifically asked because in many cases infertility could be related to the history of amenorrhea, which the woman may specifically tend to hide.
- Symptoms suggestive of thyroid dysfunction.
- Recent change in body weight, extreme dieting and symptoms suggestive of anorexia nervosa.

Family History

- Pubic hair pattern: Androgen insensitivity syndrome, which shows autosomal recessive inheritance, is associated with breast development but no pubic or axillary hair development.
- Age of menarche and menopause and menstrual history shows similarity among various family members (e.g. mother and sisters).
- Constitutional delay of growth and puberty shows a hereditary pattern.

Menstrual History

It is important to ask the patient if she had been experiencing menstrual cycles previously in order to determine whether amenorrhea is primary or secondary. In case of secondary amenorrhea, the woman needs to be asked if there is any possibility of pregnancy, e.g., is the urine pregnancy test positive?

Previous Obstetric History

If the woman has previously conceived, her amenorrhea is secondary in nature. It is important to take the history regarding the use of oral contraceptive pills in these cases. Prolonged use of oral contraceptive pills can result in post-pill amenorrhea.

Treatment History

History of intake of drugs such as progestogens, combined oral contraceptive and chemotherapy drugs needs to be elicited. Use of these drugs can sometimes result in amenorrhea.

General Physical Examination

General physical examination involves the following steps:

- Assessment of the patient's nutritional status and body mass index (BMI): Increased body mass index could be associated with polycystic ovarian disease.
- Anthropomorphic measurements and growth chart: These measurements may detect abnormalities such as constitutional delay of growth and puberty.
- Signs of androgen excess such as hirsutism or acne could be associated with polycystic ovary syndrome.
- Signs of virilization, e.g. deep voice, clitoromegaly, etc in addition to hirsutism, and acne could be related to the presence of androgen-secreting tumors.
- Clitoral measurement: Measuring the clitoris is an effective method for determining the degree of androgen effect. The clitoral index can be determined by measuring the glans of clitoris in the anteroposterior and transverse

Table 27.1: Tanner stage of development of secondary sexual characteristics

Breast	
Stage 1	Elevation of papilla
Stage 2	Elevation of breast and papilla as a small mound, increased aereolar diameter (median age: 9.8 years)
Stage 3	Further enlargement without the separation of breast and areola (median age: 11.2 years)
Stage 4	Secondary mound of areola and papilla above the breast (median age: 12.1 years)
Stage 5	Recession of areola to the contour of breast (median age: 14.6 years)
Pubic hair	
Stage 1	No pubic hair, prepubertal
Stage 2	Sparse, long pigmented hair mainly along labia majora (median age 10.5 years)
Stage 3	Dark, coarse curled hair, sparsely spread over the mons (median age 11.4 years)
Stage 4	Adult-type, abundant hair, but limited to the mons (median age 12.0 years).
Stage 5	Adult type spread in quantity and distribution (median age 13.6 years) i.e., spread occurs to the medial aspect of thighs.

diameters. A clitoral index greater than 35 mm^2 is an evidence of increased androgen effect. A clitoral index greater than 100 mm^2 is an evidence of virilization.

- Dysmorphic features (e.g., webbed neck, short stature, widely spaced nipples) could be suggestive of Turner's syndrome.
- Symptoms suggestive of Cushing' disease such as striae, buffalo hump, central obesity, easy bruising, hypertension or proximal muscle weakness.
- *Thyroid examination:* Thyroid examination is especially important to rule out hypothyroidism or hyperthyroidism. Thyroid diseases serve as a cause of amenorrhea and menstrual irregularities.
- *Breast examination:* Breast examination is important to check for galactorrhea. If galactorrhea is present, it is important to evaluate whether it is spontaneous or present only after careful expression by the examiner; whether it is unilateral or bilateral and persistent or intermittent. Breast secretions due to hormonal imbalance come from multiple duct openings in comparison to pathological discharge which comes from a single duct.
- *Fundoscopy and assessment of visual fields:* This must be done if there is suspicion of pituitary tumor.
- *Pubertal development:* A thorough physical examination must be conducted in patients with amenorrhea in order to assess normal female pubertal development. Tanner stage of development of secondary sexual characteristics has been described in table 27.1 and figures 27.2A and B.

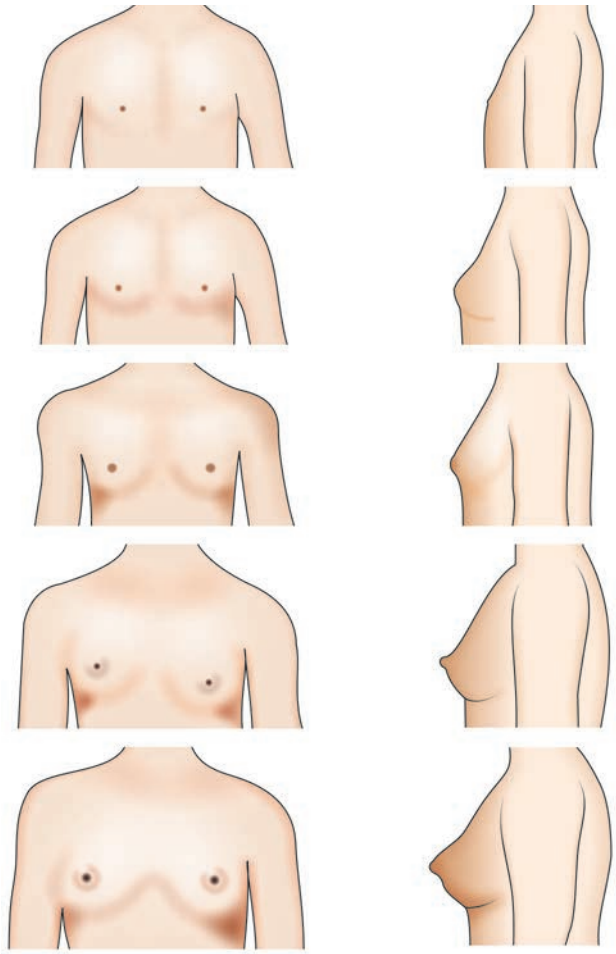


Fig. 27.2A: Tanner stages of breast development

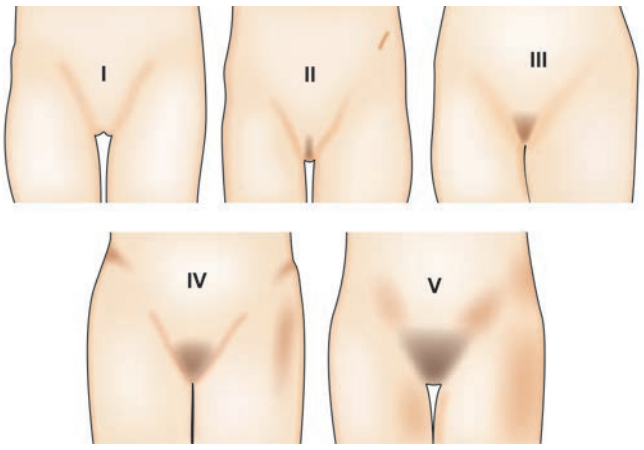


Fig. 27.2B: Tanner stages of pubic hair

Specific Systemic Examination

Pelvic Examination

Per speculum examination and inspection can help in detection of outflow tract abnormalities such as transverse vaginal septum; imperforate hymen, etc. The appearance of external genitalia and the distribution of pubic hair pattern may provide a clue regarding the presence of relevant pathology, for example the typical absence of pubic hair pattern in patients with androgen insensitivity syndrome. The Tanner stage of development of pubic hair must be established on inspection of external genitalia.

Rudimentary or absent uterus can be detected on bimanual examination.

Differential Diagnosis

The various causes of amenorrhea depending upon the compartment involved are described below:

Compartment I

Müllerian agenesis (Mayer-Rokitansky-Küster Hauser Syndrome)

This may be the probable diagnosis in an individual with primary amenorrhea and no apparent vagina. There is usually an absence or hypoplasia of the internal vagina and absence of fallopian tubes and uterus. The syndrome occurs due to defect in fusion of the müllerian ducts resulting in absence of proximal one-third of vagina with or without the uterus (figures 27.3A and B). Since the ovaries are not müllerian

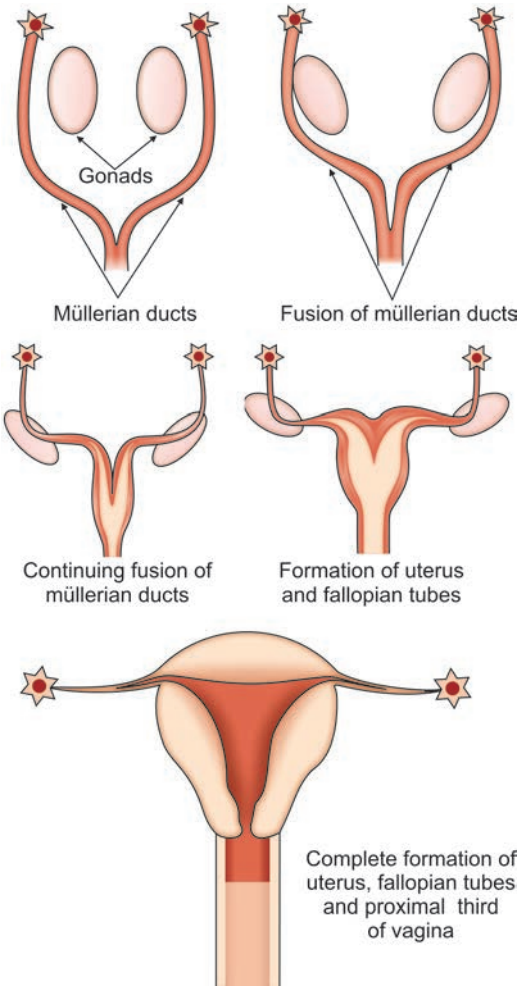


Fig. 27.3A: The sequence of embryological development of female gonads

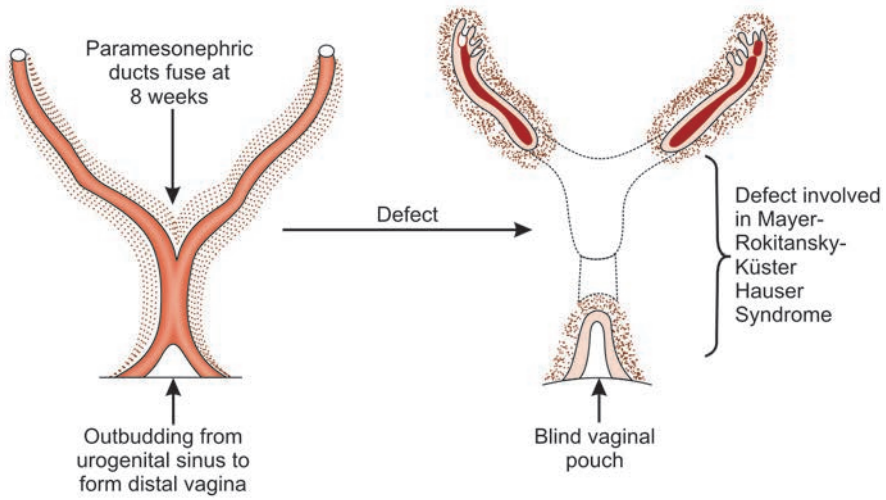


Fig. 27.3B: The defect involved in Mayer-Rokitansky-Küster Hauser syndrome

structures, they are normal. The cause of this syndrome is unknown and is probably related to the mutations in the gene for anti-müllerian hormones or the gene for anti-müllerian hormone receptor. Other anomalies including the renal tract anomalies such as ectopic kidney, renal agenesis, horse shoe kidney and abnormal collecting ducts are frequently present. Extirpation of the müllerian remnants, if any present, is not required unless they are causing some problem such as fibroid growth, hematometra, endometriosis, etc. Treatment of the condition usually involves progressive dilatation using Frank's dilators. Initially, the dilatation is begun in posterior direction and then after two weeks, it is changed to upward direction in the line of vaginal axis. This must be performed daily for 20 minutes to the point of modest discomfort. By utilizing increasingly larger sized dilators, a functional vagina can be created within a period of several months. Operative treatment is used in the patients in whom the Frank's method is unacceptable or fails. It is important for the gynecologist to provide adequate reassurance and support in these cases. Adequate counseling helps in avoiding problems with altered body image, which are likely to develop in these cases. Creating an artificial vagina either through the use of Frank's dilators or surgical procedure (McIndoe's vaginoplasty) at the time the patient plans to get married, helps in ensuring that she and her partner would be able to obtain adequate sexual enjoyment following their marriage. Having regular sexual intercourse helps in maintaining the patency of newly created artificial vaginal orifice. Though the patient remains infertile, she can lead an almost normal life. Genetic offsprings can be achieved by collecting oocytes from genetic mother, fertilizing them with sperms obtained from genetic father and their placement in a surrogate carrier.

Androgen insensitivity syndrome

Androgen insensitivity syndrome is another condition which is commonly associated with a blind vaginal canal and absent uterus. Androgen insensitivity syndrome was formerly known as testicular feminization syndrome. The patients with this syndrome are male pseudohermaphrodites. This implies that the patient is genetically a male, i.e. has a male karyotype (46XY). Since the karyotype is male, the patient has male gonads or testes. Pseudohermaphrodite implies that the genitalia are opposite of the gonads. The individual is phenotypically a female with absent or scant pubic and axillary hair. In these cases, the receptors are insensitive to androgens, due to which there is failure of normal masculinization of the external genitalia in individuals who are genetically male. As a result, the patient is phenotypically a female (figure 27.4). The pubic hair and axillary hair fail to develop as testosterone is unable to exert its action. The testes may remain undescended. Affected individuals have normal testes with normal production of testosterone and normal conversion to dihydrotestosterone (DHT), unlike 5-alpha reductase deficiency, which is characterized by reduced levels of DHT. The transmission of this disease is via X-linked recessive inheritance. The gene responsible for androgen intracellular receptor is defective. A karyotype analysis is required to reach the proper diagnosis in these cases. The female child may present

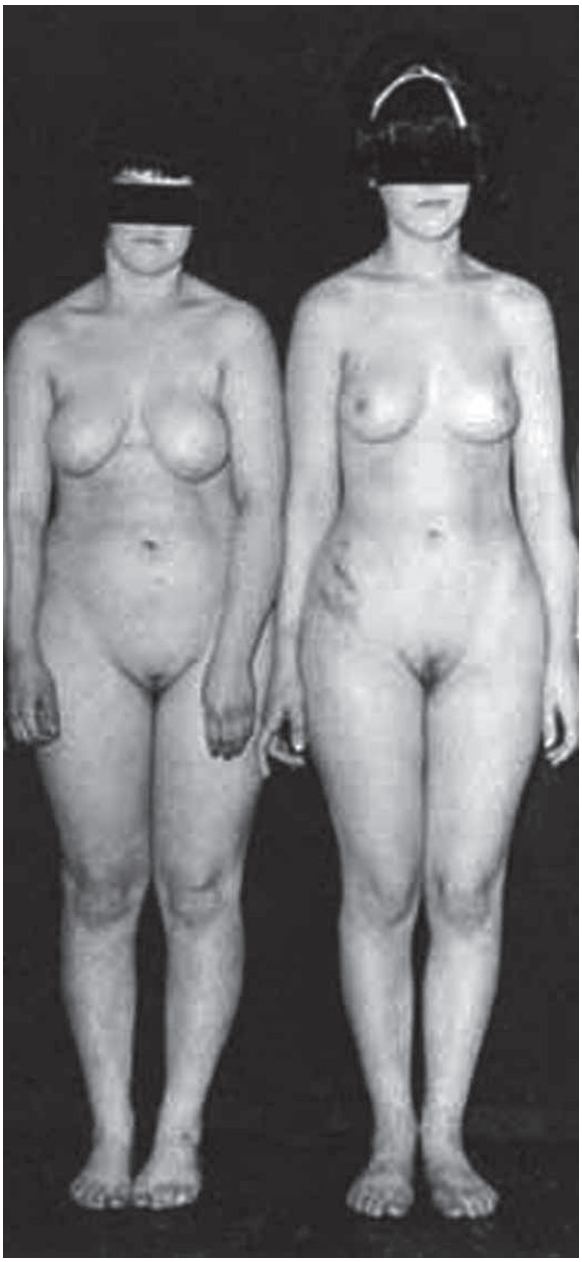


Fig. 27.4: Two individuals both having well developed breasts with juvenile nipples and absent pubic hair and blind ending vagina. The karyotype analysis revealed male sex (46 XY chromosomes). The final diagnosis was of androgen insensitivity syndrome

with inguinal hernia because the testes are frequently partially descended.

While the growth and development are normal, there may be an eunuchoidal tendency (long arms, big hands and big feet). The breasts are large as testosterone gets converted into estrogens which stimulate their growth. However, the breasts are abnormal as the glandular tissue is not abundant, nipples are small and the areolae are pale. Female internal genitalia (uterus and fallopian tubes) are either rudimentary or absent. In such a patient, the testes may be intraabdominal or present in form of hernia. However even if present, the testes are immature and do not show any spermatogenesis. Due to high incidence of malignancy in the gonads with Y chromosomes, they must be removed at the age of 16–18 years once full development has been attained after puberty. The plasma levels of testosterone are within normal to high male range. As a result of failure of action of testosterone, the critical steps in sexual differentiation which require testosterone fail to take place.

5-alpha reductase deficiency (5-ARD)

This syndrome with autosomal recessive inheritance is characterized by inability to convert testosterone to the more physiologically active dihydrotestosterone (DHT). Since DHT is required for the normal masculinization of the external genitalia in utero, genetic males with 5-ARD are born with ambiguous genitalia (i.e., male pseudohermaphroditism). The condition affects only genetic males (having a Y chromosome) because dihydrotestosterone has no known role in female development. The clinical abnormalities of the disease range from individuals with normal male genital anatomy to underdeveloped male individuals with hypospadias to those with predominantly female external genitalia, most often with mild clitoromegaly. Since these patients have primary female characteristics, they are often raised as girls. At the time of puberty, these individuals often experience amenorrhea and virilization.

Asherman's syndrome

This is an important cause of secondary amenorrhea occurring as a result of overzealous postpartum curettage which can result in the destruction of endometrial lining due to the formation of intrauterine scars. These adhesions can completely obliterate the endometrial cavity, internal cervical os and cervical canal. The condition can also occur following uterine surgery, including cesarean section, myomectomy or metroplasty. Asherman's syndrome can also occur following uterine surgery such as cesarean section, myomectomy or metroplasty. Besides amenorrhea, patients with this syndrome can present with symptoms such as miscarriage, dysmenorrhea or hypomenorrhea. The diagnosis and treatment of this condition is by hysteroscopic resection. Following the resection of adhesions, an intrauterine device is inserted inside the uterine cavity in order to prevent the adherence of the raw uterine walls. The uterine cavity can also be distended with help of a pediatric Foley's catheter, distended with about 3 ml of fluid and is removed after seven days.

Imperforate hymen

Imperforate hymen occurs as a result of abnormal or incomplete embryologic development. This condition commonly causes amenorrhea which is usually associated with cyclical abdominal pain, which tends to worsen over time. If a hematocolpos is present, bluish discoloration is visible behind the translucent membrane (figures 27.5A and B).

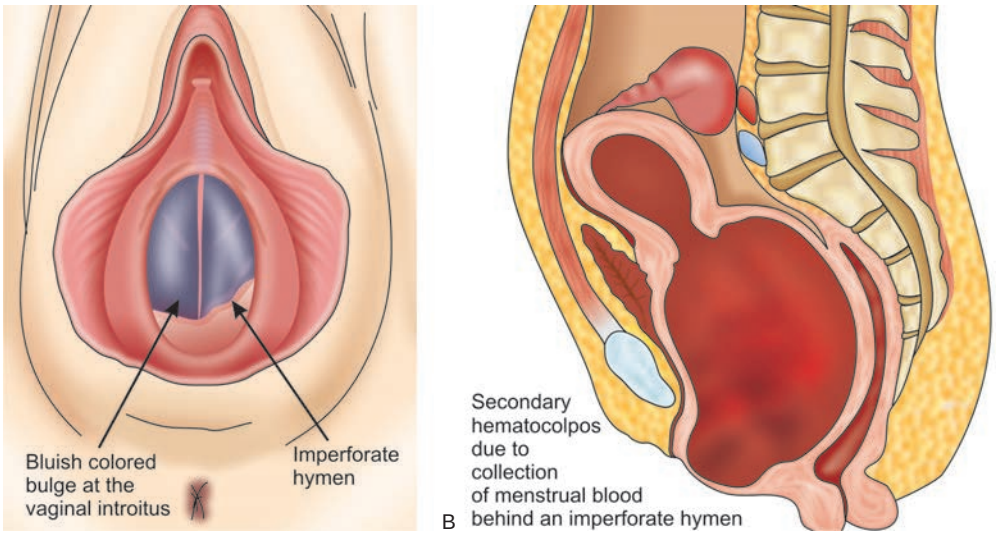


Fig. 27.5A and B: (A) Imperforate hymen (B) Accumulation of blood in the uterine cavity as a result of imperforate hymen

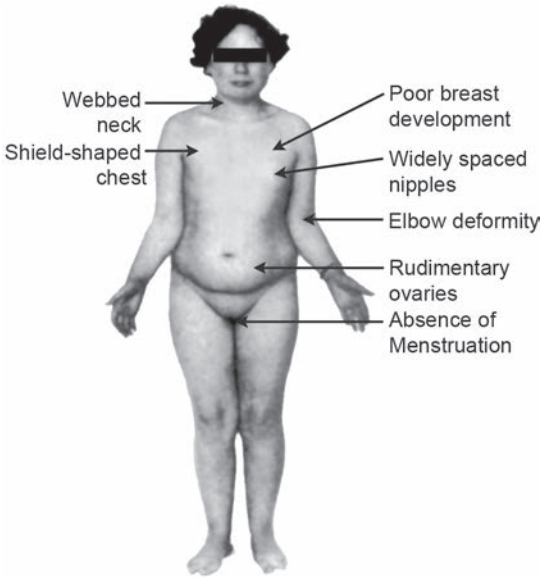


Fig. 27.6: An 18 years old with primary amenorrhea who was diagnosed to be suffereing from Turner's syndrome

Compartment II Disorders (of the Ovary)

Gonadal dysgenesis (Turner's syndrome)

This is associated with absence of one X chromosome and is characterized by short stature, webbed neck, shield chest, increased carrying angle at the elbow and hypergonadotropic hypoestrogenic amenorrhea (figure 27.6). Due to presence of streak gonads which lack ovarian follicles, no gonadal sex hormones are produced at the time of puberty and the patients present with primary amenorrhea. Karyotype analysis must be done in all cases with elevated gonadotropin levels.

Premature ovarian failure

In these cases, the failure of ovarian function occurs prematurely before the age of 40 years. Ovarian failure could also occur as a result of radiation therapy to the pelvis or chemotherapy. There is no risk of premature ovarian failure if the radiation field excludes the pelvis. Chemotherapy drugs, typically alkylating agents (cyclophosphamide, methotrexate and fluorouracil) are very toxic to the gonads.

Polycystic ovarian syndrome

Polycystic ovarian syndrome may be associated with amenorrhea in about 15–20% cases and has been described in details in chapter 26.

Post-pill amenorrhea

This is defined as absence of menstruation for 6 months following cessation of the combined oral contraceptive pills and probably results from transient inhibition of gonadotropin-releasing hormone.

Compartment III (Disorders of Anterior Pituitary)

Hyperprolactinemia

Adenomas (both microadenomas and macroadenomas) are the most common cause of anterior pituitary dysfunction. Prolactin secreting pituitary tumors may account for nearly 50% cases of pituitary adenomas. The increased dopamine concentration present in hyperprolactinemic women with pituitary tumors is likely to reduce pulsatile LH secretion and produce acyclic gonadotropin secretion, which most probably results in menstrual irregularities. Patients with pituitary adenomas having markedly elevated prolactin levels (especially those greater than 100 ng per ml), often experience symptoms such as galactorrhea, headaches, or visual disturbances, etc. Imaging with MRI must be done in these patients to rule out pituitary adenomas. The treatment of these patients comprises of the use of the drug bromocriptine (dopamine agonist), which is available in form of 2.5 mg tablets. A total 5–15 mg of oral dose of bromocriptine may be required. Depot bromocriptine preparations are also available which must be administered in the monthly dosage of 50–75 mg intramuscular injection. Use of bromocriptine can be associated with numerous side effects such as nausea, headache, fainting due to orthostatic hypotension, dizziness, fatigue, etc. Cabergoline is another ergot-derived dopamine agonist, which is usually administered in the dosage of 0.5 to 30.0 mg once weekly. It is associated with lower rates of side effects in comparison to those associated with bromocriptine.

Besides pituitary tumors, other important cause of hyperprolactinemia includes use of medications such as oral contraceptive pills, antipsychotics, antidepressants, antihypertensives, opiates, etc. However in these cases, prolactin levels are raised to levels of less than 100 ng per mL.

Compartment IV (Defects at the Level of Hypothalamus)

Hypothalamic amenorrhea could be associated with anorexia nervosa. These patients with anorexia nervosa are characterized by weight loss of 25% or weight of 15% below the normal for the particular age and height. Other important features of this disease include denial of the problem by the patient, distorted body image, unusual hoarding or handling of food and amenorrhea. The patient may indulge in self-induced vomiting in order to lose weight. There are no other underlying medical or psychiatric disorders.

Summary

The likely causes for primary amenorrhea are described in table 27.2 whereas the causes for secondary amenorrhea are described in table 27.3.

Management

Primary Amenorrhea

The first step of management in case of primary amenorrhea is to determine whether the patient has developed secondary sexual characteristics or not. In these patients, the presence or absence of secondary sexual development directs further course of evaluation. Evaluation of the patient with primary amenorrhea is described in flow chart 27.1.

Table 27.2: Differential diagnosis in a patient with primary amenorrhea

Presence of secondary sexual characteristics
Genito-urinary malformation, e.g. imperforate hymen, transverse vaginal septum, absent vagina with or without a functioning uterus
Müllerian agenesis (Mayer-Rokitansky-Küster Hauser Syndrome)
Androgen insensitivity: XY female or testicular feminization
Absence of secondary sexual characteristics
Resistant ovary syndrome
Hypothalamic dysfunction, e.g. chronic illness, anorexia, weight loss, stress
Gonadotropin deficiency, e.g. Kallman's syndrome
Tumors of the hypothalamus or pituitary
Hypopituitarism
Hyperprolactinemia
Gonadal failure, e.g., ovarian dysgenesis/agenesis, premature ovarian failure
Hypothyroidism

Secondary sexual characteristics have developed

If a patient with amenorrhea has experienced normal breast development, but minimal or no pubic hair, the usual diagnosis is androgen insensitivity syndrome (i.e. patient is phenotypically female, but genetically male with undescended testes). In case of genital tract abnormalities, a karyotype analysis is required in order to determine proper treatment (flow chart 27.2). If testes are present, they should be removed because of the high risk of malignant transformation after puberty.

If a patient has normal secondary sexual characteristics, including pubic hair, the clinician should perform MRI or ultrasonography to determine if a uterus is present. If the ultrasound examination shows presence of a normal uterus, outflow tract obstruction should be considered. An imperforate hymen or a transverse vaginal septum can cause congenital outflow tract obstruction. Imperforate hymen typically results in cyclic abdominal pain due to accumulation of the blood in the uterus and vagina. If the outflow tract is patent, the physician should continue an evaluation similar to that for secondary amenorrhea. If the uterus is absent or abnormal, a karyotype analysis should be performed to determine if the patient is genetically female. If the patient is genetically a female (46XX), the cause of amenorrhea could be müllerian agenesis, where there is congenital absence of vagina and abnormal (usually rudimentary) uterine development. If the karyotype is that of a genetic male (46XY), the patient is probably suffering from androgen insensitivity syndrome.

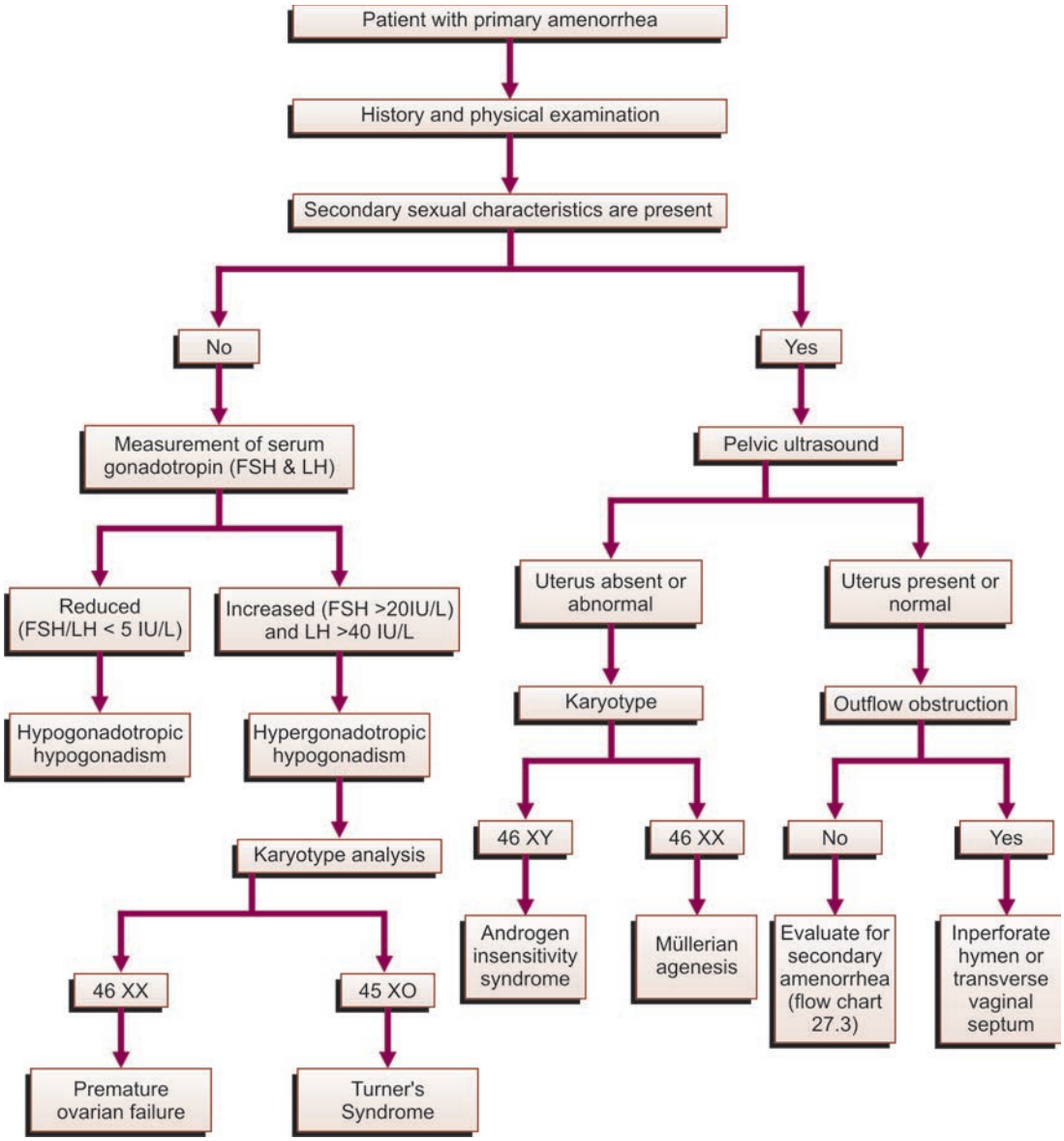
Secondary sexual characteristics have not developed

If there is absence of secondary sexual characteristics, estimation for serum gonadotropin levels must be performed. This test helps in diagnosis of two causes of amenorrhea: Hypogonadotropic hypogonadism and hypergonadotropic hypogonadism. In cases of hypergonadotropic hypogonadism, a karyotype analysis must be performed to determine

Table 27.3: Differential diagnosis of secondary amenorrhea

No features of androgen excess	*Features of androgen excess are present*
Physiological, e.g. pregnancy, lactation, menopause	Polycystic ovary syndrome
Iatrogenic, e.g. depot medroxyprogesterone acetate contraceptive injection, radiotherapy, chemotherapy	
Systemic disease, e.g. chronic illness, hypo- or hyperthyroidism	Cushing's syndrome
Uterine causes, e.g. cervical stenosis, Asherman's syndrome (intrauterine adhesions)	Late-onset congenital adrenal hyperplasia
Ovarian causes, e.g. premature ovarian failure, resistant ovary syndrome	Adrenal or ovarian androgen-producing tumor
Hypothalamic causes, e.g. weight loss, exercise, psychological distress, chronic illness, idiopathic	
Pituitary causes, e.g. hyperprolactinemia, hypopituitarism, Sheehan's syndrome	
Hypothalamic/pituitary damage, e.g. tumors, cranial irradiation, head injuries, sarcoidosis, tuberculosis	

Flow chart 27.1: Evaluation of primary amenorrhea



whether the cause of amenorrhea is related to premature ovarian failure (46XX) or to Turner's syndrome (46XO).

Hypogonadotropic hypogonadism

Hypogonadotropic hypogonadism is associated with low levels of FSH and LH, usually less than 5 IU/L. This could be related to the abnormalities in the secretion of gonadotropin-releasing hormone (GnRH), which is commonly due to disruption of the hypothalamic-pituitary-ovarian axis. The important causes for this include constitutional delay of growth and puberty and hypothalamic or pituitary failure. Hypothalamic amenorrhea is often caused by excessive weight loss, exercise or stress. Body mass index (BMI) of less than 19 (normal range 20–25) has been found to be associated with amenorrhea.

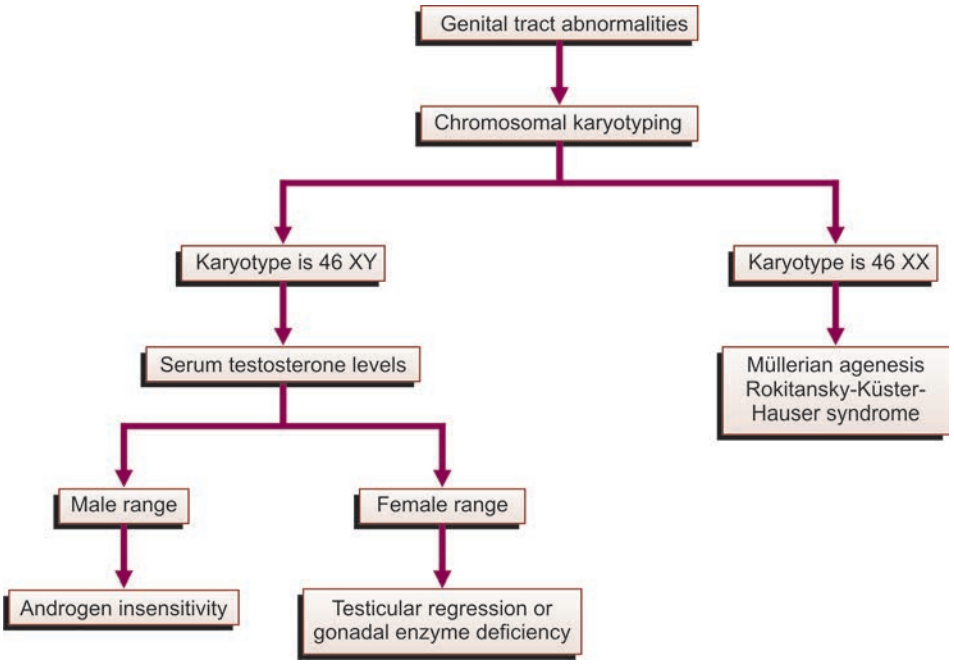
The mechanism by which stress or weight loss affects GnRH secretion is presently unknown.

Kallmann syndrome, which is associated with anosmia, also can cause hypogonadotropic hypogonadism.

Hypergonadotropic hypogonadism

Hypergonadotropic hypogonadism (elevated FSH and LH levels) in patients with primary amenorrhea may be caused by gonadal dysgenesis or premature ovarian failure. These two causes can be differentiated from one another by performing a karyotype analysis.

Flow chart 27.2: Management protocol in case of genital tract abnormalities



Gonadal dysgenesis: Turner's syndrome (45, XO karyotype) is the most common cause for female gonadal dysgenesis. About 50% have mosaic forms such as 45X/46XX or 45X/46XY. Characteristic physical findings of turner's syndrome include webbing of the neck, lymphedema, shield chest with widely spaced nipples, scoliosis, wide carrying angle, coarctation of the aorta, streak ovaries and short stature. Individuals with the various forms of gonadal dysgenesis typically present with hypergonadotropic amenorrhea regardless of the extent of pubertal development and the presence or absence of associated anomalies or stigmata. It is well known that cytogenetic abnormalities of the X chromosome can impair ovarian development and function.

Premature ovarian failure: Normally, menopause occurs at 50 years of age and is caused by ovarian follicle depletion. Sometimes ovarian failure can occur prematurely. Premature ovarian failure is characterized by amenorrhea, hypoestrogenism, and increased gonadotropin levels occurring before 40 years of age. Women with premature ovarian failure are at an increased risk of osteoporosis and heart disease. Premature ovarian failure can also be sometimes associated with autoimmune endocrine disorders such as hypothyroidism, Addison's disease, and diabetes mellitus. Therefore, fasting glucose levels, thyroid stimulating hormone (TSH), and, if clinically appropriate, morning cortisol levels should be measured. A karyotype analysis must be performed because surgical removal of the gonads is indicated in any individual in whom a Y chromosome is identified. Two types of inherited enzymatic defects also may be associated with premature ovarian failure. These include 17α-hydroxylase deficiency and deficiency of the enzyme galactose-1-phosphate uridyltransferase.

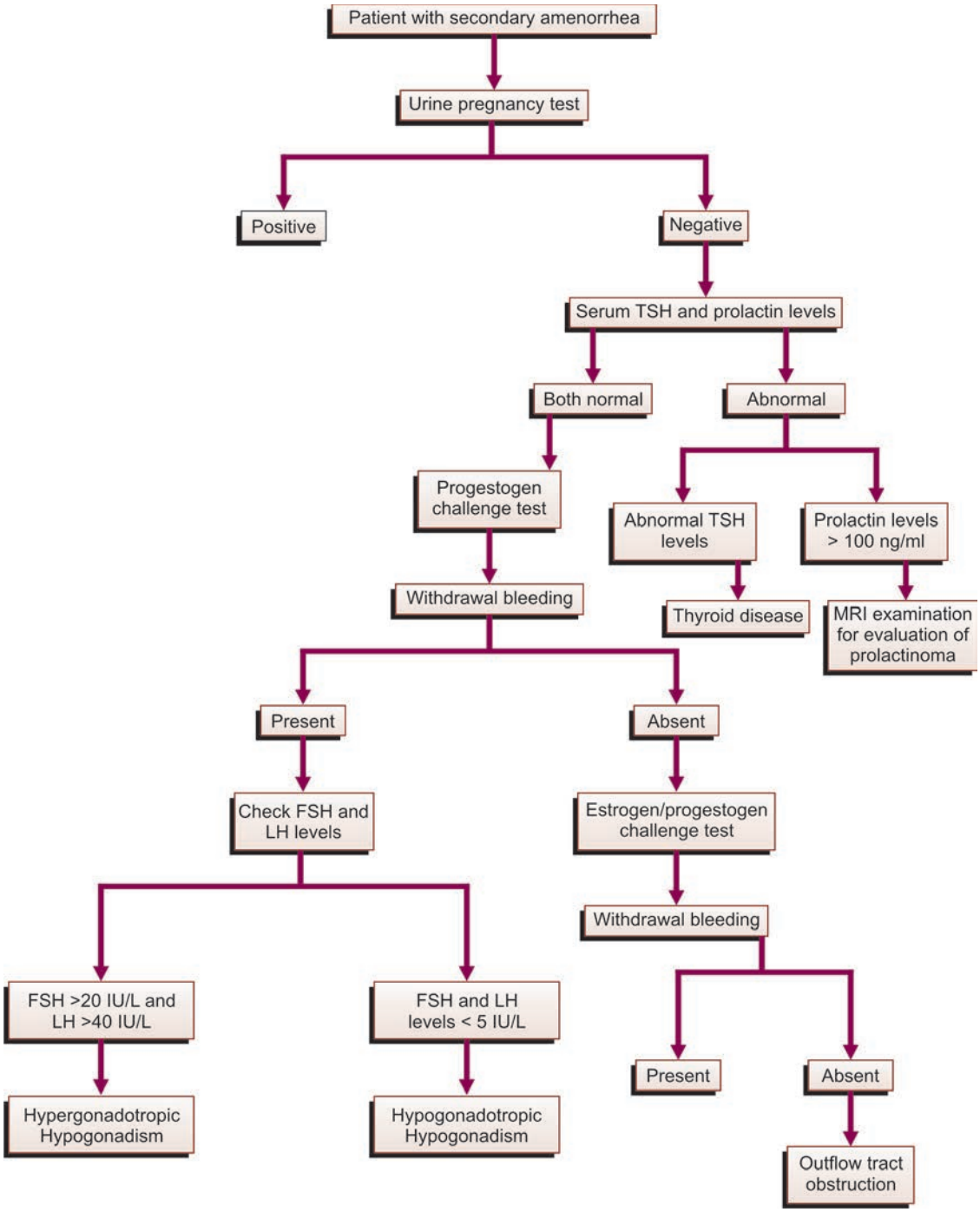
Secondary Amenorrhea

The management plan of a patient with secondary amenorrhea is described in flow chart 27.3. The first step in the management of patients with secondary amenorrhea is to rule out pregnancy because that is the most common cause of secondary amenorrhea. Once the pregnancy has been ruled out, the initial workup involves measurement of TSH and prolactin levels and a progesterone challenge test. In case, the patient with amenorrhea also presents with galactorrhea, imaging of sella turcica may also be required. Hypothyroidism may also produce galactorrhea by reducing the levels of dopamine (a prolactin inhibitory substance). Hypothyroidism also causes unopposed TRH production, resulting in stimulation of pituitary cells which produce prolactin.

The progestational challenge test can be performed using the following:

- 200 mg of parenteral progesterone in oil.
- Oral micronized progesterone in the dose of 300 mg daily.
- Medroxyprogesterone in the dosage of 10 mg daily for 5 days.

Flow chart 27.3: Management plan of a patient with secondary amenorrhea



- Micronized progesterone gel (4-8%): Intravaginal application for at least six applications.

Following 2–7 days of conclusion of a progestational challenge test, the patient either does or does not bleed. If the patient bleeds, the diagnosis of anovulation can be established. Presence of bleeding confirms the presence of a functional outflow tract and a uterus lined by reactive endometrium prepared by endogeneous estrogens. Significant hyperandrogenemia associated with anovulation and PCOS is an important cause of amenorrhea which responds to the progesterone challege test. Chronic unopposed exposure of the endometrium to endogeneous estrogens can serve as a

risk factor for the development of endometrial cancer. At the minimum, these women must be prescribed a progestational agent (5 mg daily) for first 2 weeks of each month in order to reduce the risk of the development of endometrial cancer. OCPs can be given in case the contraception is desired.

If the withdrawal bleeding does not occur in response to progestational medications, there can be two causes: Either the outflow tract is not patent or the endometrium has not been adequately prepared by endogenous estrogens. In order to differentiate between the two, orally active estrogens (1.25 mg of conjugated estrogens) must be administered for at least 21 days. An orally active progestational agent (10 mg of medroxyprogesterone) can be added in the last 5 days to achieve withdrawal bleeding. If no withdrawal bleeding occurs even after the addition of estrogens, amenorrhea is probably related to a defect in compartment I (outflow tract and uterine endometrium). If withdrawal bleeding occurs, there is no defect in compartment I. It also implies that compartment I has normal functional activities if properly stimulated by estrogens. Compartment I defects could be related to problems in the outflow tract or to non-responsive endometrium generally resulting from an overzealous curettage or due to infection.

If the withdrawal bleeding occurs, the next step aims at finding if the ovaries and the pituitary gland are functioning normally or not. This involves the assay of serum gonadotropin levels. In normal adult females, FSH ranges between 5–10 IU/L, with ovulatory mid-cycle peak of about two times the baseline level, whereas the LH levels vary between 5–20 IU/L, with an ovulatory mid-cycle peak of about three times the baseline level. Hypogonadotropic hypogonadism which is associated with levels of both FSH and LH less than 5 IU/L could be due to prepubertal state and hypothalamic or pituitary dysfunction. Hypergonadotropic hypogonadism could be due to postmenopausal state, castrate females and ovarian failure. In these cases, FSH levels are > 20 IU/L and LH levels are >40 IU/L.

Investigations

Various investigations and the reasons for conducting them have already been discussed in the text. This section would be merely enumerating a few of these important investigations.

Karyotyping

Karyotype analysis is important for identifying the patient's genetic sex.

Serum Testosterone/Androgen Level

Women with polycystic ovarian syndrome may have mildly raised level, while women with androgen-secreting tumors of the ovary or adrenal gland, may have high levels of serum testosterone.

Gonadotropins Levels [Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH)]

Measurement of gonadotropin levels help in differentiating between hypogonadotropic and hypergonadotropic causes of hypogonadism. Low level of gonadotropins is associated with hypogonadotropic hypogonadism, while high level of gonadotropins is associated with hypergonadotropic hypogonadism.

Serum Prolactin Levels

Serum prolactin levels may be raised in women with prolactinomas.

Thyroid Function Tests

These tests are indicative of thyroid dysfunction which could be the possible cause of amenorrhea.

Treatment/Gynecological Management

The treatment of primary and secondary amenorrhea is based on the causative factor. Treatment goals include prevention of complications such as osteoporosis, endometrial hyperplasia, heart disease etc; preservation of fertility; and, in case of primary amenorrhea, progression of normal pubertal development.

Hypothalamic amenorrhea

Treatment of hypothalamic amenorrhea depends on the etiology.

Anorexia nervosa: Women with excessive weight loss should be screened for eating disorders and treated accordingly if anorexia nervosa or bulimia nervosa is diagnosed. Menstrual cycles usually return after a healthy body weight has been achieved.

In patients with amenorrhea caused by eating disorders or excessive exercise, the use of oral contraceptive pills or menopausal hormone therapy may decrease bone turnover and partially reverse bone loss. However, neither therapy has been shown to significantly increase the bone mass. Adequate calcium and vitamin D intake are recommended for these patients.

Hyperprolactinemia: Microadenomas are slow growing and rarely malignant. Treatment of microadenomas should focus on management of infertility, galactorrhea and breast discomfort. Macroadenomas may be treated with dopamine agonists or removed with transsphenoidal resection or craniotomy, if necessary. A dopamine agonist can help improve the symptom of amenorrhea and fertility. Bromocriptine, a

dopamine agonist, is the most commonly used drug for treatment and has been discussed previously in the text.

PCOS

Treatment of PCOS has been discussed in detail in chapter 26.

Thyroid dysfunction

Hypothyroidism is treated using thyroid preparations such as levothyroxine sodium (e.g. eltroxin).

Hypopituitarism

Hypopituitarism is associated with generalized deficiency of various hormones. In these cases, thyroid replacement therapy should not be instituted until adrenal function has been assessed and treated. Serum gonadotropin and gonadal steroid levels are typically low in cases of hypopituitarism. In cases with hypopituitarism where oocytes are still present, ovulation can be induced with exogenous gonadotropins when pregnancy is desired. hMG is the treatment of choice for patients with primary amenorrhea due to hypopituitarism. In order to prevent the risk of ovarian hyperstimulation syndrome, hMG should be started at the minimal dose (75 IU SC qd for 7 d). Exogenous pulsatile GnRH may also be used to induce ovulation if the disorder is hypothalamic. When pregnancy is not desired, signs and symptoms of estrogen deficiency can be prevented by instituting maintenance therapy with cyclic estrogen and progestogens.

Complications

Certain complications which may be present in the patient with amenorrhea are as follows:

Osteoporosis

Women with amenorrhea associated with estrogen deficiency are at significant risk of developing osteoporosis. This increased risk persists even if normal menses are resumed. Estrogen deficiency is of particular concern in younger women as a desirable peak bone mass may not be attained. Use of HRT, calcium and vitamin D preparations in these patients may prove to be useful.

Cardiovascular Disease

Young women with amenorrhea associated with estrogen deficiency may also be at an increased risk of developing cardiovascular disease, hypertension and type 2 diabetes in future.

Endometrial Hyperplasia

Women with amenorrhea with unopposed estrogen secretion (without an associated progesterone secretion) are at an increased risk of developing endometrial hyperplasia and endometrial carcinoma (see chapter 17).

Infertility

Women with amenorrhea generally do not ovulate and are usually infertile.

Psychological Distress

Amenorrhea often causes considerable anxiety, because it may cause women to start having concerns regarding the loss of fertility, or loss of femininity. The diagnosis of Turner's syndrome, testicular feminization, or müllerian agenesis can be traumatic for both the girls and their parents.

Important Questions and Answers

Q.1. What is the most likely diagnosis in this case?

Ans. In this case, secondary sexual characteristics are present and the ultrasound shows absence of uterus. Therefore in this case amenorrhea could be related to two main causes: Müllerian agenesis or androgen insensitivity syndrome (flow chart 27.1).

Q.2. What should be the next line of management in the above mentioned case study?

Ans. In order to differentiate between androgen insensitivity syndrome and müllerian agenesis, a karyotype analysis must be done.

Q.3. The karyotype analysis in this case revealed a female pattern (i.e. 46XX). How should the case be further managed?

Ans. Due to absence of uterus and vagina, both in this patient, it would not be possible for her to have menstrual cycles or to be fertile. This news may cause significant distress to the woman and her family. Therefore, it is important for the gynecologist to provide adequate reassurance and support in these cases. Adequate counseling helps in avoiding problems with altered body image, which are likely to develop in these cases. Though the patient remains infertile, she can lead an almost normal life. Creating an artificial vagina either through the use of Frank's dilators or surgical procedure (McIndoe's vaginoplasty) at the time the patient plans to get married helps in ensuring that she and her partner would be able to obtain adequate sexual enjoyment following their marriage. Both these procedures are undertaken at the time the marriage is planned because having regular sexual intercourse would help in maintaining the patency of newly created artificial vaginal orifice. Genetic offsprings can be achieved by collecting oocytes from genetic mother, fertilizing them with sperms obtained from genetic father and their placement in a surrogate carrier.

Q.4. What are the likely causes for ambiguous external genitalia?

Ans. Some important causes of ambiguous external genitalia include the following:

- Congenital adrenal hyperplasia: The commonest cause of congenital adrenal hyperplasia which can cause ambiguous genitalia is 21-hydroxylase deficiency in a genetically female infant.
- Androgen-secreting tumor.
- XX females with Mayer-Rokitansky-Küstner-Hauser (absent vagina with or without the uterus) syndrome.
- 5-Alpha reductase deficiency.

Q.5. What should be the initial investigations in a patient presenting with galactorrhea?

Ans. The investigations which need to be carried out include levels of TSH and prolactin in the blood and imaging with MRI. Imaging can be safely omitted in patients with regular ovulatory menstrual cycles.

Bibliography

1. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists: Number 41, December 2002. Obstet Gynecol. 2002;100:1389-402.
2. American College of Obstetricians and Gynecologists. Amenorrhea (ACOG Technical Bulletin 128). Washington, D.C.: ACOG, 1989.
3. Folch M, Pigem I, Konje JC. Müllerian agenesis: etiology, diagnosis, and management. Obstet Gynecol Surv. 2000;55: 644-49.
4. Kalantaridou S, Davis SR, Nelson LM. Premature ovarian failure. Endocrinol Metab Clin North Am. 1998;27:989-1006.
5. Kalro B. Impaired fertility caused by endocrine dysfunction in women. Endocrinol Metab Clin North Am. 2003;32:573-92.
6. Kiningham RB, Apgar BS, Schwenk TL. Evaluation of amenorrhea. Am Fam Physician. 1996;53: 1185-94.
7. Kolodziejczyk B, Duleba AJ, Spaczynski RZ, Pawelczyk L. Metformin therapy decreases hyperandrogenism and hyperinsulinemia in women with polycystic ovary syndrome. Fertil Steril. 2000;73:1149-54.
8. Marshall WA, Tanner JM. Variations in patterns of pubertal changes in girls. Arch Dis Child. 1969;44:291-303.
9. McIver B, Romanski SA, Nippoldt TB. Evaluation and management of amenorrhea. Mayo Clin Proc. 1997;72:1161-9.
10. Mitan LA. Menstrual dysfunction in anorexia nervosa. J Pediatr Adolesc Gynecol. 2004;17:81-5.
11. Pickett CA. Diagnosis and management of pituitary tumors: recent advances. Prim Care. 2003;30:765-89.
12. Pletcher JR, Slap GB. Menstrual disorders. Pediatr Clin North Am. 1999;46:505-18.
13. Reindollar RH, Byrd JR, McDonough PG. Delayed sexual development: A study of 252 patients. Am J Obstet Gynecol. 1981;140:371-80.
14. Simpson J, Rajkovic A. Ovarian differentiation and gonadal failure. Am J Med Genet. 1999;89:186-200.
15. Solomon CG. The epidemiology of polycystic ovary syndrome. Prevalence and associated disease risks. Endocrinol Metab Clin North Am. 1999;28:247-63.
16. Speroff L, Fritz MA. Amenorrhea. In: Clinical gynecologic endocrinology and infertility. (7th Ed.) Philadelphia, Pa.: Lippincott Williams & Wilkins, 2005;401-64.
17. Speroff L, Glass RH, Kase NG. Normal and abnormal sexual development. In: Clinical gynecologic endocrinology and infertility. 6th ed. Baltimore, Md. Lippincott Williams & Wilkins. 1999:339-79.
18. The Practice Committee of the American Society for Reproductive Medicine. Current evaluation of amenorrhea. Fertil Steril. 2004;82(suppl 1):S33-9.
19. Traggiai C, Stanhope R. Delayed puberty. Best Pract Res Clin Endocrinol Metab. 2002;16:139-51.
20. Webster J, Piscitelli G, Polli A, Ferrari CI, Ismail I, Scanlon MF, et al. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. N Engl J Med. 1994;331:904-9.

Index

D

M

N