Case Discussions in OBSTETRICS & GYNECOLOGY

YM Mala • Madhavi M Gupta • Swaraj Batra

JAYPEE

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Dedicated to
all our patients who have taught us the art of
case discussion and will continue to do so

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Foreword

Obstetrics and gynecology is a very challenging specialty which requires combination of both good clinical as well as surgical skills.

This book, entitled *Case Discussions in Obstetrics and Gynecology* is a complete book covering all the common problems in a comprehensive manner easily understood by the students.

The case discussions in question and answer pattern will be helpful to students in viva as well as theory examinations. Each discussion is followed by the ideal management and recent advances in that area along with adequate references.

The authors' endeavor to review the various cases in an elaborate manner is commendable. I recommend this book since it will be helpful to students for learning a particular topic as well as for the final revision before the examination. I wish this book and its readers all the success.

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Preface

Case discussions are an integral part of teaching in medicine. Since time immemorial, all practitioners of medicine have been learning on patients. Medicine has been evolving at a fast pace with many advances in science and technology and new discoveries every other day. With advent of modern methods of teaching, there have been drastic changes in all aspects. But case discussions continue to hold the same importance may be, more because with the availability of a multitude of investigations and diagnostic aids we might be missing on to something when we rely more on these. Trainees and young practitioners need to realize the significance of a good history and a thorough clinical examination before ordering only the most required investigations to arrive at the right diagnosis.

Also, case discussions are part of all examinations and this book tries to present the near ideal case discussion of the commonly encountered problems in obstetrics and gynecology on a daily basis.

Case Discussions in Obstetrics and Gynecology is an ideal combination of evidence-based knowledge and years of clinical experience of faculty in patient management and conducting both undergraduate and postgraduate exams. It includes recent advances in this field which might not be included in the textbooks.

The approach in this book is problem based and tells how a list of differential diagnosis can be eliminated step-wise before clinching the diagnosis. In standard textbooks the approach is retrospective that is, what symptoms and signs can be found or expected in a particular pathology. The book is in the form of question and answers to make it more problem based and telling the art of postgraduate and undergraduate exams and reaching a clinical diagnosis.

This book, prepared and produced by the Department of Obstetrics and Gynecology at the Maulana Azad Medical College and Associated Lok Nayak Hospital, New Delhi contains the long teaching experience of the faculty. They are teachers who have been training postgraduate students for a number of years and are very well aware where even a well read, hard working student is likely to falter in the exam.

Learning to diagnose a patient via a systematic approach is the key and basis of proper management. Many of the students after clearing the exam will go out in the society and practice what they have learnt during the course of their postgraduate training. Having a scientific basis made easier will help them to diagnose and treat patients correctly to their fullest capability.

We invite you to join us on a roadmap to preserve and pass on the art of case discussions to the coming generations for the larger good of our patients.

YM Mala
Madhavi M Gupta
Swaraj Batra

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SECTION 1: OBSTETRICS

Sangeeta Gupta, Sonali Gupta

1 Pregnancy with Previous Congenital Disorders

Fetal congenital disorders are an important cause of prenatal loss and perinatal morbidity and mortality. Congenital disorders can be broadly classified into structural anomalies, aneuploides and genetic disorders. Prenatal diagnosis is the science of identifying structural and functional abnormalities birth defects in the fetus.[1] Prenatal diagnosis helps couples to make reproductive choices and the clinicians to provide appropriate counseling and optimize treatment. In the following section, a case based approach to common congenital defects from each catogery will be discussed.

NEURAL TUBE DEFECTS

CASE 1

Mrs X 30 years old G3+1+0+1+0 with history of both pregnancies affected by neural tube defects (NTD) presented at 8 weeks and 3 days period of gestation. In the first pregnancy patient had conceived spontaneously after one year of marriage and did not seek any antenatal care. Patient delivered at a hospital and anencephaly was detected at birth. However, no comment was made on presence or absence of other anomalies. In the second pregnancy she booked at fifteen weeks pregnancy and had level 2 ultrasound at 19 weeks of gestation. She was diagnosed as occipitomeningomyelocele and opted to terminate the pregnancy. On neonatal review the diagnosis of occipitomeningomyelocele was confirmed and no other gross congenital anomalies were detected. The parents did not consent for postmortem autopsy or chromosomal study.

Relevant History

Present Pregnancy

- Gestational age
- History of exposure to drugs particularly which interfere with folic acid metabolism
- Any history of hyperthermia and hyperglycemia
- Intake of folic acid in periconceptional period
- History of consanguinity.

History of Previous Pregnancies

- Any history of folic acid intake in periconceptional period.
- History of hyperthermia or hyperglycemia in periconceptional period.
- History of antifolate drug intake in periconceptional period.

- Mode of diagnosis of NTDs (prenatal ultrasound, postnatal diagnosis)
- Associated malformations and dysmorphisms to delineate genetic disorders
- Fetal autopsy done or not
- Fetal karyotype done or not
- Family history of neural tube defects.

Examination

In the first half of pregnancy, there may not be anything remarkable in the examination. However, with advanced gestational age, polyhydramnios may cause increased fundal height and presence of fluid thrill. The presentation of the fetus may be breech or face.

Q.1. How will you counsel this woman?

Ans: The woman would be counseled on the issues regarding the risk of recurrence in this pregnancy. The risk of having a baby with neural tube defect in this pregnancy is about 10%.

Anencephaly can be detected as early as 10 weeks of pregnancy and hence she would be advised an early anomaly scan. However, for the defects in the spinal cord patient would be taken up for level II sonography between 18 to 20 weeks of pregnancy.

Q.2. If this woman comes in the preconceptional period what counseling should be done?

Ans: She is advised to take high dose of folic acid supplementation (4 mg) starting 3 months prior to conception.

She will be counseled regarding the risk of recurrence of NTD in this pregnancy and early detection of NTDs by ultrasonography is advised.

If the woman is hyperglycemic, then she is referred to a physician for adequate control of her glycemic status before she conceives. If her glycemic status is not known then she would be evaluated with blood sugar fasting and postprandial.

If the woman is on antiepileptic therapy particularly valproate or multidrug therapy, it is advisable to switch her to monotherapy in the preconceptional period and valproate should be replaced by lesser teratogenic drugs like phenytoin. Time to change the medication is before conception as organogenesis is almost complete in the first trimester.

Q.3. What are the high risk factors which predispose to neural tube defect in fetus?

Ans: Neural tube defects are example of multifactorial inheritance. The following factors influence the development of neural tube defects:

1. **Environmental agents** like diabetes, obesity, hyperthermia.
2. **Antifolate medications:** The antifolate medications implicated in causation of NTD are valproate,[2] carbamazepine, coumadin and aminopterin.

   Neural tube defects associated with type 1 diabetes are more likely to be cervical and cervicothoracic; with valproic exposure lumbosacral defects and with hyperthermia anencephaly.[3-5]
3. **Genetic Causes**
   - Family history
   - Autosomal recessive condition—Meckel-Gruber syndrome
   - MTHFR gene polymorphism such as C677T and A1298C mutations are associated with hyperhomocystinemia and folate insufficiency is thought to play a role in the phenotypic expression of MTHFR mutations.[6]
   - Recurrent NTD have been reported to be associated with partial trisomy 2p22 and 20p, resulting from a maternally derived translocation.[7,8]
4. **Geographical Distribution**

   Certain populations in particular geographic areas have increased incidence of NTDs. United Kingdom has the highest frequency of NTD that

is 1%[1]. In India, the incidence is 0.5-11 per 1000 births.[9]

Q.4. What is the significance of parental consanguinity in a case of pregnancies with recurrent neural tube defects?

Ans: There is evidence of major gene involvement in familial neural tube defects with parental consanguinity and is likely to be recessive in inheritance. A single gene cause of recurrent NTD is the Meckel-Gruber syndrome. It is a rare autosomal recessive disorder and carries a 25% risk of recurrence. Other features of this syndrome triad include polycystic kidneys and polydactyl.[10,11]

Q.5. What is the recurrence risk for NTDs?

Ans: Recurrence risk with one affected child is 3-4% and after two affected children it is 10%.

The recurrence risk is 4-5% if one parent is affected.

The recurrence risk is 25% when NTD is part of Meckel-Gruber syndrome.

Recurrence risk for first degree relatives of affected children in 1 in 30 and second degree relatives is 1 in 220.[12]

Q.6. What is the role of folic acid supplementation in prevention of neural tube defects?

Ans: There are two aspects in the administration of folic acid supplementation for prevention of NTD- the timing and the dose.[2] Pre-conceptional intake of folic acid, beginning 3 months prior to conception in the dose of 400 microgram daily has been recommended for prevention of first occurrence of NTDs and should be continued through the first trimester of pregnancy[13,14] However, higher doses of folic acid supplementation (4 mg) are recommended for women at higher risk of NTDs. These include women with prior affected children or if the women or the partner has NTD. In women with previous affected offspring there is 70% reduction in recurrence rate.[15,16] Similar doses are used in patients who are diabetic or on antifolate medication but data is limited about their benefit.

Q.7. Disruption of folic acid metabolism predisposes to which congenital abnormalities?

Ans: Several congenital abnormalities like neural tube defects, cardiac defects, cleft lip and palate, and even Down syndrome are known to arise, at least in part from disturbance of folic acid metabolic pathways.

Q.8. Besides NTD folic acid intake prevents which other congenital malformations?

Ans: Congenital heart diseases and cleft lip and palate are also prevented to certain extent by folic acid intake.[17]

Q.9. What is the screening strategy for neural defects?

Ans: Universal screening of NTDs in antenatal period is recommended as 95% of the cases are seen in the low risk populations.

The screening for open neural tube defects is done by estimation of maternal serum alfa-feto-protein (MSAFP) between 15-20 weeks of pregnancy. The levels are raised in open neural tube defects. Cut-offs between 2 and 2.5 MOMs as upper limits yield detection rates of 100% for anencephaly and 85-94% for open spina bifida. For efficient MSAFP screening determination of accurate gestational age by first trimester scan is important. Other factors which influence MSAFP are maternal weight and ethnicity.

Q.10. How are patients with elevated MSAFP evaluated?

Ans: For patients with elevated MSAFP, further testing with targeted ultrasound or amniocentesis is required. Presently, the best approach to evaluate elevated MSAFP is ultrasound. *Ultrasound evaluation is done to confirm the gestational age,*

rule out twin pregnancy, fetal demise and identify structural defects that cause elevated MSAFP. Targeted sonographic evaluation for spina bifida in high risk cases has sensitivity of about 97% and specificity of 100%. Amniocentesis for the measurement of amniotic fluid AFP and the detection of acetylcholinesterase (AChE) has been replaced by ultrasonography.

When no fetal abnormality is detected, MSAFP elevation may be associated with adverse pregnancy outcomes like fetal growth restriction, oligohydramnios, placental abruption, preterm membrane rupture, preterm birth and even fetal death.[18] However, optimal management is unclear and prenatal care for these women is not altered unless specific complication arises.

Q.11. What are the causes of raised MSAFP?

Ans: *In 50% of cases, incorrect dating* will be identified and adjustment of initial value resolves the issue.

Fetal demise is also associated with raised MSAFP.

The various structural defects associated with raised MSAFP are open neural tube defects, fetal abdominal defects such as omphalocele and gastroschisis, sacrococcygeal teratoma, fetal urinary tract obstructions and urinal atresia.

Q.12. What are the causes of low MSAFP?

Ans: Obesity, diabetes, chromosomal trisomies, gestational trophoblastic disease, fetal death, overestimated gestational age.

Q.13. What are the sonographic features in various neural tube defects?

Ans: The antennal diagnosis of anencephaly is based on absence of fetal calvaria.

Anencephaly can be identified by ultrasound as early as 10 weeks of gestation but should be reconfirmed by a scan at around 13 weeks because ossification of the skull in some cases may not be completed until that time.[19]

Ultrasound diagnosis of meningomylocele is frequently based on a cystic mass protruding from the dorsal vertebral bodies without skin covering. This is ideally seen in the transverse plane as a wide separation of the lateral processes of lamina (Fig. 1.1).

Indirect sonographic signs of meningomylocele have been found to be as important as visualization of the spinal lesion and are somewhat easier to image. These include ventriculomegaly, microcephaly, frontal bone scalloping (lemon sign) (Fig. 1.2), and obliteration of the cisterna magna with either an absent cerebellum or abnormal anterior curvature of the cerebellar hemispheres (banana sign)[20] (Fig. 1.3). Banana and lemon sign are produced by caudal displacement of cerebellar vermis, fourth ventricle and medulla constituting the *Arnold-Chiari II malformation*. These findings are seen in over 95% of cases of neural tube defects in the middle of the second trimester. The banana sign and the lemon sign may not be present after 22 to 24 weeks' gestation.

The presence of neural tissue in the meningeal sac and level and length of the lesion should be

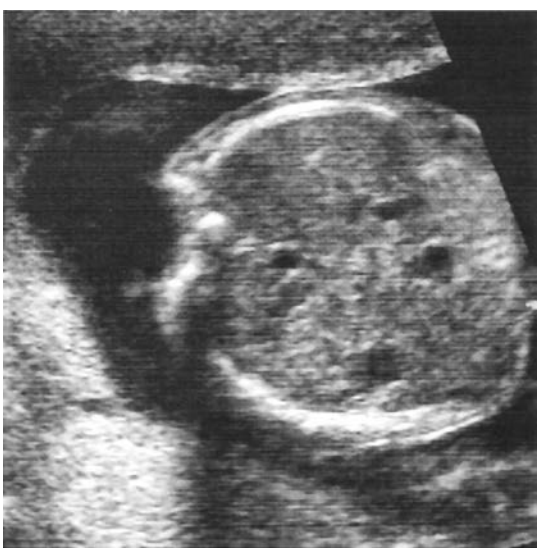


Fig. 1.1: Axial view of spina bifida

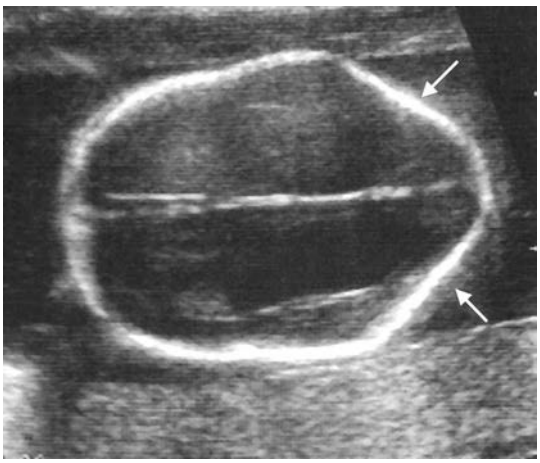


Fig. 1.2: Lemon sign

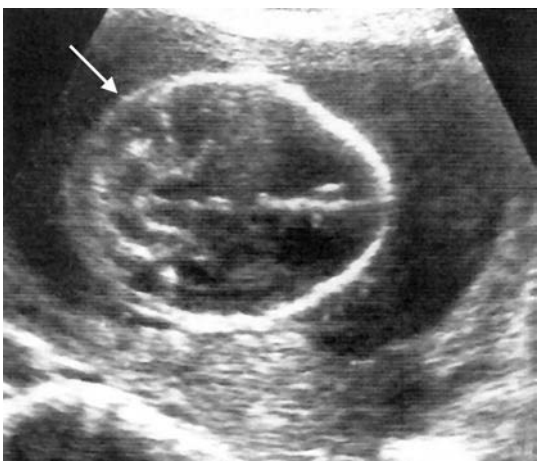


Fig. 1.3: Banana sign

ascertained on sonography to predict the extend and severity of the neurological deficits.

Besides the detailed evaluation of the cranium and spine, comprehensive ultrasound examination should be performed to exclude genetic syndromes.

Q.14. When does neural tube close in the embryo?

Ans: Neural tube closure occurs in the 3rd to 4th week after fertilization.[21] Closure in the region of the developing head and sacrum is completed approximately 24 and 26 days after conception, respectively.

Q.15. How will you counsel and manage the couple if anencephaly is detected?

Ans: Anencephaly is lethal and can be diagnosed accurately by antenatal ultrasound.

In our country termination of pregnancy can be offered till 20 weeks of gestation as per the PNDT act. Fetal autopsy should be offered for all fetuses with anencephaly to detect other anomalies as it may form a part of genetic syndrome and helps in predicting the recurrence risk.

In recurrent NTDs fetal and parental karyotyping could be useful in the future management since partial trisomies are the implicated cause.[22]

However, couples who refuse termination are followed up with routine antenatal care. The woman is more likely to have complications like polyhydramnios, malpresentation (face, breech) and postmaturity. Polyhydramnios, may result from diminished fetal swallowing, secretion of cerebrospinal fluid directly into the amniotic cavity and excessive micturition. Postmaturity is a consequence of absent or hypoplastic pituitary gland.

During labor, shoulder dystocia and obstructed labor should be anticipated.

Q.16. How will you counsel the patient if meningomyelocele is detected?

Ans: Patient should be counseled regarding the prognosis which depends on the presence of neural tissue in the meningeal sac and spinal level and length of the lesion. The spinal cord below the lesion is dysplastic and lower limb paralysis and incontinence of bowel and bladder is common. Intelligence may be affected from either the lesion itself or the impact of treatment (shunt placement). Early closure of the defect and ventriculoperitoneal shunting of any associated hydrocephalus should be performed.[23,24]

The option of pregnancy termination should be included in counseling if the gestational age is less than 20 weeks.

If patient plans to continue the pregnancy, a multidisciplinary team consisting of a pediatric neurologist, neurosurgeon, obstetrician, and neonatologist should manage the patient to optimize the neonatal outcome and plan surgical management.

In utero surgical repair of NTDs is still in experimental phase and currently there is insufficient data to judge the benefits and risk of this approach.[25]

DOWN'S SYNDROME

CASE 2

Mrs B, 24 years old had a previous baby with Down syndrome one year old.

History

- Age of the mother at delivery
- Period of gestation at which the pregnancy was registered
- First trimester scan for nuchal translucency
- Whether first or second trimester screening was done
- Second trimester anomaly scan
- Pregnancy outcome: Miscarriage, stillborn or live born
- Obstetrical history: P1+0+0+1

Her first pregnancy was a spontaneous conception. She sought antenatal care at 20 weeks of pregnancy. She had a term delivery at a hospital of a small for gestational age baby. The baby had mongoloid facies and a ventricular septal defect was diagnosed. The baby had delayed milestones and on investigations the baby was diagnosed with Trisomy 21.

Case: ***The woman is desirous of further child-bearing but is apprehensive about similar problem in the next baby and has come for preconceptional counseling. The karyotype of the effected child showed Trisomy 21 (47,XY).***

Q.17. What recurrence risk would you attribute to this lady?

Ans: Down's syndrome cases result from nondisjunction, translocation or mosaic.

With a pregnancy complicated by trisomy 21 from nondisjunction, the woman has 1% risk of having a pregnancy with trisomy in subsequent pregnancy. This risk pertains unless her age related risk exceeds it.

Because of this risk, she would be offered invasive prenatal diagnosis.

Parental karyotype is not indicated in this couple.

Q.18. What is the incidence of Down syndrome in general population?

Ans: Down's syndrome occurs in 1 in 800 to 1 in 1000 newborns.[26]

Q.19. What are the different cytogenetic mechanisms associated with Down syndrome?

Ans: Chromosomal abnormalities in Down syndrome.[27]

Abnormality	*Frequency (%)*
Trisomy	95
Translocation	4
Mosaic	1

Ninety-five percent of Down syndrome cases have primary trisomy of chromosome 21(47 instead of normal 46). These cases show the well-known relationship to maternal age. Ninety-five percent of trisomy children inherit their additional chromosome as a result of nondisjunction of maternal gametes while only 5% are paternally derived.[28]

Four percent of Down syndrome cases have Robertsonian or unbalanced translocation. By contrast, translocations show no definite relationship to parental age and may be either sporadic (two third) or familial (one third).[28] The familial translocations carry greater risk of recurrence for future offspring.

Children with mosaicism are often less severely affected than in the full syndrome.

Q.20. What recurrence risk is attributed for Down syndrome with unbalanced or Robertsonian translocation?

Ans: If a child has down syndrome as a result of *de novo* translocation, that is neither parent will have a balanced translocation, the likelihood of Down syndrome offspring's recurring in such a couple is 0.5 to 1%.

However, if either of the parents harbors balanced translocation, the risk of recurrence exists. For female carriers of Robertsonian 14;21 translocation, the risk of having a liveborn infant with Down syndrome is approximately 10%. The risk is approximately 1% for a male carrier.[29,30] When parental translocations involve homologous chromosomes, that is 21, 21 possibility of a normal liveborn infant is precluded. For such couples, donor gametes should be considered.

Q.21. What is the indication of parental karyotype in cases of Down syndrome?

Ans: When a fetus or child is found to have a translocation trisomy, chromosomal studies of both parents should be performed. If neither parent is a carrier and the translocation occurred spontaneously, the recurrence risk is extremely low.[26] In one third cases one parent will be a carrier. Other relatives can also be carriers and efforts should be made to identify all adult translocation carriers in a family so that they can be alerted to possible risks to future offspring. This is sometimes referred to as *translocation tracing* or *chasing*.[28]

Q.22. What is the risk of Down syndrome in offspring of parents with Down syndrome?

Ans: Females with Down syndrome are fertile and a third of their offspring will have Down syndrome. Males with Down syndrome have markedly decreased spermatogenesis and are almost always sterile. The risk of a chromosomally normal fetus having a birth defect or mentally handicapped could be as high as 30%.[31]

Q.23. What is the fetal death rate with trisomy 21?

Ans: With trisomy 21, the fetal death rate is about 30% between 12 and 40 weeks, and about 20% between 16 and 40 weeks.[32]

Q.24. What is the significance of parental aging in Down syndrome?

Ans: There is well documented association between advancing maternal age and nondisjunction trisomy 21. The most favored explanation is an aging effect on the primary oocyte which can remain in a state of suspended inactivity. Paternal age has no association with Down's syndrome though in nondisjunction, in 5% children the extra chromosome is paternally derived. *The parental age has no bearing in the Down syndrome due to translocations.*[33]

Maternal age at delivery (in years)	*Risk of Down syndrome*
20	1 in 1500
25	1 in 1350
30	1 in 900
35	1 in 400
37	1 in 250
40	1 in 100
45	1 in 30

Case: The woman in the above scenario reports to you at 8 weeks pregnancy.

Q. 25 What is your plan of management in the current pregnancy?

Ans: Since the recurrence in this pregnancy is about 1%, the women will be directly offered invasive testing with chorionic villous sampling to ascertain the chromosomal configuration of the fetus. In such patients there is no role of serum screening or combined screening. If she reports later than 14

weeks she is offered prenatal diagnosis with amniocentesis.

Q.26. What are the indications of invasive prenatal testing?

Ans:

1. Maternal age > 35 years
2. Previous offspring with aneuploidy.
3. Multiple or major congenital malformations on ultrasonography
4. Positive screening test.
5. Parental aneuploidy.
6. Intracytoplasmic sperm injection: there is increased risk of (1%) sex chromosomal abnormalities in pregnancies established by ICSI.
7. Recurrent spontaneous miscarriages.
8. Family history of single gene defects.
9. Structural chromosomal rearrangements.
   a. Either parent with Robertsonian translocations
   b. Parental reciprocal translocations: mode of ascertainment is very important. If a balanced reciprocal translocation is ascertained through an unbalanced child or another liveborn relative, the likelihood of unbalanced liveborns is approximately 20%. If balanced translocation is ascertained through a history of repeated miscarriage, the risk for an abnormal liveborn is much lower (1-5%).[34]

Case 3: A 28 years old primigravida comes to your antenatal clinic at 10 weeks pregnancy for routine antenatal care. The woman is offered prenatal screening for aneuploides.

Q.27. What options are available for the woman?

Ans: The options available for the woman along with their detection rates are as per Table 1.1.[35]

It is very important to remember that whichever method is chosen for screening, determination of correct gestational age by ultrasonography is mandatory for correct risk assessment.

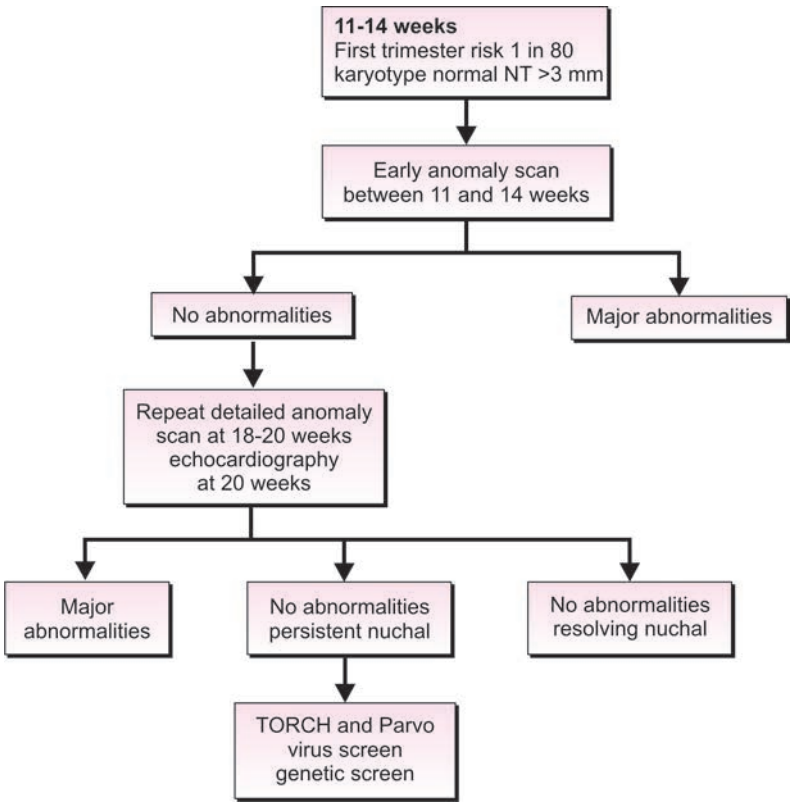
The maternal age is another important determinant of risk estimate as discussed earlier that increasing maternal age predisposes to a higher risk for aneuploides. Thus, it forms an integral part of any screening test. Patient's weight, diabetic status, ethinicity and smoking should be taken into account as they have bearing on serum markers level.

Case: A 28-year-old primigravida on Ist trimester combined screening is found to have a high risk of trisomy 21 (1:80).

Table 1.1: Options available for prenatal screening for aneuploides along with their detection rates

Methods of screening	*Detection rate (%)*	*False positive*
Maternal age	30%	5%
Maternal age and triple test at 15-18 weeks (alpha fetoprotein, free beta-hCG, uE3)	50-70	5%
Maternal age and quad test at 15-18 weeks (alpha fetoprotein, free beta-hCG, uE3, inhibin-A)[36,37]	80%	5%
Maternal age and nuchal translucency (NT) at 11-13 weeks	70-80%	5%
Maternal age and fetal NT and maternal serum free beta-hCG and PAPP-A at 11-13 weeks	85-90%	5%
Maternal age and fetal NT and nasal bone and maternal serum free beta-hCG and PAPP-a at 11-13 weeks	95%	5%
Serum integrated- PAPP-A in first trimester and Quad test in second trimester[38]	85%	5%
Fully integrated- PAPP-A and NT in first trimester and Quad in second trimester)	85-90%	1-2%

Flow chart 1.1: Management of the woman with normal karyotype and NT > 3 mm



Q.28. What will be the future course of management including patient counseling?

Ans: A cut off of more than or equal to 1 in 250 is classified into high risk group. Hence, all patients with risk more than 1 in 250 should be offered invasive testing. Definitive diagnosis is established by invasive testing only.

The invasive tests available are chorionic villous sampling between 11 to 14 weeks and amniocenteses between 15 to 20 weeks. The advantages, disadvantages and complications of each test should be discussed with the couple.

If the result of the karyotype is abnormal, the couple has the option to terminate or continue the pregnancy. The methods of termination of pregnancy available at various gestational ages and their complications should also be discussed.

Q.29. How will you manage this woman if on chorionic villous biopsy the karyotype is normal but the NT is 4 mm?

Ans: In this woman, since the nuchal translucency (NT) was more than 3 mm and the karyotype is normal, the protocol is followed as per Flow chart 1.1.

Q.30. What are the inferences drawn from NT evaluation? Do you think cystic hygroma confers a different risk estimate?

Ans: The prevelance of fetal abnormalities and adverse pregnancy outcome increases exponentially with NT thickness. However, the parents can be reassured that the chances of delivering a baby with no major abnormalities is more than 90% if the fetal NT is between the 95th and 99th centiles, about

70% for NT of 3.5-4.4 mm, 50% for NT 4.5-5.4 mm, 30% for NT of 5.5-6.4 mm and 15% for NT of 6.5 mm or more.[39]

Increased fetal NT thickness at 11-13 weeks is a common phenotypic expression of chromosomal defects and a wide range of fetal malformations and genetic syndromes.

Increased NT is associated with[40]

1. Aneuploidy
2. Major cardiac defects
3. Diaphragmatic hernia
4. Omphalocele
5. Body stalk anomaly
6. Skeletal defects
7. Fetal akinesia deformation sequence
8. Noonan syndrome
9. Smith-Lemli-Opitz syndrome
10. Spinal muscular atrophy

First trimester cystic hygroma has the strongest prenatal association with aneuploidy with significantly worse outcome compared with simple increased nuchal translucency.[41]

In about 75% of fetuses with cystic hygroma, there is a chromosomal abnormality and in majority of cases, the abnormality is Turner syndrome.

Q.31. What is pathophysiology associated with increased NT?

Ans: The following mechanisms are implicated in the pathophysiology of increased NT:[39]

1. Cardiac dysfunction
2. Venous congestion in the head and neck
3. Altered composition of the extracellular matrix
4. Failure of lymphatic drainage
5. Fetal anemia
6. Fetal hypoproteinemia
7. Fetal infection

Q.32. What is the role of second trimester sonography in risk estimation of aneuploidy?

Ans: If the second trimester scan demonstrates major abnormalities like congenital heart disease, diaphragmatic hernia, omphalocele, it is advisable to offer fetal karyotyping, even if these abnormalities are apparently isolated, as chances of associated aneuploidy are high.[42]

If the abnormalities are either lethal or they are associated with severe handicap, such as holoprosencephaly, fetal karyotyping constitutes one of a series of investigations to determine the possible cause and thus the risk of recurrence.

Genetic sonography refers to systematic use of composite of diverse mid trimester markers to estimate the risk of Down syndrome. This screening was developed and has been found to be of value **in high risk population.** The highest yield is achieved with the combination of serum and ultrasound screening in the general population. Various studies have revealed low diagnostic sensitivity for mid trimester ultrasound screening in low risk population.the composite rather than isolated sonographic markers are the current paradigm for sonography based down syndrome risk estimation.

- Genetic sonogram should be an option for women with advanced maternal age even if their serum screen results are normal, as few additional fetuses with Down syndrome could be identified. For those patients who have a normal genetic sonogram and a normal maternal serum screening results, the risk of trisomy 21 is very low and probably does not warrant invasive testing.[43] Seuter and coworker demonstrated that serum screening and the genetic sonogram were largely independent of each other and therefore, could be used as independent modifiers of the risk of Down syndrome.[44]
- Minor fetal abnormalities or soft markers like nuchal thickness, middle phalanx, sandal gap, echogenic bowel, echogenic cardiac focus, short femur, short humerus are common and they are not usually associated with any handicap, unless there is an underlying chromosomal defect.

Q.33. What are the new advances in noninvasive diagnosis of Down syndrome?

Ans: With the use of chromosome- specific DNA probes and fluorescent *in situ* hybridization (FISH) it is possible to suspect fetal trisomy by the presence of three-signal nuclei in some of the cells of the maternal blood enriched for fetal cells. There is evidence that increased level of cell free fetal DNA is present in trisomy 21 pregnancies. However, this method is more likely to find an application as a method for assessment of risk, rather than the non-invasive prenatal diagnosis of chromosomal defects.[45,46]

Beta Thalassemia

Beta thalassemia is the most common single gene disorder in our country. Carrier frequency varies from 3-17% in different populations. The most effective approach to reduce the burden of the society and reduce the disease incidence is implementation of a carrier screening program, offering genetic counseling, prenatal diagnosis and selective termination of affected fetuses.

Q.34. What are various variants of β thalassemia?

Ans: β thalassemia is characterized by diminished production of β globin chains which causes unmatched α globin chains to accumulate and aggregate. The deficiency of β globin synthesis may be compensated partially by an increase in δ and γ chain synthesis. This leads to increased levels of HbA_2 (α2, δ2) and HbF (β2, γ2) on hemoglobin electrophoresis. β thalassemia has three major clinically important syndromes. β thalassemia minor, β thalassemia major and β thalassemia intermedia.

β Thalassemia Minor

Patients who have β thalassemia minor are heterozygous for β globin mutation. They have mild or no anemia. Peripheral smear shows hyperchromia and microcytosis with basophilic stippling.

HbA_2 and HbF levels are increased.

Unlike iron deficiency anemia, it is characterized by normal to increased proliferation of RBCs.

β Thalassemia Major

Results from homozygous or double heterozygous mutations in the β globin gene.

In ***β^0 thalassemia***, the most severe form, no β globin chains are synthesized. Only HbA_2 and HbF are found on electrophoresis.

When small amount of β globin chains are synthesized, the condition is called ***β^+ thalassemia***. HbA_2, HbF and HbA are found on electrophoresis. It is milder than β^0 thalassemia.

β Thalassemia Intermedia

These patients carry two β thalassemia mutations but present with symptoms later in life and have milder anemia than patients who have β thalassemia major. They are not transfusion dependent but may require transfusions periodically. Despite the low transfusion rate, iron overload occurs in these patients as a result of increased intestinal absorption of iron that is caused by ineffective erythropoiesis. The complications of iron overload present later but may be as severe as those seen in patients who have β thalassemia major.

Q.35. How will you screen for thalassemia in pregnancy?

Ans: Screening is offered to the women if she is identified as belonging to an ethic population whose members are at higher risk of being carriers. Ideally screening should be done preconceptionally or as early as possible in the pregnancy.

1. The preliminary screening method for all forms of thalassemia relies on **hematologic index**

cutoffs, which involves an accurate blood count using an electronic cell counter. Individuals with mean corpuscular volume (**MCV) < 80fl** and mean corpuscular hemoglobin (**MCH) < 27pg** should be further examined to confirm or exclude the diagnosis of β thalassemia. This, however, requires an expensive electronic blood cell counting apparatus and cannot be applied in rural areas where laboratory facilities and economic resources are limited.[47]

2. A cheaper, rapid, simple and cost effective alternative for screening is **NESTROF** (naked eye single tube red cell osmotic fragility test).

Principle: It is based on the limit of hypotonicity which the red blood cells can withstand.

Method: 2 ml of 0.36% buffered saline solution is taken, 0.02 ml of patient's blood is added to it and allowed to stand for 20 minutes.

After 20 minutes reading is taken on a NESTROF stand on which thin black line is marked.

Interpretation: If the line is visible through the solution the test is taken as negative and if the line is not visible, the test is positive.

In β thalassemia trait cases, black line is not clearly visible since microcytic hypochromic red cells of thalassemia trait are more resistant to lysis than normal normocytic normochromic red cells.

Limitations: other conditions which give positive result are:

- Iron deficiency anemia
- Hb E thalassemia
- Hb D thalassemia

NESTROF has sensitivity ranging from 94-99%.

NESTROF has been recommended for the mass screening due to its low cost, simplicity and high negative predictive value.

Combination of NESTROF and red cell indices increases the sensitivity and negative predictive value to almost 100%.

The finding of any abnormality (low MCV, low MCH, abnormal hemoglobin electrophoresis) requires screening of the partner.

Q.36. How will you proceed if screening tests are positive?

Ans: Raised HbA_2 level is the gold standard for the diagnosis of thalassemic trait. The definitive test for β thalassemia status is HbA2 of >3.5%.

Next step is hemoglobin electrophoresis or HPLC (High performance liquid chromatography) for the quantification of HbA_2 and HbF.

Hemoglobin Typing

HbA (96-99%) + HbA_2 (2-3.5%), MCV normal	Normal
HbA (92-96%) + HbA_2 (>3.5%), MCV < 80fl	β-thal trait
HbA (96-99%) + HbA_2 (<3.5%), MCV < 80 fL	Iron deficiency anemia
HbA (0-0.4%/2.1-10.6%), HbA_2 (4-10%), HbF (>90%)	Thalassemia major (β^0/β^+).

Case: Mrs Y 24 yr old G2P1L0 presented at 8 weeks of gestation

O/H: She had mild anemia during the pregnancy. Previous child had history of repeated blood transfusions with delayed milestones and died at 5 year of age because of heart failure.
Past history: No history of blood transfusions in the woman.

Q.37. What is your provisional diagnosis?

Ans: Couple may be a thalassemia carrier

Q.38. How will you confirm the diagnosis?

Ans: The carrier status of the couple is confirmed by performing HPLC on both the partners.

Mr. X, 29 years

Clinical Pathology LNH
B-THAL Short Program
REPORT 23-3-10

ANALYTE ID	%
F	5.5
P_2	4.0
P_3	3.6
A_0	79.9
A_2	5.6

Mrs. X, 25 years

ANALYTE ID	%
F	0.0
P_2	4.7
P_3	3.6
A_0	85.7
A_2	6.3
Unknown I	0.3

In this case, the HbA2 of both the partners was more than 3.5% and hence diagnosed as β-thalassemia traits.

Q.39. What is the risk of transmission to the fetus in this couple ?

Ans: Since both the partners are found to be carriers, they should be referred for genetic counseling.

It is single gene disorder and has autosomal recessive pattern of inheritance. Since both parents are carrier there are 25% chances for thalassemia major, 50% chances for thalassemia trait and 25% chances that baby will be normal.[47]

To offer the prenatal diagnosis to the couple it is essential to characterize the DNA mutations of the parent.[48] The β thalassemias are extremely heterozygous at the gene level, more than 200 mutations have been described from different parts of the world. The mutations are distributed geographically so that for a given high risk population, there are only 4 to 10 dominant mutations. Therefore, the general approach to the molecular diagnosis of β thalassemia is to identify and test for the region specific mutations based on the patient's ethnic background. This approach identifies the mutation in more than 90% of the cases. If the mutation is not identified, screening for the broader range of mutations is performed.

Studies conducted in India have identified about 28 mutations in Indian population. Generally, when both the partners are carriers, their DNA is studied for 5 common and 12 rare mutations. Prenatal diagnosis is offered if mutations are identified.[48]

Case: The couple was desirous of prenatal diagnosis and the mutations in both the partners were identified

Q.40. How will you carry out prenatal diagnosis in this couple?

Ans: Once the carrier status of the couple is confirmed and the DNA mutations of the couple have been identified, the next step is to offer prenatal diagnosis and selective abortion of fetuses affected with thalassemia. In this couple, prenatal diagnosis can be accomplished by chorionic villi sampling between 11-14 weeks of pregnancy. CVS is preferred as the results of prenatal diagnosis are available early in pregnancy. Usual reporting time is about one week.

Q.41. What are the various methods of prenatal diagnosis?

Ans: Prenatal diagnosis of hemoglobinopathies is best accomplished by DNA analysis of cultured amniocytes or chorionic villi by amniocentesis or chorionic villous sampling (CVS).

Early and specific diagnosis by molecular methods has almost completely replaced cordocentesis. Cordocentesis is only performed for the following indications:

- pregnant patients who report late,
- CVS is unconclusive,[49]
- DNA diagnostic facilities are not available
- One or both mutations are unidentified or molecular markers for linkage are uninformative.[50]

If the test shows that the baby is affected, the couple is counseled regarding the natural history of the disorder, prospects for treatment and cure and their risk. Termination of pregnancy can be offered upto 20 weeks of gestation.

The role of the genetic counselor and the obstetrician in these cases is extremely important. Even at this stage decision may be taken by the couple to continue the pregnancy accepting the life long treatment of the affected child.

For some couples preimplantation genetic diagnosis in combination with in vitro fertilization may be a desirable option to avoid termination of an affected pregnancy.[51]

Case: On prenatal diagnosis the fetus is diagnosed to be β thalassemia carrier.

Q.42. The couple continues the pregnancy, how will you manage the pregnancy?

Ans: β thalassemia minor is well tolerated pregnancy. Pregnancy outcome and obstetric complications do not differ from general population.

- Periconceptional folic acid supplementation should be given as the risk of fetal neural tube defects may be increased in pregnant woman who are thalassemia carriers, possibly because of relative folic acid deficiency secondary to increased erythropoiesis. The optimum dosage of folate has not been determined, however, high dose supplementation of at least 4 mg daily should be considered based on benefits in other populations who are at higher risk for neural tube defects.[52]
- Iron supplementation should be given and concomitant iron deficiency anemia should be diagnosed (S. Ferritin levels, S iron, total iron binding capacity) and treated.[50] In absence of documented iron deficiency anemia, replacement beyond prophylactic doses of iron is not indicated.[51] Parental iron therapy is contraindicated as it causes iron overload.
- Fetal growth and well being should be followed. Women with β thalassemia minor are found to have significantly higher rate of intrauterine growth restriction and oligohydramnios than non-thalassemic females.[51]

Q.43. How will you manage pregnant woman with β thalassemia major or thalassemia intermedia?

Ans: Until recently, pregnancy in females with β thalassemia major was extremely rare. However, with the introduction of hypertransfusion and iron chelation therapy several reports have been documented with favorable pregnancy outcome in female with β thalassemia major. Pregnancy should be managed by interdisciplinary team who is familiar with high-risk pregnancy and care of patients with thalassemia.

- Periconceptional folic acid supplementation should be given.
- Baseline cardiac, hepatic and endocrine evaluation is recommended at initial visit and should be repeated at second and third trimester.
- S. ferritin levels and blood counts should be followed regularly.
- Hemoglobin levels should be maintained at or near 10 gm/dl with transfusions.
- Fetal growth and well being should be followed closely because of increased risk of intrauterine growth restrictions.
- Mode of delivery should be individualized with cesarean section reserved for obstetrics indications.

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2 Recurrent Pregnancy Loss

Miscarriage in the general reproductive population is a frequent occurrence with nearly 30% to 50% of all conceptions and 15% of all clinically recognized pregnancies resulting in pregnancy failure.[1-3]

Recurrent pregnancy loss (RPL), also referred to as recurrent miscarriage or habitual abortion, is historically defined as 3 consecutive pregnancy losses prior to 20 weeks from the last menstrual period; **however, newer guidelines from the American Society of Reproductive Medicine have defined RPL as the loss of two or more pregnancies.[4]**

Epidemiologic studies have revealed that 1% to 2% of women experience recurrent pregnancy loss.[5] Because the incidence of recurrent miscarriage is higher than that expected by chance alone (0.34%),[6,7] a proportion of couples with recurrent miscarriage have a persistent underlying cause for their pregnancy losses.

The risk of miscarriage in subsequent pregnancies is 30% after 2 losses, compared with 33% after 3 losses among patients without a history of a live birth.[8] Hence, there is a role for evaluation after just 2 losses in patients with no prior live birth. An earlier evaluation is recommended if fetal cardiac activity was documented prior to a loss, the age of the female partner is more than 35 years, or there is a history of infertility.

CASE 1

A 36-year-old P0+1+3+1 presents with a history of one preterm birth of a healthy unaffected female infant at 33 weeks period of gestation followed by three consecutive miscarriages at 8-10 weeks period of gestation (POG) in the past 4 years. She has unremarkable medical, surgical, and gynecological histories. All three miscarriages required curettage. The products of conception of her last loss were karyotyped and revealed a normal karyotype, 46 XY.

Important points in history

- Age of the patient and her partner. The risk of miscarriage is highest when the woman is 35 years or older and the man is 40 years or older.[9]
- A detailed history of her prior pregnancies.
  - Antepartum period in the first pregnancy
  - Any history of high blood pressure record. If so, at what gestation and whether required any treatment. Associated complications.
  - Any special investigations ordered and was treatment instituted based on the results.
  - Fetal growth restriction. If so,when was it diagnosed and how was the pregnancy monitored after that.
  - Reason for preterm birth, spontaneous or induced. If induced, reason for induction. If cesarean birth, indication for the same. It

is advisable to ask for the previous discharge ticket.
  - Postpartum period—any specific treatment or complication
- A descriptive sequence of all previous pregnancies including the estimated gestational age of each miscarriage, on the basis of ultrasound, embryopathology and serum hCG results. Gestational age may not be as informative as fetal death occurs several weeks before symptoms appear.
- Previous cytogenetic results to determine any numeric chromosome abnormality.

Menstrual History
- Length and regularity of the menstrual cycle may indicate oligo-ovulation, PCOS, and dyssynchronous fertilization. Polycystic ovary syndrome with insulin resistance has higher rate of miscarriage.
- History suggestive of thyroid dysfunction like lassitude, weakness, extreme changes in weight, diet, hyperactivity. ***Untreated hypothyroidism*** may increase the risk of miscarriage.
- How long the couple has been attempting conception as difficulty in achieving conception may in some instances indicate subclinical (preimplantation) pregnancy loss.[10]

- **Family History**
  - History of thrombosis would indicate inherited thrombophilias
  - Recurrent pregnancy loss
  - Stillbirths
  - Birth defects
- History of exposure to smoking, alcohol, and caffeine.[11-13] The risk of caffeine, alcohol, and nicotine intake with RPL is even weaker than their association with sporadic loss.
- History of occupational and environmental exposures to organic solvents, medications, ionizing radiation, and toxins as they could possibly have a role in RPL but may be confounded by alternative or additional environmental exposures.[8,14]
- History of any surgical procedure on the cervix which can lead to pregnancy losses (mostly mid-trimester) like conisation, forcible dilatation which can cause cervical tear and also weakness in future pregnancies.

Examination

General physical examination

A complete examination is a must so as to identify any previously undiagnosed underlying systemic disorder. A review of systems should include assessing for features of rheumatic disease.
- General built and nutritional status (Body habitus).
- Height and weight
- BMI (kg/M^2) may be abnormal in diabetics and in thyroid dysfunction. Poorly controlled diabetics have an increased risk of miscarriage.[15]
- Thyroid swelling
- Evidence of galactorrhea as hyperprolactinemia may be associated with recurrent pregnancy loss through the hypothalamic-pituitary-ovarian axis but the supporting evidence is insufficient.[16]
- Skin texture
- Clinical features of hyperandrogenemia
- Pedal edema

Pelvic examination
- A per speculum and a bimanual pelvic examination will identify local infection, uterine size and shape and any gross uterine anomaly.
- A per speculum will also identify a torn cervix, or a grossly short cervix.

Q.1. What investigations will you offer this patient?

Ans:
- Parental karyotype
- Pelvic ultrasound for intrauterine cavitary assessment
- Luteal phase endometrial biopsy
- Screening for antiphospholipid antibodies.

Q.2. What are the different etiological factors contributing to RPL?

Ans:

- Genetic 2%-5%
- Anatomic 10%-15%
- Autoimmune 20%
- Infections 0.5%-5%
- Endocrine 17%-20%
- Unexplained 40%-50%
  (including non-APS thrombophilias)

Q.3. What are the different tests available for diagnostic evaluation based on the causative factors and what percent of each will have an abnormal result?

Ans: Shown in Table 2.1.

Q.4. Is glucose tolerance test and thyroid function tests done in all patients of recurrent pregnancy loss?

Ans: Routine screening for occult diabetes and thyroid disease with oral glucose tolerance test and thyroid function tests in asymptomatic women presenting with recurrent miscarriage is uninformative.[18] Also, routine screening for thyroid antibodies in women with recurrent miscarriage is not recommended.[18]

Women with diabetes who have high hemoglobin A1c levels in the first trimester are at risk of miscarriage and fetal malformation. However, it is not so in cases of well controlled diabetes mellitus and, treated thyroid disorder.[15]

The prevalence of diabetes mellitus and thyroid dysfunction in women who suffer recurrent miscarriage is similar to that expected in the general population.[19]

The above patient underwent immunologic tests, parental karyotype, a pelvic ultrasound and an endometrial biopsy. The anticardiolipin IgG was

Table 2.1: Standard evaluation of recurrent early pregnancy loss[17]

Factor	*Diagnostic evaluation*	*Abnormal result*
Immunologic	Lupus Anticoagulant Anticardiolipin IgG/IgM β_2-glycoprotein-1 IgG/IgM Phosphatidylserine IgG/IgM Embryotoxic assay Immunophenotyping	15% to 20%
Parental structural chromosome rearrangement	Cytogenetic analysis of both partners	2.5% to 8%
Endocrinologic	Endometrial biopsy or midluteal progesterone Thyroid-stimulating hormone, Prolactin Fasting insulin and glucose	8% to 12%
Anatomic	Hysteroscopy, hysterosalpingogram or sonohysterography, 2D or 3D ultrasound, Magnetic Resonance Imaging	15% to 20%
Thrombophilic	Factor V Leiden Prothrombin gene Fasting homocysteine Antithrombin activity? Protein C activity? Protein S activity?	8% to 12%
Microbiologic	Endometrial biopsy Cervical/vaginal cultures?	8% to 10%
Psychologic	Mental status evaluation	
Iatrogenic	Review tobacco, alcohol and caffeine use Review exposure to toxins, chemicals	5%

50GPL and IgM was 45GPL. Rest all of the test results were normal.

Q.5. What is the patient suffering from and how will you manage her further?

Ans: The patient is most probably a case of primary Antiphospholipid Antibody Syndrome (APS) but the anticardiolipin antibody titers should be positive in medium or high titers repeated 12 weeks apart.

The antibody titers need to be estimated in the non-pregnant state for a definite diagnosis.

APS in patients with chronic inflammatory diseases, such as systemic lupus erythematosus is referred to as "secondary APS". In contrast, "primary APS" affects patients with no identifiable underlying systemic connective tissue disease.

The patient will require low-dose aspirin from conception till 36 weeks and, heparin since conception till delivery.

A recent meta-analysis concluded that the combination of unfractionated heparin and aspirin confers a significant benefit in live births in APS. However, the efficacy of low molecular weight heparin plus aspirin remains unproven.[20]

Q.6. What are antiphospholipid antibodies?

Ans: Antiphospholipid antibodies are a family of heterogenous antibodies that react with epitopes on proteins that are complexed with negatively charged phospholipids.

Q.7. What is the mechanism of pregnancy loss in patients with APS?

Ans: Placental damage resulting from thrombosis is thought to be the end result of autoimmunity to phospholipids.

Originally, antiphospholipid antibodies were reported in patients with slow, progressive thrombosis and infarction in the placenta;[21] however this finding is not seen on the histopathology of the first trimester deciduae. In recurrent preembryonic or embryonic miscarriage inhibition of cytotrophoblast fusion, invasion, and differentiation has been noted.[22-24]

Q.8. What are the diagnostic criteria for APS?

Ans: The antiphospholipid syndrome is strictly defined, on the basis of both clinical and laboratory criteria.

Diagnosis of the Antiphospholipids Syndrome[25]

Clinical Criteria

- One or more episodes of arterial, venous, or small vessel thrombosis.
- One or more unexplained pregnancy loss of a morphologically normal fetus of atleast 10 weeks of gestation.
- One or more premature births of a morphologically normal newborn at or before the 34th week of gestation because of severe pregnancy induced hypertension or severe placental insufficiency.
- Three or more unexplained consecutive miscarriages before 10 weeks of gestation, with anatomic, hormonal, and parental structural genetic factors excluded.

Laboratory Criteria: The same antibody must be positive twice when drawn at least 12 weeks apart.

- Anticardiolipin IgG and/or IgM, present in medium or high titers (>40 GPL or MPL).
- Anti β_2-glycoprotein-1 IgG and/or IgM, present in titer >99th percentile.
- Lupus anticoagulant, detected according to the guidelines of the International Society on Thrombosis and Hemostasis.

Patients should have at least one clinical and one laboratory criteria.

Q.9. How should this patient be managed in future pregnancy as she is very keen on further child bearing?

Ans: Once the diagnosis is confirmed, whenever the patient conceives she can be started on

low-dose aspirin (LDA, 81-100 mg/day) plus prophylactic heparin as she is an otherwise healthy woman (i.e. absence of a systemic autoimmune disease such as systemic lupus erythematosus, or a history of thrombosis).

LDA should be started before conception or with a positive pregnancy test.

Heparin should be started with a positive pregnancy test.[26] Heparin is a large complex of molecules that do not cross the placenta and, as such, is regarded safe during pregnancy.

In case the patient presents after conceiving, she should be immediately started on LDA 81mg/day and heparin.

Q.10. Is treatment with LDA and heparin mandatory in APS?

Ans: Yes.

Combination therapy with aspirin and heparin may reduce pregnancy loss in women with antiphospholipid antibodies by 54%.[27]

In untreated pregnancies with APS the live birth rate may be as low as 10%.[28]

The American College of Obstetricians and Gynecologists (2005a) recommends low-dose aspirin—81mg orally per day, alongwith unfractionated heparin-5000 units subcutaneously, twice daily.

Q.11. In what other conditions is antithrombotic therapy effective?

Ans: Apart from APS antithrombotic therapy is recommended in inherited thrombophilias. (discussed in detail in a separate case discussion)

Q.12. Is there any role of Intravenous Immunoglobulin (IVIG) and steroids in the treatment of APS?

Ans: Heparin is more effective than intravenous immunoglobulin as the first line treatment of antiphospholipid syndrome.[29]

However, in a few studies the role of Intravenous Immunoglobulin has been documented and found to be useful in secondary miscarriage in women with recurrent early pregnancy losses following one previously successful birth.[30] But till date no definite guidelines exist about the beneficial role and use of IVIG in recurrent pregnancy loss.

Steroids are associated with a lower live birth rate but significantly increase maternal and fetal complications.[31,32] Also, they should not be used concomitantly with heparin, because of the potentiation of osteoporosis with these agents but, the risk appears lower with low-molecular weight heparin.

Q.13. Apart from APS does this patient have any other risk factor for RPL?

Ans: The patient is 36 years of age.

Maternal age is a well known risk factor for sporadic miscarriage and is a likely risk factor for RPL as well. Women over the age of 35 years ("advanced maternal age" AMA) have an increased rate of meiotic errors in oocyte development leading to increased embryonic aneuploidy.

The reported miscarriage rate among women under 35 years of age is 14% compared with 40% for women over 40 years old.[33]

Hence, this patient should be counseled for and offered invasive testing for aneuploidies.

Q.14. The above patient had no significant medical history and general examination was unremarkable. Should antinuclear antibody levels be ascertained?

Ans: Routine testing for an antinuclear antibody (ANA), in the absence of rhematic autoimmune disease, is not indicated. Steroid therapy in recurrent pregnancy loss with an elevated ANA without clinical criteria, increases maternal and fetal complications without improving the live birth rate.

Q.15. How should a patient with secondary APS, (with SLE) be counseled with respect to pregnancy outcome and impact of pregnancy on their disease?

Ans: The prevalence of antiphospholipid antibodies in patients with SLE is ~37% and are the most sensitive indicator of poor obstetrical outcomes.[34,35] Such women have a higher rate of pregnancy losses in all three trimesters.

Underlying renal disease and prepregnancy lupus flares are associated with poor pregnancy outcomes.[36,37]

Q.16. What are the other obstetric risks associated in the antenatal period with APS?

Ans:

- Preterm labor
- Prematurely ruptured membranes
- Fetal growth restriction due to placental insufficiency
- Preeclampsia, Eclampsia
- Placental abruption

Inspite of treatment with aspirin and heparin these pregnancies are at high risk for complications necessitating careful antenatal surveillance.

Q.17. Will progesterone supplementation in early pregnancy help support the pregnancy in this patient?

Ans: No, the definitive treatment in APS is LDA plus heparin.

There is insufficient evidence to evaluate the effect of progesterone supplementation in pregnancy to prevent miscarriage in early to mid-pregnancy. However, there might be some benefit in women with recurrent miscarriage.

Treatment for these women may be warranted given the reduced rates of miscarriage in the treatment group and the finding of no statistically significant difference between treatment and control groups in rates of adverse effects suffered by either mother or baby in the available evidence.[38]

Progestogen supplementation is recommended only in either unexplained losses or where luteal phase deficiency exists.

Q.18. How is luteal phase deficiency (LPD) defined and diagnosed?

Ans: Luteal phase deficiency has been historically defined as a lag of more than 2 days in the histologic development of the endometrium vis a vis the day of the cycle.

Midluteal progesterone of <10 ng/ml is also taken to be diagnostic. Also, a sum of three random serum progesterone measurements less than 30 ng/ml measured during the luteal phase is suggestive of luteal phase deficiency.

Q.19. Is ascertaining progesterone levels necessary in determining luteal phase insufficiency?

Ans: No, as there is considerable overlap between progesterone levels and endometrial biopsy specimens. Biopsy specimens can be normal despite low levels of progesterone in peripheral blood. Considerable overlap also exists between normal and abnormal levels in women having successful pregnancies.

Q.20. Had this patient had the results of all the tests normal, would treatment with aspirin, or aspirin plus heparin be of any help presuming the losses to be unexplained?

Ans: No, Neither aspirin combined with LMWH (nadroparin) nor aspirin alone improved the live-birth rate, as compared with placebo, among women with unexplained recurrent miscarriage.[39]

In another study there was no reduction in pregnancy loss rate with antithrombotic intervention in pregnant women with 2 or more consecutive previous pregnancy losses with no identifiable cause.[40]

Q.21. What if this patient has a parental balanced structural chromosome rearrangement and all the other investigations are normal? How should she be counseled?

Ans: Of the two partners, women are more likely then men to carry most types of chromosomal rearrangements.[41] The ratio of female-to-male abnormalities was approximately 2:1.

The most common types of parental chromosomal abnormalities are balanced translocations either reciprocal (50%), or Robertsonian (24%).

Other abnormalities are: X chromosome mosaicism such as 47, XXY—Klinefelter syndrome (12%); and inversions.[42]

Although carriers of a balanced translocation are phenotypically normal, their pregnancies are at an increased risk of miscarriages or birth of a baby with multiple congenital malformations and mental handicaps due to unbalanced chromosomal rearrangements.

This warrants genetic counseling offering prognosis for future pregnancies, prenatal diagnostic options, and the opportunity to perform familial chromosomal studies.

Q.22. What are the various reproductive options in such a patient?

Ans:

- Proceed to a further natural pregnancy with or without, prenatal diagnostic tests, chorionic villous sampling, or amniocentesis.
- Gamete donation
- Adoption
- Preimplantation genetic diagnosis in translocation carriers and in unexplained RPL.

There is a 40% to 50% chance of a healthy live birth in future untreated pregnancies after natural conception.

Q.23. What is the role of alloimmune factors in RPL?

Ans: Normal pregnancy requires formation of blocking factors preventing paternally derived foreign fetal antigens. If the female shares the Human Leukocyte Antigens (HLA) with the male partner she fails to produce the blocking factors. The role of endometrial immunity in recurrent early pregnancy loss is currently under investigation.

Previously, sharing of HLA between partners was thought to be associated with recurrent pregnancy loss. A large RCT, however, did not confirm this association.[43]

Immunotherapy, including paternal cell immunization, third-party donor leucocytes, trophoblast membranes and intravenous immunoglobulin (IVIG), in women with previous unexplained recurrent miscarriage does not improve the live birth rate.

Immunotherapy is expensive and has serious adverse effects including transfusion reaction, anaphylactic shock and infections.

Hence, it should not be offered to women with unexplained recurrent miscarriage and routine tests for HLA type and anti-paternal cytotoxic antibody should be abandoned.[18]

CASE 2

A 28-year-old G4P0+1+2+0 presents at 10 weeks pregnancy with history of one preterm birth at 28 weeks period of gestation followed by two consecutive losses at 18-20 weeks gestation. She has unremarkable medical, surgical, and gynecological histories.

Q.24. • What is the most likely cause of these losses?
• What history will point to the likely cause?
• How should she be managed in this pregnancy?

Ans:

- The most likely cause is cervical weakness.
- There is no history of bleeding, pain or clear signs of labor preceeding the miscarriage. The late miscarriage is preceded by spontaneous rupture of membranes or painless cervical dilatation.

- The losses occur at progressively earlier gestations.
- A transvaginal ultrasound assessment of the cervical length and shape is called for.
- ***The three ultrasound signs*** that suggest cervical incompetence are shortening of the endocervical canal, funneling of the internal os, and sacculation or prolapse of the membranes into the cervix, either spontaneously or on applying fundal pressure.

A short cervix (< 25 mm) is the best independent predictor of spontaneous birth before 34 weeks'gestation.

- *The cervical length on the second-trimester ultrasound was 20 mm hence, a cervical cerclage is offered at ~16 weeks, after a fetal anomaly scan. The stitch can be put either vaginally or abdominally. This is* ***therapeutic cerclage****, applied when the ultrasound reveals a short cervix.*
- *Preoperatively, a long-acting progesterone generally, 17 Hydroxy Progesterone Caproate preparation is given for uterine quiescence and can be repeated.* There are, however, limited data supporting the utilization of supplemental progesterone after cerclage.
- *The stitch should be removed at 37-38 weeks pregnancy or whenever the patient goes into labor.*
- *A* ***prophylactic cerclage*** *is applied before the cervix is dilated and* ***emergency****, when the cervix has started to shorten and dilate with fetal membranes bulging at times.*

Q.25. Who are the candidates for cervical cerclage?

Ans: The current literature suggests that women with a history of at least three second-trimester or at least three preterm births or those with a history of prematurity who have < 25 mm cervical length on ultrasound will benefit from cerclage by preventing preterm delivery.[44]

The use of a cervical stitch should not be offered to women at low or medium risk of mid trimester loss.[44]

Transabdominal or laparoscopic cerclage seems to be a promising alternative where transvaginal cerclage has failed in the previous pregnancy.[44]

Q.26. Apart from cervical incompetence what are the other anatomic factors implicated in RPL and prognosis?

Ans: *Acquired*

Intrauterine synechiae—Asherman syndrome, leiomyomas (intramural of >5 cm and submucosal fibroids of any size), short cervix because of conisation, amputation, cervical weakness owing to forcible dilatation of the internal os during some procedure.

Developmental defects

Septate, unicornuate and bicornuate uterus as well as uterine didelphys.

Anatomic abnormalities are believed to cause miscarriage by interrupting the vasculature of the endometrium, prompting abnormal and inadequate placentation.

Near normal pregnancy outcomes with term delivery rates of ~75% and live birth rates of ~85% are seen after successful hysteroscopic septum resection.[45]

Myomectomy is to be considered in case of intramural fibroids of > 5 cm and submucosal fibroids of any size improving live birth rates from 57 to 93%.[46]

CASE 3

A 32-year-old P0+0+4+0 with all the four mid trimester losses at ~20 weeks of gestation is being evaluated. On bimanual pelvic examination the fundus of the uterus appeared broad, although the per speculum examination was unremarkable. All other investigations for recurrent pregnancy loss were normal, except that the pelvic ultrasound

had a suspicion of two endometrial cavities. Outline the plan of management.

- Hysteroscopic evaluation of the endometrial cavity revealed a uterine septum.
- Hysteroscopic septal resection in the post-menstrual phase.
- Post resection, start on combined oral contraceptive pills for 6-months which in addition to contraception, will help in tissue healing.
- Patient can attempt conception after 6-months with ~85% live birth rates.
- Monitor the pregnancy closely.
- Cervical studies.
- No indication for cerclage. Although she has had four second-trimester miscarriages the causative factor has been corrected. The patient should undergo a transvaginal scan for the length of the cervix ~15-16 weeks and if found to be < 25 mm (associated factor) a stitch can be applied ~18 weeks after an anomaly scan.

Q.27. Are any infections responsible for RPL?

Ans: Those particular infections speculated to play a role in RPL include *Ureaplasma, Chlamydia trachomatis, L monocytogenes, and Herpes simplex virus*.[47]

The most pertinent risk for RPL secondary to infection is chronic infection in an immunocompromised patient.

Evaluation and therapy should be individualized. Usually investigations for chronic infections is warranted only in immunocompromised patient with RPL and with a history of sexually transmitted infections.

Routine TORCH screening should be abandoned.[47,48]

Q.28. Inspite of extensive investigations if no causative factor is found in a patient with RPL how is the patient counseled and managed further?

Ans: The patient is labeled as "UNEXPLAINED" accounting for nearly 40%-50% of cases of RPL.

These patients should be encouraged to continue attempts at pregnancy, because prospective studies show that these women, even with advanced maternal age, have a high rate of live births with their subsequent pregnancies.[49]

The most effective therapy for patients with unexplained RPL is most simple: Antenatal counseling and psychological support. These measures have been shown to have subsequent pregnancy success rates of 86% as compared to 33% when no additional antenatal care was given.[50]

General advice about quitting smoking, avoiding excess alcohol, and caffeine intake and weight loss in obese women, and dietary balance is important. Folic acid (400 µg/day) for atleast 2 months prior to attempting conception is indicated to prevent neural tube defects.

Q.29. How should the patients of recurrent pregnancy loss be monitored in the postconception period?

Ans:

First Trimester

- Close monitoring, psychological support and reassurance in the first trimester to allay anxiety.
- Confirm intrauterine pregnancy. Recurrent pregnancy loss appears to be a risk factor for both ectopic pregnancy and complete molar gestation.[51]
- Continue folic acid.
- Start progesterone (Unexplained RPL).
- Treatment with antithrombotics depending on the etiology of RPL.
- Assessment of fetal karyotype for all women as they are more likely to have aneuploid pregnancies.[52]
- Glucose Challenge Test (GCT) with 50 Gm glucose or Glucose Tolerance Test (GTT) as Indians belong to the high risk group for developing diabetes. May be helpful for women with PCOS because of the increased risk of gestational diabetes.

- Ultrasound examination is recommended every two weeks and continued till that time in gestation when the woman had lost her pegnancies.[53]

Second Trimester

- When cervical incompetence is suspected Transvaginal assessment of the cervix is done. It is an objective means of assessing the cervical length and shape for predicting preterm birth in high-risk population.[54]
- Prophylactic cervical cerclage may be applied at 13 to 16 weeks in women at increased risk for second trimester miscarriage including those with three or more second-trimester miscarriages or spontaneous preterm births without bleeding or clear signs of labor preceeding the miscarriage. An ultrasound scan to assess fetal viability and exclude apparent fetal anomalies should be offered to the woman. The stitch can be removed at 37 to 38 weeks or earlier if the patient goes into labor.
- The stitch can also be applied in a high-risk patient with a singleton pregnancy who has a short cervix in the second-trimester.
- A second trimester anomaly scan at 18-20 weeks gestation.
- Repeat (GCT) with 50 Gm glucose or Glucose Tolerance Test (GTT) at 24-28 weeks if previous test results were normal.
- Uterine artery Doppler ultrasonography at 22 to 24 weeks may be useful in predicting preeclampsia and intrauterine growth restriction in women with APS.[55]

Third Trimester

Due to the high risk for intrauterine growth restriction in patients with RPL especially those with APS and thrombophilias:

- Serial growth scans
- Umbilical artery Doppler.

Delivery and Puerperium

- If no associated obstetric complication no indication for increased intervention before 40 weeks but the pregnancy should not be allowed to go beyond the expected date of delivery. Labor can be induced at term electively.
- Mode of delivery to be decided in consultation with the patient. Recurrent pregnancy loss per se is not an indication for cesarean delivery. Cesarean section to be done for any associated obstetric or medical complication. Patients may request for elective cesarean delivery.
- Aspirin to be stopped at 36 weeks.
- Anesthesia to be planned accordingly in patients on heparin (LMWH/UFH) keeping in mind the half-life of the preparation used.
- Postpartum thromboprophylaxis may be indicated in women with certain types of inherited thrombophilias.
- In women with APS and no additional thrombotic risk factors, postnatal thromboprophylaxis is not recommended.

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Shakun Tyagi

3 Thrombophilia in Pregnancy

Thrombophilias are inherited or acquired conditions which predispose an individual to thromboembolism. Severe pregnancy complications such as severe pre-eclampsia, intrauterine growth retardation, abruption placentae and stillbirth have been shown to be associated with thrombophilia. Recurrent miscarriage has also been associated with thrombophilia.

CASE

A 26-year-old lady, Mrs T, G4P1A2L0 presents to antenatal clinic when 5 days overdue for confirmation of pregnancy. On detailed history, it was revealed that patient had previous 2 intrauterine fetal demise at 10 weeks and 12 weeks detected at around 14 weeks period of gestation followed by dilatation and evacuation. In the third pregnancy, patient had severe placental abruption at 31 weeks, 1.4 kg male baby was delivered by cesarean section. The baby had early neonatal death due to complications of prematurity and hypoxia. Anti-cardiolipin antibody test, which was performed one year back during interpregnancy period, was found to be positive.

Q.1. What further history needs to be taken?

Ans:

- Past history suggestive of thromboembolic episode in the self will point towards thrombophilia in the patient. 50% of patients with past history of thromboembolic episode have underlying thrombophilia.
- Detailed obstetric history is required to elicit the history which is suggestive of thrombophilia. All previous available clinical records, i.e. OPD records, discharge slips, USG scans, histopathological examination of products of conception, karyotyping reports and autopsy records if available should be evaluated. Questions should be asked to specifically know the period of gestation of onset of adverse fetal and maternal outcomes such as intrauterine growth restriction, fetal demise or early onset pre-eclampsia. Mode of delivery in previous pregnancy should be asked. In case of induction of labor or LSCS the indication for same should be clarified.
- Family history of thromboembolic episode should be taken to rule out inherited thrombophilias.
- History should also try to exclude other systemic complications related to Antiphospholipid Syndrome (APS) like endocarditis, associated SLE.

Q.2. What are the specific signs to look on examination?

Ans: The specific signs will depend on previous history of complications related to antiphospholipid Syndrome, i.e. venous, arterial and microvascular thrombosis; livedo reticularis and associated disorders like SLE or other autoimmune

disorders which might be present along with APS.

Q.3. How the diagnosis of APS will be confirmed?

Ans:

- Definite Antiphosphoplipid Syndrome may be diagnosed if at least one of the clinical criteria and at least one of the laboratory criteria are met.

Clinical criteria

Vascular thrombosis-

- Arterial
- Venous
- Superficial/small vein thrombosis.

Pregnancy related morbidity

- One or more unexplained death of a morphologically normal fetus at or beyond 10 weeks of gestation, normal fetal morphology documented by ultrasound or by direct examination of the fetus.
- One or more premature birth of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe pre-eclampsia or recognized features of placental insufficiency such as:
  i. Abnormal or non-reassuring fetal surveillance tests, e.g. a nonreactive nonstress test.
  ii. Abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, e.g. absent end diastolic flow.
  iii. Oligohydramnios—AFI< 5
  iv. Post natal weight < than 10th percentile for the age of gestation.
- Three or more consecutive spontaneous abortions before tenth week of gestation with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria

- Anticardiolipin antibodies IgG and/or IgM in blood present in medium or high titre, on two or more occasions, at least 6 weeks apart.
- Anti-β_2-glycoprotein I antibodies IgG and/or IgM in blood present in medium or high titre, on two or more occasions, at least 6 weeks apart.
- Lupus Anticoagulant (LA) Antibodies- LA present in plasma, on two or more occasions, at least 6 weeks apart, detected according to following guidelines:
  – Prolonged phospholipid dependent coagulation demonstrated on a screening test, for example, activated partial thromboplastin time, Kaolin clotting time, dilute Russel's viper venom time.
  – Failure to correct the prolonged coagulation time on the screening test by mixing with normal platelet poor plasma.
  – Shortening or correction of the prolonged coagulation time on screening test by the addition of excess phospholipid.
  – Exclusion of other coagulopathies, for example, factor VIIIc deficiency.

In this patient antiphospholipid antibody test was previously performed once only and that also one year back therefore it needs to be repeated before making the diagnosis.

Q.4. What other investigations should be performed in the above described patient, Mrs T?

Ans:

- **Confirmation of the pregnancy:** Following pervaginal examination pregnancy should be confirmed by a urine pregnancy test. A Transvaginal Sonography should be performed to confirm an intrauterine pregnancy, also whether the sac diameter corresponds to the period of

gestation and if fetal node is present, whether cardiac activity is there.
- **Routine antenatal investigations:** BG and Rh factor, Hb, PCV, STS, HIV after pretest counseling, HBsAg and urine routine and microscopy examination.
- Other investigations for recurrent pregnancy loss like Glucose Tolerance Test and Thyroid Stimulating Hormone should be done if the clinical findings are suggestive of Diabetes or Hypothyroidism.
- **Platelet count** – thrombocytopenia may be present along with APS.

Q.5. What is the possible differential diagnosis?

Ans: If tests for APLS come out to be negative when repeated, this patient needs to be investigated for inherited thrombophilias. It will include
- Polymerase chain reaction to detect prothrombin 20210A and MTHFR mutations.
- Activity assays for antithrombin, protein C, and Protein S (with consideration of the normally reduced protein S level in pregnancy).
- Fasting homocystein levels
- Thrombocythemia

Ideally the lab investigations for these disorders are best performed in the nonpregnant state when not on hormonal or anticoagulation therapy and more than six months of any acute thromboembolic episode.

Q.6. What are the indications of performing thrombophilia profile during pregnancy?

Ans: Thrombophilia testing is recommended if there is:
- Personal history of thrombosis.
- Prior early onset severe pre-eclampsia (<34 weeks gestation).
- Prior severe fetal growth restriction, severe placental insufficiency (oligohydramnios, abnormal Doppler velocimetry, abnormal fetal testing, abnormal placental histology).
- Family history of thrombosis.
- Family history of thrombophilia (especially AT-III deficiency).

Q.7. What are the physiologic changes during pregnancy that predispose to thromboembolism?

Ans: The physiologic changes in the clotting system during pregnancy are geared up towards reducing hemorrhage postabortal and in postpartum period but in turn lead to a hypercoagulable state.

Changes in clotting and fibrinolytic proteins as follows:
- Two to three fold increase in concentration of fibrinogen.
- 20 to100% increased factors VII, VIII, IX, X and XII.
- Upto 55% decline in protein S and C leading to increase in resistance to protein C. This decline has been found to be exacerbated by cesarean delivery and infection.
- 3 to 4 fold increase in type I Plasminogen Activator Inhibitor (PAI) as well as type II PAI.

Mechanical factors
- Venous stasis in lower extremities due to compression of inferior vena cava and pelvic veins by the enlarging uterus and hormone – mediated increase in deep vein capacitance secondary to increased circulating levels of estrogens and local production of nitric oxide.
- Vascular damage – tissue trauma during vaginal delivery and cesarean section.

Q.8. What is the prevalence of thrombophilias in patients with adverse pregnancy outcome in India?

Ans: In Indian studies, thrombophilia is an important contributing factor for both early and late pregnancy losses which is in line with other western studies.[1] Approximately two-third of all the cases of unexplained fetal losses could be explained by acquired or heritable thrombophilia or both. A clear

association has been established between fetal loss and antiphospholipid antibody syndromes and antithrombin deficiency, and combined defects. However, reports on the prevalence of inherited prothrombotic defects such as factor V Leiden mutation and methylene tetrahydrofolate reductase C677T polymorphism in fetal loss are contradictory.[2] Larger, well planned studies are lacking in this regard.

Q.9. What are the prevalence rates of thrombophilias in patients with VTE?

Ans: The prevalence rates of thrombophilias in patients with VTE is given in Table 3.1.

Table 3.1: Prevalence of inherited thrombophilias[3]

Thrombophilia	*General population*	*Patients with VTE*
Antithrombin, Protein C, Protein S deficiency	1%	7%
Factor V Leiden	Caucasians 4-7%	21%
	Non- Caucasians 0-1%	6%
Prothrombin 20210A	Caucasian 2-3%	6%
	Non- Caucasians 0-1%	
Elevated FVIII;c levels	11%	25%
Mild hyperhomocysteinemia	5%	10%

Q.10.What is the risk of thromboembolism during pregnancy with thrombophilia?

Ans: The risk of thromboembolism during pregnancy with thrombophilia is given in Table 3.2

Table 3.2: Risk for venous thromboembolism during pregnancy in women who have thrombophilia[4]

Thrombophilic defect	*Odds ratio for thromboembolism*
Factor V Leiden heterozygous	9.32
Factor V Leiden homozygous	34.40
Protein C deficiency	4.76
Protein S deficiency	3.19
Prothrombin 20210A heterozygous	6.80

Q.11. This patient did not report before planning the pregnancy. Had this patient come at pre-pregnancy, what counseling should be done in such patients?

Ans: At the time of pre-pregnancy counseling

- The levels of anticardiolipin antibodies should have been repeated.
- The various maternal and fetal complications should have been discussed with her.
- She should have been assessed for various long term complications of APLS by performing kidney function tests, platelet counts and Hemogram.
- The requirement for anticoagulation throughout pregnancy should be discussed along with the side effects of long term heparin therapy, i.e. heparin induced osteoporosis and heparin induced thrombocytopenia.

Q.12. What will be the antepartum management in this patient, Mrs T with APLS?

Ans:

- **Anticoagulation:**
  - For women with these pregnancy complications who test positive for APLAs and have no history of venous or arterial thrombosis, antepartum administration of prophylactic UFH or prophylactic LMWH combined with aspirin is recommended (Grade 1B).
  - Prophylactic LMWH: Deltaparin, 5000 units/day SC, Enoxaparin, 40 mg/d SC
  - Prophylactic UFH: SC 5000-10,000U 12 hrly, SC
  - Low dose aspirin (75mg OD) should be started as soon as pregnancy test is positive.
  - Heparin (Low molecular weight heparin or Unfractionated Heparin) should be started as soon as cardiac activity is found to be positive on sonography.
  - During first few weeks of starting Unfractionated Heparin careful watch must be kept

on Platelet count of the patient due to risk of immune mediated severe thrombocytopenia due to unfractionated heparin. The risk of immune mediated thrombocytopenia is much less with low molecular weight heparin as compared to unfractionated heparin.

- **Monitoring of anticoagulation:** No monitoring is required when low dose aspirin alone is given to the patient. When unfractionated heparin is prescribed, APTT should be monitored biweekly when starting the dose and it can be made weekly later on. Low molecular weight Heparin may need to be monitored with Anti-Xa activity at extremes of maternal weight (Anti-Xa level should be .6 to 1.0U/ml 4 to 6 hours after injection).
- Calcium supplementation and weight bearing exercises should be encouraged.
- All women with previous VTE or a thrombophilia should be encouraged to wear graduated compression stockings throughout their pregnancy and for 6–12 weeks after delivery. Good hydration and mobilization along with Compression Stockings reduce the chances of VTE during pregnancy.
- **Antenatal care:** Regular antenatal care and close maternal and fetal monitoring is required for detection of fetal growth restriction, hypertensive disorders of pregnancy and placental insufficiency. Umbilical Artery Doppler velocimetry is recommended at the age of viability. The NICU should be informed about severe growth restriction if it is present. Early transfer to a higher facility should be considered in case of nonavailability of good NICU facilities for the neonate. The mode of delivery should be decided according to obstetric considerations.

Q.13. What will be anticoagulation regimen in women with APLA and history of thrombotic event?

Ans: Recommended regimen in women with history of thromboembolic episode will be:

- Unfractionated heparin: 8-12 hrly adjusted dose SC according to aPTT, to keep the mid-interval (between two doses) aPTT 1.5 times the control mean.
- LMWH: Weight –adjusted (Enoxaaparin 1/mg/kg 12 hrly or Deltaparin 200 U/kg 12 hrly SC.

Q.14. What are the various obstetric and non-obstetric complications of APLS and other thrombophilias?

Ans: Obstetric Complications

- Gestational Hypertension/Pre-eclampsia: 30-50% of all patients with APLS suffer from Gestational Hypertension/Pre-eclampsia which might be early in onset.
- Intra Uterine Growth Restriction (IUGR) and preterm Birth: The rate of IUGR is almost 30% in patients with APLS. The preterm delivery rate ranges from 32-65% partly due to high rate of Pre-eclampsia and IUGR.
- 10 to 20% of all women with recurrent pregnancy loss have circulating antiphospholipid antibodies.

Thrombotic complications of APS in pregnancy

- Venous thrombotic events constitute 70% of all thrombotic events in patients with APLS. The rate of thromboses and stroke during pregnancy has been reported to be 5-12%.

Q.15. What are the side-effects of long-term LMWH?

Ans:

- The side-effects of LMWH are much less than unfractionated heparin. The incidence of osteoporotic fractures with LMWH is reported to be 0.04% (95% CI 0.01–0.2), and of allergic skin reactions as 1.8% (95% CI 1.34–2.37). The risk of significant bleeding is likely to be less than 2% with prophylactic doses.[5]

Q.16. What intrapartum care will be provided in this patient?

Ans:

- For women receiving heparin, the dose of heparin should be withheld 24 hours prior if the woman is planned for induction of labor or elective cesarean section.
- If the patient goes into spontaneous labor further dose of heparin need to be omitted and coagulation profile needs to be performed. If patient is receiving unfractionated heparin its action may be neutralized using protamine sulfate at the doses of 1mg Protamine sulphate/100 IU of Unfractionated Heparin to be neutralized. As only sixty percent of activity of LMWH is reversed by Protamine sulphate, Fresh frozen plasma may be used if the patient who has recently received low molecular weight heparin goes into labor.
- Good hydration and mobilization must be maintained during first stage of labor.
- Continuous electronic fetal heart rate monitoring is recommended during labour. LSCS should be performed for obstetric indications.

Q.17. How can the chances of epidural hematoma in a patient on LMWH be reduced?

Ans: To minimize or avoid the risk of epidural hematoma:

- Regional techniques should not be used until at least 12 hours after the previous prophylactic dose of LMWH.
- When a woman presents while on a therapeutic regimen of LMWH, regional techniques should not be employed for at least 24 hours after the last dose of LMWH.[5]
- LMWH should not be given for 4 hours after use of spinal anesthesia or after the epidural catheter has been removed; the cannula should not be removed within 10–12 hours of the most recent injection.[5]

Q.18. What are the principles of postpartum management of patient with APLS?

Ans:

- Good hydration, mobilization and compression stockings should be continued during postpartum period also.
- In postpartum period the risk for thrombosis should be re-evaluated and decision should be made regarding anticoagulation during postpartum period. The duration of anticoagulation can be 7 days only if there is no history of prior thromboembolic episode. In case of history of any thromboembolic episode, anticoagulation is recommended for 12 weeks postpartum. Both heparin and warfarins are safe during breastfeeding.
- Contraceptive advice will depend on the obstetric outcome and whether the couple have completed the family. Combined hormonal contraceptives are contraindicated in the patients with thrombophilias. Barrier method and intrauterine contraceptive devices may be used.

Q.19. Is there any randomized controlled trial of efficacy of LMWH in preventing pregnancy complications in women with thrombophilias?

Ans:

- **The Thrombophilia in Pregnancy Prophylaxis Study (TIPPS)[6]** is under way to determine the safety and efficacy of Low Molecular Weight Heparin (LMWH) in preventing pregnancy complications (venous thromboembolic events (VTE), pre-eclampsia, intrauterine growth restriction (IUGR), abruptio placentae, miscarriage and stillbirth) in thrombophilic women. It is a multicentre, multi-national open-label randomized controlled clinical trial. Three hundred and eighty-five (385) thrombophilic women at risk for VTE or placenta mediated pregnancy complications are being recruited.

Patients who require anticoagulant prophylaxis during this pregnancy (as judged by the local investigator) or have participated in TIPPS before will not be eligible for the trial. Inclusion critera are–Thrombophilic women < 16 weeks gestation with: (1) a history of previous pre-eclampsia, IUGR, abruptio placentae, miscarriage or stillbirth; or (2) a symptomatic first degree relative with thrombophilia would be randomized to subcutaneous injections of deltaparin or saline placebo throughout pregnancy. Main Outcome Measures would be: (1) VTE, (2) Pre-eclampsia, (3) IUGR, (4) Abruptio placentae, (5) Miscarriage, (6) Stillbirth, (7) Pre-term delivery, and (8) Safety outcomes (bleeding, heparin induced thrombocytopenia, reductions in bone mineral density and fractures). The results of this ten year study are expected by year 2011.

Q.20. What are the latest guidelines of American College of Chest Physicians Guidelines for the antenatal and peripartum management of thrombophilia?

Ans:

- Summary of 2008 Guidelines of American College of Chest Physicians for the antenatal and peripartum management of thrombophilia (2008)[7] are as follows:
  1. For women with recurrent early pregnancy loss or unexplained late pregnancy loss, screening for antiphospholipid antibodies (APLA) is recommended [Grade 1A].
  2. For women with these pregnancy complications who test positive for APLA and have no history of venous or arterial thrombosis, antepartum administration of prophylactic or intermediate-dose UFH or prophylactic LMWH combined with aspirin is recommended (Grade 1B).
  3. Both antepartum and postpartum prophylaxis for pregnant women with no prior history of VTE but antithrombin deficiency[6] is recommended (Grade 2C).
  4. For pregnant patients with a single prior episode of VTE associated with a transient risk factor that is no longer present and no thrombophilia, clinical surveillance antepartum and anticoagulant prophylaxis postpartum is recommended (Grade 1C).
  5. Pregnant women with a history of a single prior episode of VTE associated with pregnancy or exogenous estrogen use who are not receiving long-term anticoagulant therapy, antepartum prophylactic LMWH/UFH or intermediate-dose LMWH/UFH or clinical surveillance throughout pregnancy plus postpartum anticoagulants is recommended (Grade 1C).
  6. For patients with a history of a single prior episode of VTE with a high risk thrombophilia or with prior multiple episodes of VTE not receiving long term anticoagulation, antepartum prophylactic or intermediate-dose LMWH or prophylactic or intermediate-dose UFH and postpartum warfarin for 6 weeks is recommended (Grade 2C).
  7. For those pregnant women with prior VTE who are receiving long-term anticoagulants, LMWH or UFH is recommended throughout pregnancy (either adjusted-dose LMWH or UFH, or intermediate-dose LMWH) followed by resumption of long-term anticoagulants postpartum (Grade 1C).
  8. For pregnant women with acute VTE, it is recommended that subcutaneous LMWH or UFH should be continued throughout pregnancy (Grade 1B) and it is suggested that anticoagulants should be continued for at least 6 weeks postpartum (for a total minimum duration of therapy of 6 months) (Grade 2C).

9. For all other pregnant women with thrombophilia but no prior VTE, antepartum clinical surveillance or prophylactic LMWH or UFH, plus postpartum anticoagulants, rather than routine care (Grade 2C) is suggested.

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4 Anemia in Pregnancy

DEFINITION

World Health Organization (WHO) has defined anemia during pregnancy as hemoglobin concentration of less than 11 gm% and a hematocrit of less than 33%.[1] CDC (Center for Drug Control) proposes a cut off point of 11 gm% in 1st and 3rd trimester and 10.5 gm% during 2nd trimester.

Magnitude of Problem

Anemia is the most common medical disorder during pregnancy, resulting in increased maternal morbidity and mortality. According to National Family Health Survey-3 (2005-2006), prevalence of anemia in pregnancy is 57.9%.[2] FOGSI-WHO study on maternal mortality revealed that 64.4% of women who died had hemoglobin of less than 8 gm% and 21.6% had hemoglobin less than 5 gm%.[3]

Severity of Anemia

According to ICMR, severity of anemia is graded as:

Mild degree	10-10.9 gm%
Moderate degree	7-10 gm%
Severe degree	Less than 7 gm%
Very severe degree	Less than 4 gm%

Etiology

- Physiological
- Acquired
  1. *Nutritional:* Iron deficiency, folate and vitamin B_{12} deficiency.
  2. *Anemia of chronic disease:* For example, chronic malaria, TB.
  3. *Bone marrow insufficiency:* Due to drugs, radiation.
  4. Chronic blood loss from any site, e.g. bleeding piles, hookworm infestation.
- *Hereditary:* Thalassemias, sickle cell hemoglobinopathies, hereditary hemolytic anemia.

Only nutritional anemias which are common in pregnancy are discussed in details in this chapter.

CASE 1

Patient Mrs X wife of Mr Y, resident of UP, belonging to lower socioeconomic class, is 30 years old fourth gravida, para 3 with 3 living issues, with 30 weeks period of gestation presented for the first time in ANC OPD with complaint of:

1. Amenorrhea since 7 months.
2. Weakness and easy fatiguability since last 3 months.
3. Breathlessness on exertion since last 15 days.

Patient complains of easy fatiguability and weakness since last 3 months which has gradually increased over last 15 days to an extent that she gets tired on doing household activities. Patient also complaints of breathlessness on exertion since last 15 days. Patient gets breathless on climbing 2 flight

of stairs. It is not associated with palpitations or any chest pain. There is no history of pedal edema, sudden onset breathlessness, cough or decreased urine output. There is no history of asthma or chronic cough. There is no history of chronic fever with chills or rigors. There is no history of passage of worms in stool nor blood loss from any site. There is no history of easy bruisability or petechiae. There is no history of yellow discoloration of urine, skin or eyes. She did not take iron folate prophylaxis in this pregnancy.

Trimester History

First Trimester

- Spontaneous conception
- No history of radiation or any teratogen exposure
- No history of fever with rash, burning micturation, discharge or bleeding per vaginum
- No history of any drug intake
- No history of hyperemesis.

Second Trimester

- She perceived quickening at 3rd month
- Only single ANC visit
- Patient did not take any IFA prophylaxis
- She has received one dose of tetanus immunization from local dispensary
- No history of high BP records, pedal edema, headache, epigastric pain, blurring of vision
- No history of polyuria, polydipsia, polyphagia
- No history of pain abdomen, leaking or bleeding per vaginum.

Menstrual History

Her LMP is _____

EDD is _____

Her menstrual cycles were regular with normal blood flow.

Obstetric History

She is gravida 4, para 3, with 3 living issues. All children were full-term normal vaginal delivery at home. All issues are alive and healthy and immunized. There is no history of postpartum hemorrhage in any pregnancy.

Past History

- There is no history of blood transfusion in the past. There is no history of jaundice, any chronic illness or recurrent urinary tract infection.
- There is no past history of tuberculosis. She is not a known case of asthma. No history of fever, joint pain or recurrent sore throat in the past.

Personal History

- My patient is a housewife. She does not have any kind of addiction.
- She belongs to endemic area for malaria.

Family History

There is no history of repeated blood transfusions or thalassemia in any of the family member.

Socioeconomic History

She belongs to lower middle class according to modified Kuppuswamy scale.

Dietary History

Total calorie intake is 1500 Kcal and protein intake is 17 gm per day which is grossly inadequate. Iron intake is around 15 mg/day.

On Examination

My patient is conscious and well oriented to time, place and person. She is thin built. Her height is 5 feet and weight is 50 kg. Her gait is normal.

Vitals

- Her pulse rate is 80/min regular, good in volume, bilateral synchronous without any radiofemoral delay.
- Her BP is 120/80 mm Hg
- Her JVP is not raised. She is afebrile
- Her Respiratory rate is 20/min

General Physical Examination

- Hair shows signs of malnutrition:
- Pallor is seen in the conjunctiva and skin
- There is no icterus
- There is no angular stomatitis, glossitis or cheilosis
- Nails show platonychia
- There is no pedal edema

Breast Examination

Breasts show normal changes of pregnancy.

Systemic Examination

Cardiovascular: Apex beat is present in 5th intercostals space and is hyperdynamic S1S2 normal.

Ejection systolic murmur grade II/VI is heard best over pulmonary area not radiating to any site.

Respiratory: Air entry equal on both the sides. No added sounds or crepts heard.

CNS: No abnormality detected

Abdominal Examination

Inspection

- Abdomen uniformly distended.
- Linea nigra and stria gravidarum present
- No scar mark
- All hernia sites are free
- No hepatosplenomegaly

Palpation

- Fundal height is around 28 weeks
- Symphysiofundal height is 28.5 cm
- Abdominal girth is around 29 inches
- *Fundal grip* – Broad irregular mass suggestive of breech
- *Lateral grip* – Back felt on right side and limbs felt on left side
- *Pelvic grip* – Smooth hard ballotable mass suggestive of head felt
- Liquor appears to be adequate.

Auscultation: Fetal heart rate is 140/min regular.

Final Diagnosis

Thirty years old G4P3L3 with 30 weeks period of gestation with single live fetus in cephalic presentation with anemia not in failure.

- She is suspected to be anemic and her blood sample was ordered for examination which showed.
- Hb 7.4 gm % (12-14 gm%)
- Hct 22 % (36-44%)
- MCV 72 fL (80-97 fL)
- MCH 25 pg (27-33 pg)
- MCHC 30 % (32-36%)
- Peripheral smear shows microcytic hypochromic RBCs with anisopoikilocytosis
- Naked eye single tube red cell osmotic fragility test (NESTROFT) is negative.

Q.1. What investigations will you order in a case of anemia?

Ans: Investigations which should be done in a case of anemia are:

Investigations which are recommended in all antenatal patients are:

- Blood group
- HIV antigen 1 and 2
- Australia antigen
- VDRL
- Glucose challenge test at 24-28 weeks
- Urine routine and microscopy
- Hemoglobin to be done at 1st visit, 28, 32 and 36 weeks
- Obstetric ultrasound at 20 weeks.

Apart from the above investigations, following investigations are required for the work-up of anemia.

1. Routine tests for anemia, i.e. if Hb < 11 gm% are as follows:
   - Complete blood count which includes hemoglobin, MCV, MCH, MCHC, reticulocyte count, total leukocyte count and platelet count.
   - Peripheral smear should be made to see the:
     – Morphology of RBC's for type of anemia
     – Hypersegmentation of neutrophils (5% neutrophils showing 5 lobes or more or even a single neutrophil with 6 or more lobes)
     – Hemoparasite
     – Evidence of hemolysis
     – Platelet count
2. Screening for thalassemia should be done in all patients attending antenatal clinic as the incidence of thalassemia is high in North India around 3-5%. The screening test done is known as NESTROFT test.
3. Iron studies are done to confirm the diagnosis of iron deficiency anemia in case the woman does not respond to the treatment. It includes:
   – Serum ferritin
   – Serum iron concentration
   – Transferrin saturation
   – Total iron binding capacity

Figure 4.1 gives the protocol for diagnosis of anemia.

Q. 2. What is the aim of the management of anemia?

Ans: The aim of the treatment of anemia is to achieve a safe level of hemoglobin at the time of delivery which is associated with minimum complications. The desired hemoglobin level at the time of delivery is around 8 gm%.

Q.3. What should the approach to the management of anemia in pregnancy?

Ans:

1. Confirm the diagnosis of anemia by hemoglobin and hematocrit estimation, i.e. Hb < 11gm% or hematocrit < 33%.
2. Grade the severity of anemia according to hemoglobin levels, i.e
   - Hb < 7 gm% severe anemia
   - 7-10 gm% moderate anemia
   - 10-10.9 gm% mild anemia
3. Find out the type of anemia which is determined by the RBC indices, i.e. MCV, MCH, MCHC and the peripheral smear.
4. Investigate for the cause of anemia and treat the cause.

Q.4. Describe the physiology of iron metabolism.

Ans: Iron is a trace element which is required for erythropoeisis. Dietary iron is found in two forms:

1. Heme: Found in meat and meat products (5-10% of dietary iron). It is the most bioavailable source of iron.
2. Non heme: Found in cereals, pulses, vegetables (90-95% of dietary iron).

Figure 4.2 depicts the process of iron metabolism.

Iron is absorbed in duodenum and upper jejunum. Fe^{2+} present in diet is oxidized to ferric state (Fe^{3+}) in presence of gastric acidic pH so that it is maintained in the solution form and is taken to the duodenum. At the brush border of the absorptive cell, Fe^{3+} is reduced to ferrous form (Fe^{2+}) by ferrireductase. Transport across membrane is accomplished by bivalent metal transporter (DMT-1). Once inside the gut cell, Fe^{2+} is oxidized again to Fe^{3+} form so that it can bind to apotransferrin to form transferrin which is the transport protein.[4]

Iron circulates in plasma bound to transferrin and binds to transferrin receptors on the surface of marrow erythroid cells. Once the iron-transferrin

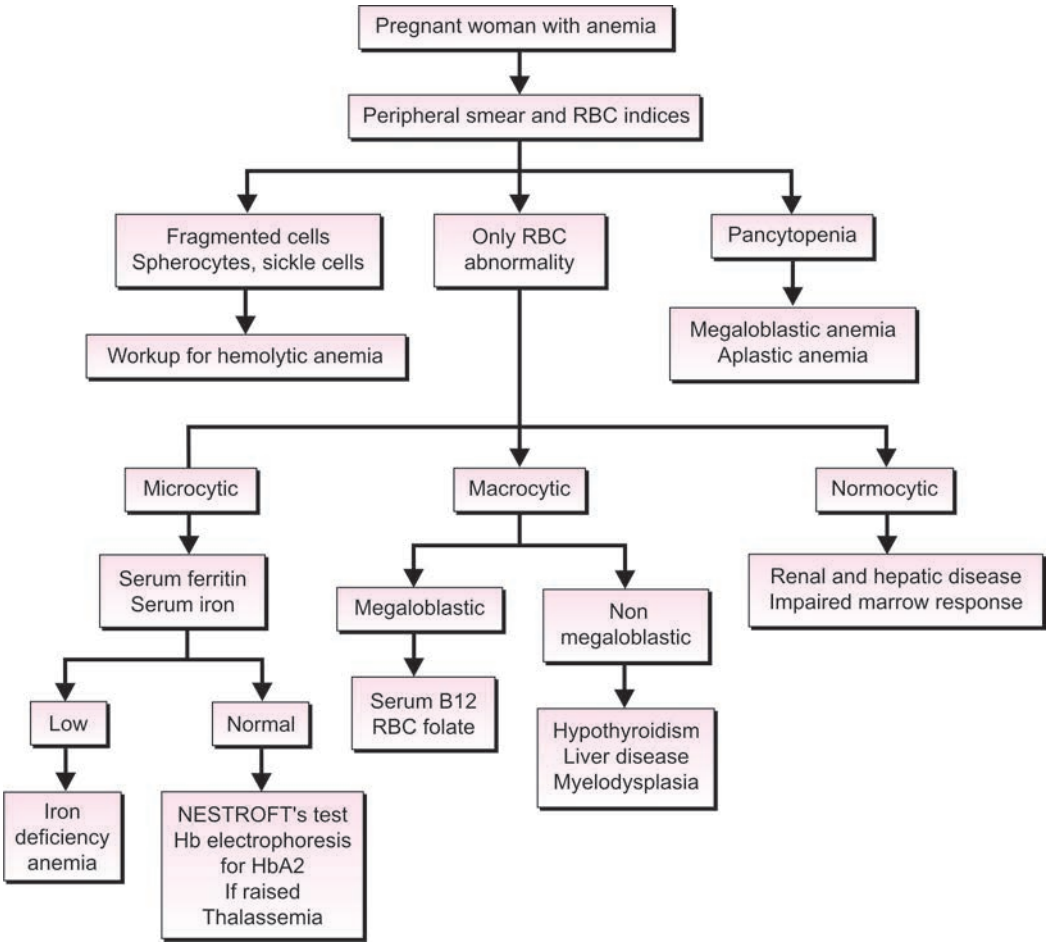

Fig. 4.1: Diagnosis of anemia

complex binds with its receptor, the complex is internalized via clathrin coated pits. The iron is then made available for heme synthesis while the transferrin receptor complex is recycled back into circulation. The iron is incorporated into heme containing enzymes for hematopoeisis and the excess iron binds to the storage protein, apoferritin, forming ferritin which gets stored mainly in bone marrow and liver.

Q.5. What are the factors affecting iron absorption?

Ans: Factors enhancing absorption: The heme form of iron has the better bioavailability and is absorbed in the ferrous form.

- Ascorbic acid
- Fermented food items and alcohol
- Gastric acidity
- Low iron stores
- Increased erythropoeitic activity

Factors inhibiting absorption:

- Phytates
- Calcium
- Tea and coffee
- High iron stores

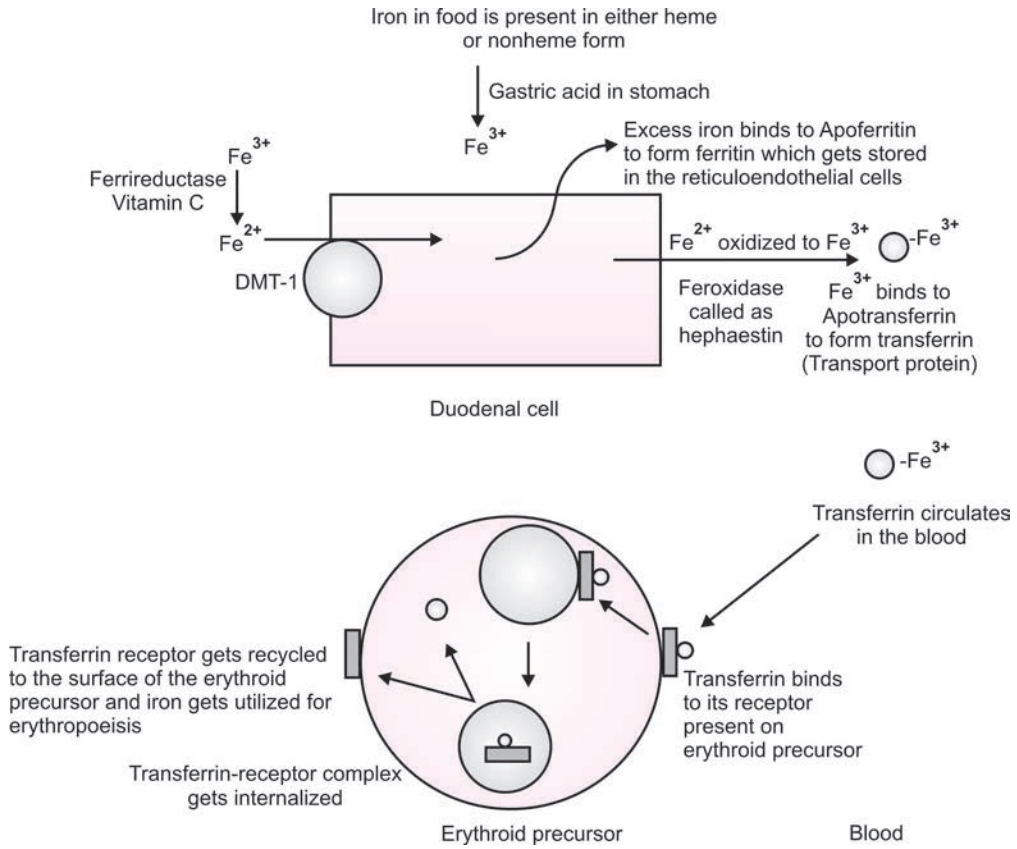

Fig. 4.2: Iron metabolism

Q.6. What are the stages of iron deficiency anemia?

Ans: Iron depletion is the earliest stage of iron deficiency, in which storage iron is decreased or absent but serum iron concentration, transferring saturation and blood hemoglobin levels are normal. Iron deficiency without anemia is a somewhat more advanced stage of iron deficiency, characterized by decreased or absent storage iron, usually low serum iron concentration and transferring saturation, but without frank anemia. Iron deficiency anemia is the most advanced stage of iron deficiency. It is characterized by decreased or absent iron stores, low serum iron concentration, low transferring saturation and low blood hemoglobin concentration.[4]

Q.7. What is iron folic acid prophylaxis?

Ans: In National Anemia Control Program under Ministry of Health and Family Welfare, all pregnant women who are not anemic are given folifer tablet containing 100 mg elemental iron along with 500 µg folic acid for at least 100 days. This prophylaxis against anemia needs to be continued till lactation.[5]

Q.8. Why is iron folic acid prophylaxis required for every antenatal woman?

Ans: This increased requirement during pregnancy is not fulfilled by normal vegetarian diet. In India, where deprived women consume only 1400 to 1800 Kcal per day, inadequate food intake is the most common reason for iron deficiency. Further, iron has a very poor bioavailability (1.5-5%), in the

	Normal balance	*Negative iron erythropoiesis*	*Iron deficient anemia*	*Iron deficiency*
Marrow iron stores	1-3 +	0-1+	0	0
Serum ferritin (µg/L)	50-200	< 20	< 15	< 15
TIBC (µg/L)	300-360	> 360	> 380	> 400
Serum iron (mg/dL)	50-150	50-150	< 50	< 30
Transferrin saturation (%)	30-50	30-50	< 20	< 10
RBC morphology	Normocytic Normochromic	Normocytic Normochromic	Normocytic Normochromic	Microcytic hypochromic

From Harrison's Principles of Internal Medicine, 17th edition.

TIBC - Total iron binding capacity, RBC - red blood cell

traditional Indian diet that chiefly comprises cereals and pulses. In endemic areas women suffer from chronic blood loss due to hookworm and malarial infestation further enhancing the incidence and severity of anemia. Hence, iron and folate prophylaxis is essential for every pregnant woman to meet the increased demands.

Q.9. What is physiological anemia of pregnancy?

Ans: The increase in plasma volume (30-40%) is much more than the increase in red cell mass (10-15%) leading to apparent decrease in hemoglobin level.

- Starts at 7th-8th weeks
- Maximum by 32 weeks
- Does not go below 11 gm% in 1st trimester, 10 gm% in 2nd and 3rd trimester. The rise in RBC volume begins at 20 weeks continues till term. Therefore, in 3rd trimester there is slight rise in hemoglobin concentration.

In severs to reduce maternal blood viscosity, thereby enhancing placental perfusion and facilitating nutrient and oxygen delivery to the fetus.

Q.10. What are the causes of iron deficiency anemia in pregnancy?

Ans: Common causes of iron deficiency anemia are:

1. Increased demand, 280, mg iron is required for basal iron + 570 mg for RBC expansion + 350 mg for fetus + 150 mg for placenta. Maternal blood loss at delivery = 250 mg. Total loss is about 1200 mg. The total amount of iron that is conserved due to amenorrhea amounts to 400 mg. Thus, net iron expenditure is approximately 800 mg.[5]

   This increased demand is not met by the daily Indian diet and thus routine iron supplementation is required for every woman.
2. *Dietary deficiency:* It is the most common cause of iron deficiency in India, more so in socio-economically weaker section. It is amplified by wrong foods and food fads.
3. *Impaired absorption:* Due to various malabsorption syndromes, chronic diarrhea, etc.
4. *Increased blood loss:* Usually 5 mg of iron is lost for loss of about 10 ml of blood. Some of the common causes are:
   a. *Hookworm infestation:* Prevalent in areas where people defecate in open fields. The larva of hookworm enters the body by penetrating the sole. The blood loss caused is about 0.2 ml/worm/day.
   b. Multiple pregnancies in Indian patients result in IDA since in each pregnancy there is loss of 650 mg iron equivalent to about 1300 ml blood.
   c. In lactation, loss of iron is to the tune of 0.5 to 1 mg/day.

Q.11. What are the complications of severe anemia during pregnancy?

Ans: The complications of severe anemia during pregnancy are as follows:

Maternal

A. During pregnancy
   1. Poor weight gain
   2. Decreased immune response
   3. Preterm labor
   4. CHF at 30-32 weeks of pregnancy
   5. Decreased work capacity

B. During labor
   1. Dysfunctional labor
   2. CHF
   3. Inability to stand even slight blood loss
   4. Anesthesia risk

C. Puerperium
   1. Puerperal sepsis
   2. Subinvolution
   3. Pulmonary embolism
   4. Lactation failure

Fetal

1. IUGR
2. Low iron stores at birth if mother has severe anemia
3. Poor Apgar score.

Q.12. What is the differential diagnosis of microcytic hypochromic anemia?

Ans: The differential diagnosis of mirocytic hypochromic anemia are :

1. Iron deficiency anemia
2. Thalassemia
3. Sideroblastic anemia

Q.13. How do we differentiate iron deficiency anemia from thalassemia?

Ans:

	Iron deficiency anemia	*Thalassemia*
RBC count	< 5.5 million	>5.5 million
Anisopoikilocytosis	Marked	Mild
Red cell distribution width	Increased	Normal
Serum ferritin	Decreased	Normal or slightly reduced
Serum iron	Decreased	Normal
TIBC	Increased	Normal
Transferrin saturation	< 15 %	30-40 %
HbA2 level	Normal or reduced (<3.5%)	Increased (3.6 – 8.0%)

TIBC - Total iron binding capacity, RBC - Red blood cell
HbA2 - Hemoglobin-A2

Q.14. How is NESTROFT test done? How it is interpreted?

Ans: NESTROFT test is 'naked eye single tube red cell osmotic fragility test'. In this test 2 ml of 0.36% buffered saline solution is taken in one tube and 2 ml of distilled water in another tube. A drop of blood is added to each test tube and both the tubes are left undisturbed for 20 minutes. Both the tubes are then shaken and held against a white paper on which a black line is drawn. Normally, the line is clearly visible through the contents of tube containing distilled water. If the line is clearly visible similarly through the contents of tube with buffered saline, the test is negative. If the line is not clearly visible the test is considered positive.

The principle is that normocytic normochromic cells when put in hypotonic solution will undergo lysis wheras in thalassemia trait, the cells are microcytic and hypochromic which are resistant to hemolysis due to decreased fragility. It has 91% sensitivity and 95% specificity and the negative predictive value is 99%.[7] NESTROFT test is only a screening test for thalassemia. The definite test is the estimation of HbA2 levels by high liquid performance chromatography. In thalassemia HbA2 levels are > 3.5%.

Q.15. What is the treatment for anemia in this patient?

Ans: Since the period of gestation is 30 weeks and the patient has iron deficiency anemia of moderate type, we can give both the the options to the patient – oral as well as parenteral iron.

We can start oral iron therapy for this patient as we have enough time to monitor the response of the treatment before she reaches term pregnancy. Secondly, oral iron is safe, easy to administer and cheap.

Deworming is done with mebendazole (100 mg twice daily for 3 days) as the prevalence of iron deficiency anemia due to hookworm infestation is high in our country.

Iron is given as 180-200 mg in elemental form in two to three divided doses in between the meals along with vitamin C to enhance its absorption. The patient is also given high protein diet which is also required for hemoglobin synthesis.

Q.16. What is the duration of oral iron therapy?

Ans: Hemoglobin levels start rising in 2-3 weeks and reaches normal value after 6 weeks of therapy.

To build-up the stores, treatment should be continued for next 3 months. Iron folic acid prophylaxis should be continued even after the treatment till lactation.[5]

Q.17. What should be done if this patient does not tolerate oral iron?

Ans:

1. Take oral iron in between the meals
2. Change the iron salt preparation
3. Switch over to parenteral route.

Q.18. How do we assess the response of treatment of iron deficiency anemia?

Ans: Clinical improvement assessed as:

1. Increased sense of well-being
2. Increase in work capacity
3. Improvement in other symptoms.

Laboratory parameters:[6]

5-7 days:	Increase in reticulocyte count to up to 5% (Normal 0.2 -2 %)
2-3 weeks:	Increase in hemoblobin level @ 0.8-1.0 gm/dL/week Improvement in RBC indices – MCV, MCH, MCHC
6-8 weeks:	Hemoglobin level comes to normal level Peripheral smear shows normocytic normochromic RBC's Increase in serum ferritin level.

Q.19. What are the causes of non-improvement of anemia after 3 weeks of iron treatment?

Ans: The causes of non-improvement of anemia after 3 weeks are:

1. Inaccurate diagnosis – Thalassemia, pyridoxine deficiency
2. Non-compliance
3. Continuous blood loss, e.g. hookworm infestation, bleeding hemorrhoids
4. Co-existing infection
5. Faulty absorption
6. Concomitant folate deficiency.

Q.20. How will you check for the compliance of the oral iron treatment?

Ans: Compliance to oral iron is checked by:

1. Repeated questioning about the intake
2. Color of the stool which should be black
3. Associated symptoms like constipation, gastritis
4. Return of the empty blister packs if she is following regularly.

Q.21. What are the management options for treatment of iron deficiency anemia?

Ans: *Oral iron*: 180-200 mg elemental iron given daily in divided doses in between meals.

The various iron salts available are ferrous sulfate, ferrous fumarate, ferrous ascorbate, etc.

Other salts are ferrous gluconate, carbonyl iron.

1. Ferrous sulfate has high amount of elemental iron and has good bioavailability but is associated with gastrointestinal side effects and staining of teeth.
2. Ferrous fumarate has a similar efficacy and GI tolerance to ferrous sulphate.
3. Of all the preparations, ferrous ascorbate is preferred because:
   - It contains high proportion of elemental iron
   - Converts ferric to ferrous form
   - Inhibits the formation of insoluble iron complexes
   - Inhibits the conversion of ferritin to hemosiderin preventing iron overload.
4. Iron polymaltose complex is a combination of ferric iron with maltol. It has less absorption than ferrous salts. It may be tried as an alternative for those patients who cannot tolerate ferrous form as compliance is of significant concern during pregnancy.

Parenteral iron: It can be given by either intramuscular or intravenous route.

Dose of parenteral iron is calculated as:[5]

Body weight in kg × (Desired Hb – patient's Hb) × 2.21 + 1000 mg

1000 mg is taken for complete restoration of the stores in patients with continuing blood loss otherwise 500 mg is adequate for patients whose blood loss has been arrested.

OR

Give 250 mg elemental iron for each gm of Hb deficit and add another 50% for replenishment of stores.

Intramuscular iron preparations available are iron dextran, iron sorbitol citrate complex.

Intravenous iron preparations available are iron dextran, iron sucrose, ferrous gluconate.

Q.22. What are the indications of parenteral iron?

Ans: The rise in hemoglobin after parenteral therapy is 0.7- 1.0 gm% per week which is same as seen with oral iron therapy. The main advantage of parenteral therapy is the certainity of its administration. The indications of parenteral iron are:

1. Intolerance to oral iron
2. Impaired iron absorption
3. Chronic blood loss
4. Gastrointestinal disorders which gets aggravated by oral iron-peptic ulcer disease, ulcerative colitis
5. After 32 weeks period of gestation, parenteral iron is preferred as the compliance is 100%.

Q.23. What are the disadvantages of intramuscular over intravenous iron administration?

Ans. Intramuscular iron has some disadvantages over intravascular iron administration:

1. It causes staining of the skin.
2. It is more painful.
3. It can cause abscess.
4. Multiple injections are required as maximum 2 ml containing 100 mg iron can be given at a time. Therefore, it causes more discomfort to the patient.
5. Its absorption is irregular.

Q.24. What are the various parenteral iron preparations available?

Ans. *Intramuscular preparation*:[6]

1. Iron sorbitol citrate complex is a low molecular weight complex, and therefore, it gets easily absorbed. The recommended single dose for injection is 1.5 mg/kg body weight after giving an intramuscular test dose. The single daily injection of more than 2 ml containing 100 mg of iron is not recommended. Hence, multiple injections are required to administer the complete dose. It is given by Z technique to avoid

staining of the skin. It can cause local discomfort, pain, flushing, metallic taste.

Severe systemic reaction can occur in case of overdose.

2. *Iron dextran*: It also requires a test dose and a maximum of 2 ml is given at a time. It is associated more systemic complications and has an erratic absorption. Therefore, it is not preferred nowadays.

Intravenous preparation:[8]

1. Iron sucrose has certain advantages over other preparation as:
   a. No test dose is recommended
   b. It has minimum side effects
   c. It is usually not associated with anaphylactic reaction
   d. Most preferred in patients undergoing hemodialysis as it has low molecular weight.

   It can be given as iv push undiluted @ 1 ml/min maximum dose being 100 mg, i.e. over 5 minutes as 5 ml contains 100 mg iron. The other way is to dilute 5 ml vial in 100 ml normal saline (1 mg/mL) and administer it over at least 20 minutes. No test dose is required. Only the initial 20-25 ml in given slowly to see for any signs of reaction. A maximum of 200 dose can be given at a time not more than thrice a week.
2. *Sodium ferric gluconate*: It is administered as direct iv push @ 12.5 mg/min as 5 ml contains 62.5 mg of iron or 125 mg, i.e. 10 ml can be diluted in 100 ml saline and infused over 60 minutes. No test dose is required.
3. *Iron dextran*: It is associated with anaphylactic reaction, so a test dose is required.The total dose can be given as one large dose or divided in many smaller doses. It is either given in iv drip by diluting 100 mg in 250 ml saline and infused over 30-60 minutes. 100 mg dose can be given undiluted as iv push maximum @ 20 mg/min. However, it is associated with systemic reactions like hypotension, urticaria, dizziness, arthralgia, lymphadenopathy, fever, etc.

Q.25. What are the advantages and disadvantages of oral and parenteral iron?

Ans:

	Advantages	*Disadvantages*
Oral	1. No anaphylaxis 2. Easy to take 3. Cheap	1. Gastrointestinal disturbances, e.g. constipation, diarrhea, gastritis 2. Metallic taste in mouth 3. Non-compliance
Parenteral	1. 100% compliance 2. Preferred in gastrointestinal malabsorption syndromes, e.g. Ulcerative colitis, Crohn's disease, Tropical sprue 3. Preferred in patients who are unable to tolerate oral iron, e.g. Peptic ulcer disease 4. Certainity of restoration of stores in shorter time span 5. Correction of anemia near term	1. Invasive 2. Painful administration 3. Staining and abscess formation at the site of intramuscular injection administration 4. Anaphylaxis reaction 5. Thromboplebhitis in intravascular administration 6. Expensive

Q.26. What are the indications of blood transfusion in anemia in pregnancy?

Ans: Blood transfusion in an anemic patient does not treat the cause of anemia nor corrects the nonhematological effects of iron deficiency.

According to WHO guidelines, the indications of blood transfusion are:[9]

1. Less than 36 weeks
   a. Hb 5 gm% or below
   b. Hb 5-7 gm% with established or incipient cardiac failure or clinical evidence of hypoxia, pneumonia or any other bacterial infection and malaria

2. 36 weeks or more
   a. Hb 6 gm% or below with established or incipient cardiac failure or clinical evidence of hypoxia, pneumonia or any other bacterial infection and malaria
3. *Elective LSCS:* When elective LSCS is planned and there is a history of antepartum hemorrhage, postpartum hemorrhage or previous section.
   a. Less than 8 gm% - 2 units of blood should be cross matched
   b. 8-10 gm% - 1 unit of blood should be cross matched.

Q.27. A woman presents at 37 weeks in active labor with hemoglobin 6 gm% not in failure. How will you manage this patient?

Ans: The hemoglobin levels at the time of delivery should be at least 7 gm% and it is known that one unit of blood increases hemoglobin levels by 0.8-1 gm%. So this patient requires at least 1 unit packed cell volume, each should be transfused slowly over 4-6 hours.

1st stage:
- Patient should be propped up
- Oxygen should be given if required
- Intermittent chest auscultation
- Sedation and analgesic
- Minimum number of per vaginum examinations
- Strict asepsis to be maintained
- Partograph to be maintained
- Fluid restriction
- Start antibiotic prophylaxis

2nd stage:
- Prophylactic ventouse or outlet forceps to cut short 2nd stage
- Strict asepsis to be maintained
- 0.2 mg intravenous methergin at delivery of anterior shoulder
- Restrict intravenous fluids
- Oxytocin if required should be given in concentrated form

3rd stage:
- Active management of 3rd stage except in very severe anemia for fear of congestive heart failure
- Slow delivery of baby in 2-3 months
- Controlled cord traction
- Avoid postpartum hemorrhage as even a small amount of blood loss can cause decompensation
- Look for any genital trauma and control bleeding.

Peurperium:
- Watch meticulously till 6 hours postpartum for any signs of failure
- Prophylactic antibiotic to prevent sepsis
- Continue iron and folic acid for at least 3 months IFA prophylaxis to be continued till lactation
- Adequate rest
- Contraceptive advice
  - Postpartum sterilization if family is completed.
  - She should not conceive for at least 2 years giving time for iron stores to recover.
  - Barrier contraception is safe.

Q.28. What is the role of erythropoietin in anemia?

Ans: Erythropoietin can be given along with parenteral iron in a dose of 50-150 U/kg given subcutaneously twice/thrice weekly. It has certain advantages like :

1. Rapid correction of severe anemia in less than 2 weeks.
2. Anemia not responding to intravenous iron alone.
3. Treatment of moderate to severe iron deficiency anemia as an alternate to blood transfusion.

Megaloblastic Anemia

Megaloblastic anemias are characterized by macrocytic blood picture and megaloblastic bone

marrow. There is impaired DNA synthesis due to lack of vitamin B_{12} and/or folic acid.

Both folic acid as well as vitamin B_{12} are required for DNA synthesis.

Mechanism resulting in anemia are:

1. *Unbalanced cell growth:* The nuclear maturation lags behind the cytoplasmic maturation because there is retarded DNA synthesis while RNA synthesis is normal.
2. *Ineffective erythropoeisis:* The destruction of intermediate and late normoblasts in bone marrow leads to formation of only few red cells although there is hyperplastic erythropoiesis.
3. *Hemolysis:* Because the late normoblasts die prematurely in the bone marrow there is a mild hemolytic component

The causes of folic acid deficiency are:

1. Insufficient intake of green leafy vegetables
2. Malabsorption syndrome and gastrointestinal diseases, e.g. Gluten induced enteropathy
3. Abnormally high demands are needed in multiple pregnancies
4. Drugs, e.g. phenytoin, pyrimethamine, OCPs.

The causes of vitamin B_{12} deficiency are:

- Dietary deficiency and in pure vegetarians
- Malabsorption syndromes
- Ileal disease, Crohn's disease
- Small bowel bacterial overgrowth

There is megaloblastic erythropoiesis in bone marrow showing an asynchrony of nuclear and cytoplasmic maturation because of impaired DNA synthesis.

CASE 2

Twenty-five years old multigravida presented at 28 weeks period of gestation with chief complaints of easy fatiguability, weakness and breathlessness on exertion since 2 months. On examination she has tachycardia, pale conjunctiva, nail beds and palmer creases. She has also got glossitis, cheilosis and angular stomatitis. Her Hb was 6.8 gm% and she was prescribed oral iron. She took treatment for 3 weeks and investigations were repeated as there was no improvement with the therapy. Hb came to be 6.5 gm% , Hct 21%, MCV 105 fL, MCHC 33%, MCH 24 pg/L. Her platelet count is 80,000/cc. Peripheral smear showed macrocytic RBC's along with nucleated RBC's. Hypersegmented neutrophils seen 7 per HPF. Diagnosis of macrocytic anemia was made.

Q.29. What are hematological findings in a case of megaloblastic anemia?

Ans: The hematological findings in a case of megaloblastic anemia are:

1. Complete blood count:
   - Hemoglobin < 10 gm%
   - Hematocrit < 33%
   - Macrocytosis MCV > 100 fL
   - MCHC will be normal
   - Reticulocyte count is normal or mildly increased to 2-3%
2. Peripheral blood smear shows:
   - Macrocytes
   - Moderate to marked anisopoikilocytosis
   - Macro-ovalocytes are diagnostic of megaloblastic anemia
   - Nucleated RBC's
   - Basophilic stippling, Cabot ring, Howel Jolly bodies
   - Hypersegmented neutrophils: Five percent of neutrophils with 5 or more lobes or even a single neutrophil with 6 or more lobe. This is the first manifestation of megaloblastic anemia.
   - 10-20% cases show pancytopenia.
3. As there is ineffective erythropoiesis, there is a component of accompanying hemolysis due to which serum unconjugated bilirubin and serum LDH rises.

Q.30. How will you confirm the diagnosis ?

Ans: After confirming the type of anemia with the help of complete blood count and peripheral smear,

empirical treatment with folate and vitamin B_{12} is started as the diagnostic tests to confirm folate and vitamin B_{12} deficiency are not available easily and are very costly.

Wherever available, Serum B_{12} levels and serum folate levels can be measured.

Fasting folate and RBC folate levels are more specific for the diagnosis of folate deficiency as there is no interference by the food.

Serum B_{12} level < 100 pg/ml suggests B_{12} deficiency.

Serum folate levels < 2 ng/ml suggests folate deficiency anemia.[6]

Fasting serum folate level < 6 µg/L and RBC Folate < 165 µg/L are diagnostic of folate deficiency.[6]

Q.31. What is the treatment of megaloblastic anemia?

Ans: Megaloblastic anemia in pregnancy is nearly always secondary to folate deficiency. Pregnancy does not greatly affect meternal vitamins B_{12} levels. In establilshed folated deficiency anemia, 5 mg folate is given orally daily during pregnancy which is continued till 3 months postpartum. Vitamin B_{12} deficiency is always caused due to malabsorption, therefore it is usually given in parental form. One mg vitamins B_{12} is given intramuscular on alternate days for 2 weeks followed by 1 mg IM once a month for 6 months.[10]

Iron preparation is given along as there is increased requirement during erythropoiesis. Figure 4.3 depicts the protocol for treatment of megaloblastic anemia.

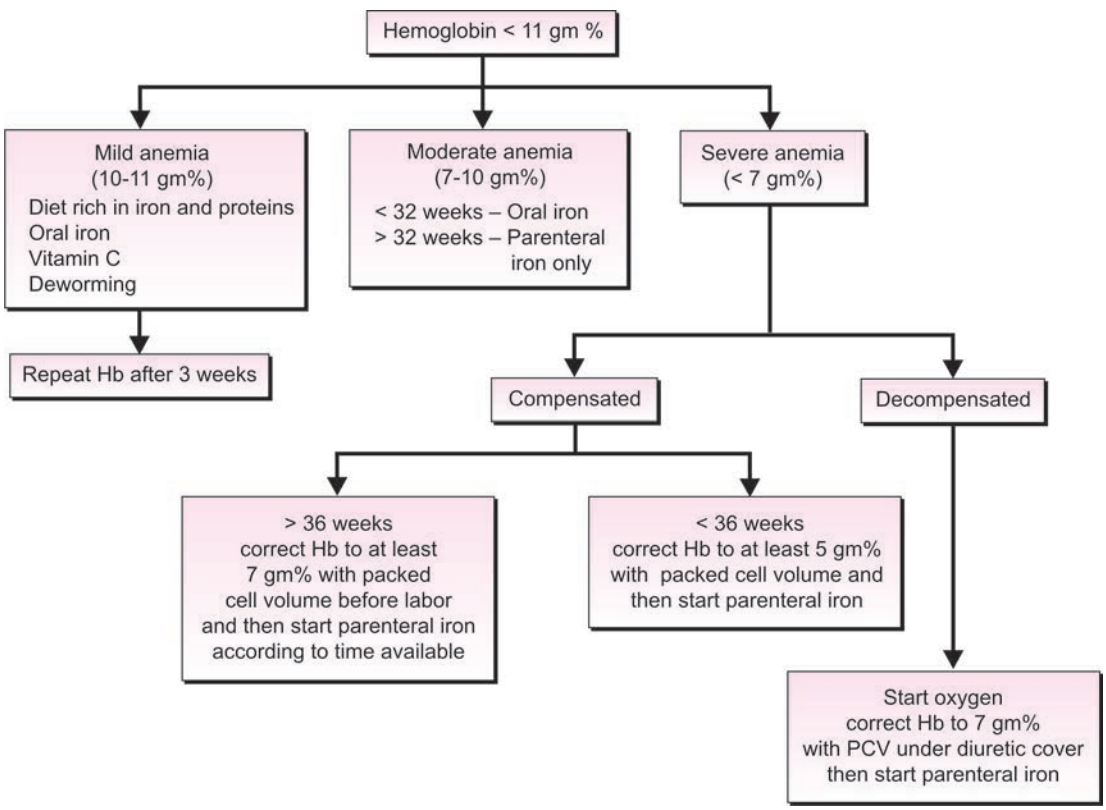

Fig. 4.3: Treatment of anemia in pregnancy

Q.32. How will you monitor the response of the treatment?

Ans: Clinical improvement assessed as:

1. Increased sense of well-being
2. Increase in work capacity
3. Improvement in other symptoms
4. Improvement of glossitis

Laboratory parameters:

3-4 days: Decrease in LDH levels.

5-7 days: Increase in reticulocyte count and gets established by day 15.

2-3 weeks: Increase in hemoblobin level @ 0.8-1.0 gm/dL/week.

Improvement in RBC indices – MCV, MCH, MCHC.

6-8 weeks: Hemoglobin level comes to normal level.

Peripheral smear shows normocytic normochromic RBC's.

Q.33. This patient was treated with folate and vitamin B_{12} for 1 month after which Investigations were repeated which showed iron deficiency picture. How do you explain this?

Ans: RBC synthesis is inhibited during the vitamin deficiency, available iron is underused. As soon as therapy with folate or B_{12} is initiated, red cell synthesis starts again, use of iron is maximal and iron deficiency becomes apparent.

Q.34. Which deficiency is more common– vitamin B_{12} or folate deficiency? Also state the reason.

Ans: Folate deficiency is more common than vitamin B_{12} deficiency because:

1. Folate stores last only for 2-4 months whereas stores of vitamin B_{12} are sufficient for 2-3 years.
2. Folate gets destroyed by prolonged cooking.
3. Dietary deficiency of vitamin B_{12} occurs only in pure vegetarians.
4. Pernicious anemia is associated with infertility.

Q.35. What is the requirement of iron, vitamin B_{12} and folate during pregnancy?

Ans: Current recommendations avise folic acid intake of 400 µg daily with 60 mg of iron for 6 months during pregnancy and continuing for 3 months postpartum, 30 µg of vitamin B_{12} is required daily during pregnncy.[11]

Q.36. What is the cause of the macrocytosis?

Ans: As the DNA synthesis is impaired and cytoplasmic maturation is normal, the hemoglobinization of cytoplasm continues for a longer time between 2 cell divisions and therefore the red cells become enlarged.

Q.37. What are the causes of macrocytic anemia with normoblastic bone marrow?

Ans:

1. Hepatic disease
2. Hypothyroidism
3. Myelodysplastic syndromes
4. Aplastic anemia

RECENT ADVANCES

1. Two injections of iron dextran 250 mg each given intramuscularly at 4 weeks interval along with tetanus toxoid injection have been recommended for prophylaxis of iron deficiency anemia as it has better compliance and better results.
2. Newer oral iron preparations are ferrous oxalate, microencapsulated ferrous sulphate and microencapsulated ferrous fumarate. These microencapsulated preparations have equal bioavailability as the other salts but have fewer gastrointestinal side effects.
3. Intravenous iron sucrose is a new drug which is given intravenously without any test dose and is associated with minimum complications. Total dose calculated is given in divided doses

on alternate days not more than 200 mg at a time. If given slowly over 1 hour it is well tolerated and very safe.

4. Other intravenous iron preparations are ferrous gluconate, ferrous carboxymaltose
5. Erythropoetin 50-150 U/kg given sub-cutaneously twice/thrice weekly till course of parenteral iron is over has additional advantages:[12]
    1. Rapid correction of severe anemia in less than 2 weeks.
    2. Anemia not responding to intravenous iron alone.
    3. Treatment of moderate to severe iron deficiency anemia as an alternate to blood transfusion.

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Ashok Kumar, Minu

5 Diabetes in Pregnancy

Abnormal maternal glucose regulation occurs in 3-10% of pregnancies. Gestational diabetes mellitus (GDM) is defined as glucose intolerance of variable degree with onset or first recognition during pregnancy. Gestational diabetes mellitus accounts for 90% of cases of diabetes mellitus in pregnancy. Type II diabetes mellitus accounts for 7-8% of cases of diabetes mellitus in pregnancy, and given its increasing incidence, pre-existing diabetes mellitus now affects 1-2% of pregnancies.

The risk of fetal morbidity is directly proportional to the degree of maternal hyperglycemia. Women with gestational diabetes are at increased risk of developing type 2 diabetes mellitus after pregnancy, while their offsprings are prone to developing childhood obesity, with type 2 diabetes later in life. Most patients are treated only with diet modification and moderate exercise but some take antidiabetic drugs, including insulin.

CASE 1

A 29 years old weighing 70 kg, G_4P_1+0+2+0 presented with single live fetus of 27 weeks estimated gestational age. On her antenatal evaluation, her glucose tolerance test was found to be deranged (Fasting 106 mg%, 1 hour 224 mg%, 2 hours 209 mg%, 3 hours 128 mg% by carpenter and coustan).

Q.1. What is the significant history to be asked in present pregnancy of this patient?

Ans:

a. ***History of polyuria, polydipsia, polyphagia.***
b. ***Curdy discharge per vaginum*** (diabetic patients are prone to vaginal candidiasis).
c. ***Presence of skin infections*** Boils, furuncles.
d. ***Recurrent urinary tract infections***.
e. ***History of excessive nausea and vomiting*** (due to diabetic gastropathy).
f. ***History of headache, epigastric pain, bilateral pedal edema, blurring of vision.***

GDM patients have 10 to 25% risk of developing pre-eclampsia.

• Obstetric history[1]

a. ***History of previous first trimester abortions***
Patients with persistent preprandial blood glucose >120 mg/dl in first trimester are at high-risk of first trimester abortions.[2]
b. ***History of previous stillbirths***
Diabetic patients have hyperglycemia mediated chronic aberrations in transport of oxygen and fetal metabolites leading to sudden fetal demise.[3]
c. ***History of malformations in previous pregnancies***
Diabetic patients are at increased risk (6-10%) of fetal congenital malformations—hydrocephalus, anencephaly, spina bifida (1.95%),

cardiovascular abnormalities (5 fold increased risk), renal abnormalities, situs inversus and caudal regression syndrome (0.2-0.5%). GDM *per se* not associated with congenital anomalies).

d. ***Weight of previous babies, any instrumental deliveries, difficult delivery***
Gestational diabetes is associated with 17 to 29% increased risk of macrosomia—baby weight > 4.5 kg (ACOG).[4]

e. ***History of early neonatal deaths***
Early neonatal deaths are common due to hypoglycemia (blood sugar < 35 mg/dl in term infants (ACOG), hypomagnesemia, hypocalcemia in baby.[4]

f. ***History of diabetes in previous pregnancy***
Fourty percent recurrence rate in subsequent pregnancies.

• Past history
History of diabetes mellitus prior to pregnancy controlled on diabetic diet, oral hypoglycemics or insulin therapy.[2]

• Family history
Family history of diabetes in first degree relatives of the patient.

• Dietary history
Caloric intake. Percentage break up of carbohydrate, fat and protein.

Q.2. What are the essential aspects of examination in this patient?

Ans:

• General physical examination
Body mass index (BMI) calculated according to prepregnancy weight.

Presence of skin infections e.g. boils are specifically noted.

Blood pressure measurement

• Cardiovascular system, respiratory system and neurological examination and fundus examination
This is performed to rule out neuropathy, retinopathy or vascular disease.

• Abdominal examination
Abdominal girth and symphysio fundal height (to monitor fetal growth).

Polyhydroamnios: Fetal hyperglycemia is associated with polyuria leading to polyhydramnios (26.4-28%).

Macrosomia: Maternal hyperglycemia prompts fetal hyperinsulinemia during second half of gestation leading to excessive deposition of fat on shoulder and trunk which predisposes to shoulder dystocia and cesarean section.

Intrauterine growth restriction (IUGR): (associated with vasculopathy (21% especially with nephropathy).

• Speculum examination
At first visit to look for vaginal infections.

• Per vaginal examination
It is done at term to rule out cephalopelvic disproportion as these patients are prone to have macrosomia.

Q.3. Apart from the routine antenatal investigations what are the special investigations would you like to order for this patient?

Ans:

- Blood glucose monitoring by capillary blood glucose levels is done in patients with deranged GTT (Table 5.1).

Table 5.1: Self-monitored capillary blood glucose levels by ACOG 2005

Specimen	*Level (mg/dl)*
Fasting	≤ 95 mg/dl
Premeal	≤ 100 mg/dl
1 hour postprandial	≤ 140 mg/dl
2 hours postprandial	≤ 120 mg/dl
2-6 am	≥ 60 mg/dl

- **Urine albumin, sugar, ketones**
These are to be assessed. Renal glucosuria during pregnancy occurs at blood sugar levels of 70 to 100 mg/dl. It is not benign as these

women are at high risk for preterm delivery and macrosomia. Patients may lose 100 gm/day of glucose in urine. Such large losses of glucose decreases amount of glucose available for caloric needs and thus lipolysis is activated to maximum leading to production of ketones and ketoacidosis.

- **Glycosylated hemoglobin levels[2] (HbA1c)**
  Basal and every 6 to 8 weekly must be performed in first trimester. It is a product of nonenzymatic glycosylation of hemoglobin. It reflects average blood sugar in preceding 6 to 8 weeks. HbA1c should be < 6 gm% during pregnancy for good glycemic control. *High HbA1c during the first trimester is associated with increased risk of gross congenital malformations and during second trimester is associated with macrosomia (HbA1c < 8.5 gm% risk of malformation is 3.4%, HbA1c > 9.5 gm% risk of malformation is 22%).*
  HbAlc should not be used routinely for assessing glycemic control in the second and third trimesters of pregnancy. Physiological changes that occur in all pregnant women lead to reduced HbA1c in women without diabetes, meaning that any apparent reduction in HbA1c in women with diabetes during the second and third trimesters of pregnancy does not necessarily indicate improved glycemic control.[6]
  - **Liver function test**
  - **Renal function test**
  - **Fundoscopy[2]**

  *Nonproliferative diabetic retinopathy***:** Capillary closure and dilatation, microaneurysm, AV shunt, dilated veins, hemorrhages (dots and blots), cotton wool spots/soft exudates, hard exudates.
  Proliferative diabetic retinopathy: Neovascularization, vitreous hemorrhage, retinal detachment.[4]
- **Twenty-four hours urinary protein.**
- **Urine routine microscopy and culture**.

Q.4. What are the various modalities of fetal assessment in the above case?

Ans:

- **Level II ultrasound:** At 18 to 22 weeks of gestation to detect gross congenital malformations.
- **Fetal echocardiography:** At 22 to 24 weeks of gestation in all diabetic patients as cardiovascular anomalies are common in fetuses of diabetic patients. Cardiac anomalies associated with GDM are atrial septal defects, ventricular septal defects and transposition of great arteries. One proposed mechanism for cardiac defects is hyperglycemia induced oxidative stress that inhibits expression of cardiac neural crest migration.
- **Ultrasound for fetal growth:** It starts at 28 weeks of gestation and is done every 4 weekly. It is done to detect macrosomia/IUGR.
- **Doppler velocimetry:** It is helpful in patients with IUGR.
- **Nonstress test/Biophysical profile:** It is advisable to do it twice weekly 32 weeks onwards, especially in patients with IUGR with abnormal umbilical artery Doppler, vasculopathy, or with high BP, suboptimal control of diabetes.

Q.5. How will you manage this patient?

Ans:

Antenatal care

Once diagnosed, patient has to be counseled regarding the need for checking periodic capillary glucose herself.

- Importance of euglycemia to prevent maternal and fetal complications .
- Treatment of complications if they arise.

Aim of the treatment is to maintain fasting capillary glucose level < 95 mg% and 2 hour postprandial < 120 mg% to prevent complications.

a. Diet:
Medical nutrition therapy (MNT): It is the cornerstone of treatment of diabetes in pregnancy. Caloric requirement is 25-35 kcal/kg body weight/ day according to body mass index (Table 5.2). It is advisable to take 3 major and 3 minor meals so that there is no intermittent hypoglycemia and still ideal blood sugars are maintained. Dietary care of diabetic patient includes determining the carbohydrate ingested in meals and snacks, so called carbohydrate counting. Carbohydrate counting estimates carbohydrate amount in each meal by determining carbohydrate serving. Each 15 gm of carbohydrate is equivalent to one carbohydrate serving. 1 gram of carbohydrate produces 4 kcal of energy.

Table 5.2: Caloric requirement

Body mass index(BMI) kg/m^2	*Calories intake*
18.5-24.9 (Normal)	30 kcal/kg/day
16.5-18.4 (Underweight)	35 kcal/kg/day
25-30 (Overweight)	25 kcal/kg/day
> 40 (Morbid obesity)	12 kcal/kg/day

Diet composition should be 50-60% of carbohydrates, 20% proteins and 25-30% fats.

b. Exercise:
Planned physical activity for 30 minutes/ day is recommended for all individuals capable of participating. Advising patients to walk briskly or do arm exercises while seated in chair for at least 10 minutes after each meal accomplishes the goal. Exercise in conjunction with diet control improves blood glucose control and may reduce the need for insulin.
Patients with newly diagnosed diabetes should have their blood sugar levels within normal limits within 2 weeks of institution of the diet regulation. Persistent elevation of fasting capillary glucose indicate increased hepatic gluconeogenesis and require treatment with oral hypoglycemic agents or insulin therapy

c. Oral hypoglycemic agents:
Easy to use, non-invasive, have minimal side effects and are better accepted by patients.

Q.6. What are the different oral hypoglycemic agents available to be used in pregnancy visa vis insulin therapy?

Ans:

Sulphonylureas: Glibenclamide (glyburide)[6] is the most commonly used agent. It reaches peak plasma level in 4 hours, its half life is 10 hours and steady state level is reached in 50 hours. It is metabolized in liver and is excreted in the bile. They act by increased insulin secretion, induce better insulin sensitivity and suppress production of hepatic glucose. Starting dose is 2.5 mg in the morning. Dose is changed every 3-5 days according to blood sugar profile till blood sugar is stabilized. Dose is increased by 2.5 mg/ week until 10 mg/ day, and then switch to twice daily dosing until maximum of 20 mg/day is reached. Glucose levels, fasting <100 mg/dl, 1 hour < 155 mg/dl, 2 hour < 130 mg/dl. Its side effects are hypoglycemia (11-38% in non-pregnant females, with much lower incidence in pregnant females), sudden intrauterine deaths near term.

Biguanides: Metformin[7] is most commonly used. It mainly acts on peripheral insulin sensitivity, counteracting insulin resistance. It decreases hepatic glucose output by decreasing glycogenolysis and increases glucose output by skeletal muscle. It is mainly excreted by kidney. Dosage is 500-850 mg in the beginning with maximum of 2000 mg/day in divided doses.

Thiazolidenediones: They are category C drugs and should be prescribed with potential risks explained.

Alpha glucosidase inhibitors: Few data exist regarding use of **Acarbose** in pregnancy. It reduces

postprandial glucose excursions in GDM patients. Dosage is 25 mg orally three times daily to maximum of 100 mg three times a day. A small amount of drug may be absorbed systemically and safety and potential transplacental passage has not been fully evaluated.

Q.7. What are the different types of insulin available and dosage recommended?

Ans:

a. **Insulin therapy[7]:** Pregnant women with type 2 diabetes mellitus and persistent hyperglycemia despite adequate nutritional intake and therapy with glyburide require insulin therapy. Normally 3 to 4 divided doses of insulin are preferred before each meal and 1 or 2 long or intermediate acting insulin dosages per day.

In type 1 diabetes generally the requirement is 0.9U/kg in first trimester, 1 U/kg in second trimester and 1.2 U/kg in third trimester. In type 2 diabetes 0.9, 1.2 and 1.6 U/kg respectively indicating greater insulin resistance.[5] Different types of insulin are given in Table 5.3.

Target plasma glucose levels with insulin therapy are:

Fasting 60-90 mg/dl.

1 hour postprandial < 140 mg/dl.

2 hour postprandial < 120 mg/dl.

Nocturnal 60-120 mg/dl.

Insulin aspart, lispro are expensive, short acting and actually ideal in pregnancy as they effectively control hyperglycemia between meals compared to regular insulin that takes longer time (3-6 hours).

Generally 2/3rd and 1/3rd distribution of intermediate acting drugs with two doses, one each at breakfast and dinner and also the same division for NPH and regular at a given time are prescribed covering at least breakfast and dinner or three doses at breakfast, lunch and dinner are given. With insulin pump1 U/hour is given continuously, there is decrease in dose requirement by 50 to 60% and it can be adjusted with boluses per meal.

1 unit of insulin takes care of 30 mg rise in blood sugar levels in gm%. Hypoglycemia is to be avoided by glucose drink. Glucagon injection is to be kept ready. The relatives are informed about this possibility and bracelet with name and dose of insulin for patient to wear is advisable.[8]

The above patient was started on tablet glyburide 5mg once daily from 30 weeks onwards. How will you monitor her and when will you decide to deliver her? Would it have been different had she developed IUGR? Preeclampsia?

Patient on glyburide should be delivered at 37 completed weeks or earlier in case of IUGR or

Table 5.3: Types of insulin

Type	*Source*	*Onset (hours)*	*Peak (hours)*	*Duration of action*
Short acting				
Humulin R	Human	0.5	2-4	5-7
Lispro	Analog	0.25	0.5-1.5	6-8
Aspart	Analog	0.25	1-3	4-5
Glulisine	Analog	0.25	1	4
Intermediate acting				
Human lente	Human	1-3	6-12	18-24
Human NPH (Isophane)	Human	1-2	6-12	18-24
Long acting				
Humulin ultralente	Human	4-6	8-20	>36
Glargine	Analog	1	5	24
Determir	Analog	1-2	5	24
Combined Mixtard (30% soluble: 70% isophane)	Human			

pre-eclampsia or any other adverse obstetrical complication.

Q.8. When will we consider termination of pregnancy in GDM patients controlled on diet or on insulin?

Ans: The timing of termination of pregnancy of diabetic patients[3] is given in Table 5.4

Table 5.4: Timing of termination of pregnancy

GDM on Diet Uncomplicated	Await spontaneous delivery till 40 weeks with fetomaternal surveillance
GDM on insulin Good control Fetal surveillance normal	Elective induction at 38 weeks (elective induction reduces risk of shoulder dystocia from 10% to 1-4%)

Q.9. What are the indications of termination of pregnancy in GDM patients before 38 weeks?

Ans:

- **Maternal indications**: Severe PIH, vascular disease, uncontrolled diabetes.
- **Fetal indication:** IUGR, fetal compromise.

Q.10. How do we monitor GDM patients during spontaneous labor?

Ans: See Table 5.5

Table 5.5: During spontaneous labor

GDM patients controlled on diet
Blood glucose is maintained between 80-110 mg/dl.Blood sugar monitoring 2 hourly, serum electrolytes 12 hourly, urine sugar, ketones 4 hourly
GDM patients controlled on insulin
Nil per orally Blood glucose is maintained between 80-110 mg/dl Blood sugar monitoring 2 hourly Serum electrolytes 12 hourly Urine sugar, ketones 4 hourly 5 unit insulin in 500 ml of 5% dextrose at rate of 100 ml/hour If blood sugar> 140 mg/dl-plain insulin to be given subcutaneously according to sliding scale Sliding scale: 140-180 mg% - 4 units 181-250 mg% - 8 units. 251-400 mg% - 12 units. > 400 mg% - 16 units. If blood sugar < 80 mg/dl, infuse 5% dextrose at rate of 100 ml/hour. Frequent fetal heart monitoring for high risk pregnancy.

Q.11. How will you induce and monitor labor in GDM patients on insulin therapy?

Ans: See Table 5.6

Table 5.6: For induction and monitoring of labor of patients with GDM on insulin therapy

Nil per mouth after midnight. Bedtime dose of insulin to be given. Unfavorable cervix: Vaginal prostaglandin to be used.(short acting insulin+ light snacks till labor commences) Blood sugar monitoring1-2 hourly. CTG monitoring preferred in active labor. Blood sugar monitoring 2 hourly Serum electrolytes 12 hourly Urine sugar, ketones 4 hourly 5 unit insulin in 500 ml of 5% dextrose at rate of 100 ml/hour If blood sugar> 140 mg/dl-plain insulin to be given subcutaneously according to sliding scale If blood sugar <80 mg/dl, infuse 5% dextrose at rate of 100 ml/hour.

Q.12. What are the indications of Elective LSCS in GDM patients ?

Ans: Indications of elective LSCS in GDM patients is given in Table 5.7

Table 5.7: Indications of elective LSCS

Macrosomia > 4 kg (for predicting macrosomia, shoulder width > 14 cm, EFW > 4 kg on ultrasound)
Demonstrable fetal compromise (Severe IUGR)
Bad obstetric history
Other obstetric indications

Q.13. How should we prepare a GDM patient on insulin for elective LSCS and and how to monitor this patient in postpartum period?

Ans: See Tabel 5.8

Table 5.8: For elective LSCS of patients with GDM on insulin therapy

Omit morning dose of insulin.
Fasting blood sugar and serum electrolytes to be done.
Regional anesthesia (epidural) preferred.
Postoperative blood sugar 2 hourly for 12 hours, 4 hourly after that.
Insulin according to sliding scale.
Urine albumin, sugar, ketone charting to be done.

Q.14. How should patients with GDM be assessed in postpartum period?

Ans: GDM patients normally do not need insulin or oral hypoglycemic agents in postpartum period. Metabolic assessments recommended after pregnancy with gestational diabetes are given in Table 5.9.

Q.15. What contraception will you advise diabetic patient?

Ans: Contraception should be discussed on individual basis with all women of childbearing age with diabetes.

Combined estrogen progesterone pill should be avoided in women with complications or risk factors for vascular disease.

Progesterone only pill may be suitable in these women, but there is increased failure rate.10,11 Mirena (Levonorgesterol containing IUCD) is a safe method of contraception, particularly suitable in diabetic women as it is as effective as sterilization and produces low circulating hormone levels.[12]

Problem Oriented Management

Case: A 35-year old G3 P2 L2 female, known diabetic for 5 years on tab metformin 1 OD came to antenatal clinic with 16 weeks of pregnancy.

Diabetic patients taking metformin for control of diabetes may either continue with oral hypoglycemic throughout the pregnancy or can switch over to insulin after titrating the dose of insulin. The side effects of metformin are polydactyly, lactic acidosis, neonatal hypoglycemia, but they are rarely seen in newborns so patient can continue oral hypoglycemic drugs.[4]

Q.16. What are the complications associated with diabetes during pregnancy?

Ans: Maternal complications associated with diabetes.[5]

Antepartum

1. Medical problems:Emotional stress, hypoglycemia, infections, starvation ketosis, diabetic ketoacidosis, hyperosmolar hyperglycemic nonketotic syndrome, retinopathy, nephropathy, cardiovascular problems, neuropathy.
2. Obstetric complications: Chronic hypertension, pre-eclampsia, preterm labor, premature rupture of membranes, hydramnios.

Table 5.9: Fifth international Workshop conference: Metabolic assessments recommended after pregnancy with Gestational diabetes[9]

Time	*Test*	*Purpose*
Post delivery (1-3 days)	Fasting or random plasma glucose	Detect persistent, overt diabetes.
Early post partum (6-12 weeks)	75 gm 2 hour GTT	Postpartum classification of glucose metabolism.
1 year postpartum Annually	75 gm 2 hour GTT	Assess glucose metabolism.
Tri-annually	Fasting plasma glucose	Assess glucose metabolism.
Pre-pregnancy	75 gm 2 hour GTT	Classify glucose metabolism.
75 gm 2 hour GTT		

Intrapartum: Prolonged labor, uterine inertia, instrumental deliveries, perineal injuries, postpartum hemorrhage, LSCS.

Postpartum: Puerperal sepsis, wound infection.

Fetal complications associated with diabetes:

1. Spontaneous abortions.
2. Congenital malformations.
3. IUGR (Intrauterine growth restriction).
4. Unexplained stillbirth.
5. Macrosomia.

Neonatal complications: Hypoglycemia, hyperbilirubinemia, hypocalcemia, hypothermia, polycythemia, neonatal jaundice, respiratory distress syndrome, renal vein thrombosis, growth restriction, perinatal mortality.

Q.17. How do we classify diabetes in pregnancy?

Ans: There are three classifications of diabetes (Tables 5.10 to 5.12).

Q.18. What are the changes in carbohydrate metabolism during pregnancy?

Ans: Pregnancy exacerbates the diabetic tendency of asymptomatic woman (Table 5.13).

Q. 19. What are the methods of screening of GDM?

Ans: Patients to be screened for GDM are divided into three groups according to recommendations at fifth international workshop of gestational diabetes, 2005.[9]

Table 5.11: Etiological classification of diabetes(NDDG)

1. Type 1: β cell destruction, usually absolute insulin deficiency
a. Immune mediated
b. Idiopathic
2. Type 2: Ranges from predominantly insulin resistance to predominantly insulin secretory defect with insulin resistance.
3. Other types:
a. genetic defects in insulin action.
b. genetic syndromes: Down, Klinefelter, Turner.
c. Diseases of exocrine pancreas: pancreatitis, cystic fibrosis.
d. Endocrinopathies: Cushing syndrome, Pheochromocytoma.
e. Drug or chemical induced: glucocorticoids, thiazides, β adrenergic agents
f. Infections: congenital rubella, cox sackie virus, cytomegalovirus
4. Gestational diabetes (GDM)

Table 5.12: Classification of American Diabetes Association[13]

Normal	*Impaired fasting glucose or impaired glucose tolerance*	*Diabetes mellitus*
Fasting < 110 mg/dl	110-125 mg/dl	≥ 126 mg/dl
2hr < 140 mg/dl	2hr ≥ 140-199 mg/dl	2 hr≥200 mg/dl

Table 5.10: Modified White's classification

Class	*Onset*	*Fasting plasma glucose*	*Two hour postprandial glucose*	*Therapy*
A1	Gestational	< 105 mg/dl	< 120 mg/dl	Diet
A2	Gestational	> 105 mg/dl	> 120 mg/dl	Insulin/Oral hypoglycemic agents
Class	*Age of onset*	*Duration*	*Vascular disease*	*Therapy*
B	> 20	< 10	None	Insulin/OHA
C	10-19	10-19	None	Insulin
D	< 10	> 20	Benign retinopathy	Insulin
F	Any	Any	Nephropathy	Insulin
R	Any	Any	Proliferative retinopathy	Insulin
H	Any	Any	Atherosclerosis, heart disease	Insulin

Table 5.13: Diabetogenic effects of pregnancy[14]

- Insulin resistance
  1. Production of human placental lactogen.
  2. Increased production of cortisol, estriol and progesterone.
  3. increased insulin destruction by kidney and placenta.
- Increased lipolysis
- The mother utilizes fat for her caloric needs and saves glucose for fetal needs.
- Changes in gluconeogenesis
- The fetus preferentially uses alanine and other amino acids, depriving mother of a major neoglucogenic source.

1. *Low-risk group:* Members of ethnic group with low prevalence of GDM, no known diabetes in first degree relatives, age < 25 years, weight normal before pregnancy, weight normal at birth, no history of abnormal glucose metabolism, no history of poor obstetrical outcome.(blood glucose testing not routinely required)
2. *Average risk:* Members of ethnic group with high prevalence of GDM, diabetes in first degree relatives, age > 25 years, overweight before pregnancy, weight high at birth (Perform blood glucose testing at 24-28 weeks using two step or one step procedure).
3. *High risk:* Marked obesity, strong family history of type 2 DM, previous history of GDM, history of stillbirth, History of delivery of large baby (> 4 kg), glycosuria, h/o unexplained neonatal death, h/o congenital malformation, polyhydramnios, h/o traumatic delivey with associated neurological disorder in infant, h/o > 3 spontaneous abortions. Recurrent monoliasis, age > 30 years. impaired glucose metabolism, glucosuria. (Perform glucose testing as soon as feasible, using one step or two step technique and repeated at 24 to 28 weeks.)

Two step technique: 50 gm glucose challenge test (GCT) followed by diagnostic 100 gm glucose tolerance test for those meeting the threshold value in GCT.

One step technique: Diagnostic 100 gm glucose tolerance test performed on all subjects.

How to perform GCT:

Measure venous plasma glucose 1 hour after administering 50 gm glucose. Cut off value ≥ 130 (90% sensitivity) and ≥140 mg/ dl or 7.8 mmol/l (80% sensitivity). It is not necessary to follow any special diet before the test and it is not necessary to be in the fasting state.

How to perform GTT[15]

The test should be performed in the morning after overnight fast of at least 8 hours but not more than 14 hours and after at least 3 days of unrestricted diet (≥ 150 gm carbohydrate/day) and physical activity. The subject should remain seated and should not smoke during test. The blood sugar values during GTT are given in Table 5.14.

Approximately 5% of women doing 3 hour GTT experience hypoglycemia during test. This reactive hypoglycemia is as a result of release of large amount of insulin by the pancreatic beta cells in response to glucose load. Two or more of venous plasma glucose concentrations indicated above must be met or exceeded for a positive diagnosis. (Table 5.14).

Table 5.14: Oral glucose tolerance test

Recommendation by	*Glucose load*	*Criteria*	*Venous plasma glucose*			
			Fasting	*1st hour*	*2nd hour*	*3rd hour*
ADA	100 gm	Carpenter and Coustan	≥95	≥180	≥155	≥140
	75 gm	Carpenter and Coustan	≥95	≥180	≥155	
ACOG	100 gm	NDDG and Carpentar	≥105	≥190	≥165	≥145
WHO	75 gm	WHO	≥126		≥140	

A fasting plasma glucose level >126 mg% or random plasma glucose level >200 mg% meets the threshold for diagnosis of diabetes and precludes the need of any glucose challenge test.

Intravenous glucose tolerance test is done in patients with gastrointestinal diseases or intolerance to glucose or polymer solutions.

Method: Measure the rate of disappearance of glucose (k value).

Equation: Logc Y= LogcA-kt

(Y=Blood glucose concentration in mg/dl, A=y intercept, t= time elapsed.)

K value from 10 minutes to 60 min glucose level after infusion of 25 gram glucose in 50% solution over 2 minutes.(lower limit of normal k= i.37(1st trimester), 1.18(2nd trimester, 1.13(3rd trimester).

HbA1c and serum fructosamine have lower sensitivity and are poor screening technique.

Q.20. What is the future risk in GDM patients?

Ans: In GDM patients, risk of developing GDM in next pregnancy is more than 50%. There is about 70% risk of developing frank diabetes over 10-20 years. Normally diabetes affects 5 to 7% of pregnancies.

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6 Hypertension in Pregnancy

INTRODUCTION

The hypertensive disorder of pregnancy complicates 5 to 10% of pregnancies and is one of the leading causes of perinatal morbidity and mortality.[1] It also causes maternal morbidity and mortality, more so in developing countries. The classification of hypertensive disorders complicating pregnancy by the **Working group of the National High Blood Pressure Education Program (NHBPEP) 2000** is as follows: (i) Gestational Hypertension (ii) Pre-eclampsia and eclampsia syndrome (iii) Pre-eclampsia superimposed on chronic hypertension (iv) Chronic hypertension

- **Gestational hypertension** occurs in 6% of pregnancies and is the hypertension developing in the latter half of pregnancy not associated with proteinuria.[2] Final diagnosis is often made 12 weeks postpartum when the blood pressure returns to normal level. Almost half of the women with gestational hypertension subsequently develop pre-eclampsia syndrome, which includes signs such as proteinuria and thrombocytopenia or symptoms such as headache or epigastric pain.
- **Preeclampsia-eclampsia** is a syndrome that manifests clinically as a new onset hypertension in the latter half of pregnancy (usually after 20 weeks), with associated proteinuria of $\geq$300 mg per 24 hours of urine collection. This syndrome occurs in 5-8% of all pregnancies. Eclampsia is defined as the occurrence of seizures in women with preeclampsia that cannot be attributed to other causes.
- **Chronic hypertension**, defined as blood pressure of $\geq$ 140/90 mm of Hg, either predating pregnancy or developing before 20 weeks gestation, complicates ~ 3% of pregnancies. It is more frequent in women who are of advanced maternal age or who are obese. Although at increased risk for superimposed preeclampsia, many will experience a physiological lowering of blood pressure during pregnancy and a reduction in the requirement for antihypertensive medication particularly in the second trimester.
- **Superimposed preeclampsia** complicates 25% of pregnancies in women with chronic hypertension.

PATHOPHYSIOLOGY OF PREECLAMPSIA

One of the earliest abnormalities noted in women in whom preeclampsia develops, is as under:

- **Failure of second wave of trophoblastic invasion into the spiral arteries** of the uterus leading to narrowing of their lumen and impairment of placental blood flow.
- **Diminished perfusion and a hypoxic environment** eventually lead to release of placental factors that incite a **systemic inflammatory response**.

- **Worsening hypoxia** at the uteroplacental interface leads to production of excessive amounts of antiangiogenic factors like **soluble fms-like tyrosine kinase 1 and soluble endoglin**. These antiangiogenic factors and other inflammatory mediators like TNF α and interleukins provoke endothelial cell injury.
- They also contribute to the **oxidative stress** associated with preeclampsia. This is characterized by **reactive oxygen species** and **free radicals** that lead to formation of self propagating lipid peroxide. These in turn generate highly toxic radicals that injure endothelial cells, modify their **nitric oxide production**, and interfere with prostaglandin balance.
- Other consequences of oxidative stess include production of lipid laden macrophages (foam cells) seen in atherosis; activation of microvascular coagulation manifested by thrombocytopenia; and **increased capillary permeability** manifested by edema and proteinuria.
- **Immunological maladaptive tolerance** between maternal, paternal and fetal tissues has also been implicated in the etiology of preeclampsia. There is dysregulation or loss of maternal immune tolerance to paternally derived placental and fetal antigens. The histological changes at the maternal-placental interface are suggestive of acute graft rejection. Tolerance dysregulation might also explain an increased risk when the paternal antigenic load is increased, that is, with two sets of paternal chromosome—a "double dose". For example, women with molar pregnancies have a higher incidence of early onset preeclampsia.
- Preeclampsia is characterized by **vasospasm** which causes increased vascular resistance and subsequent hypertension. At the same time endothelial cell damage causes interstitial leakage through which blood constituents, including platelets and fibrinogens, are deposited subendothelially. With diminished blood flow, because of maldistribution, ischemia of the surrounding tissues would lead to necrosis, hemorrhage and other end organ disturbances characteristics of the syndrome. As a result of this defect in placentation, there is a failure of cardiovascular adaptations (increased plasma volume and reduced systemic vascular resistance) that are characteristics of normal pregnancy. Unless delivery supervenes, these changes ultimately result in **multiorgan involvement** with a clinical spectrum ranging from barely noticeable to one of cataclysmic pathophysiological deterioration that can be life threatening for both mother and fetus.
- Preeclampsia, as of now, is not preventable as it is considered to be also a **multifactorial polygenic disorder.**

Half of the women with gestational hypertension later on develop preeclampsia. Gestational hypertension – preeclampsia appears to be a continuum of same worsening disease.[3]

Figure 6.1 shows the pathogenesis of hypertension and preeclampsia in pregnancy.

CASE 1

Q.1. A 25-year old 2nd gravida with a pregnancy of 28 weeks of gestation comes for antenatal visit and on routine check up, she is found to be having blood pressure of 150/100 mm of Hg. What is the diagnosis?

Ans: Repeat blood pressure measurement should be performed after 6 hours for the diagnosis of hypertension in pregnancy.[4] Urine should be checked for presence or absence of proteinuria, diagnosis of the patient will depend on the presence or absence of the proteinuria.

If blood pressure is found to be same or ≥ 140/90 mm of Hg on two occasions, 6 hours apart without proteinuria, it is gestational hypertension.

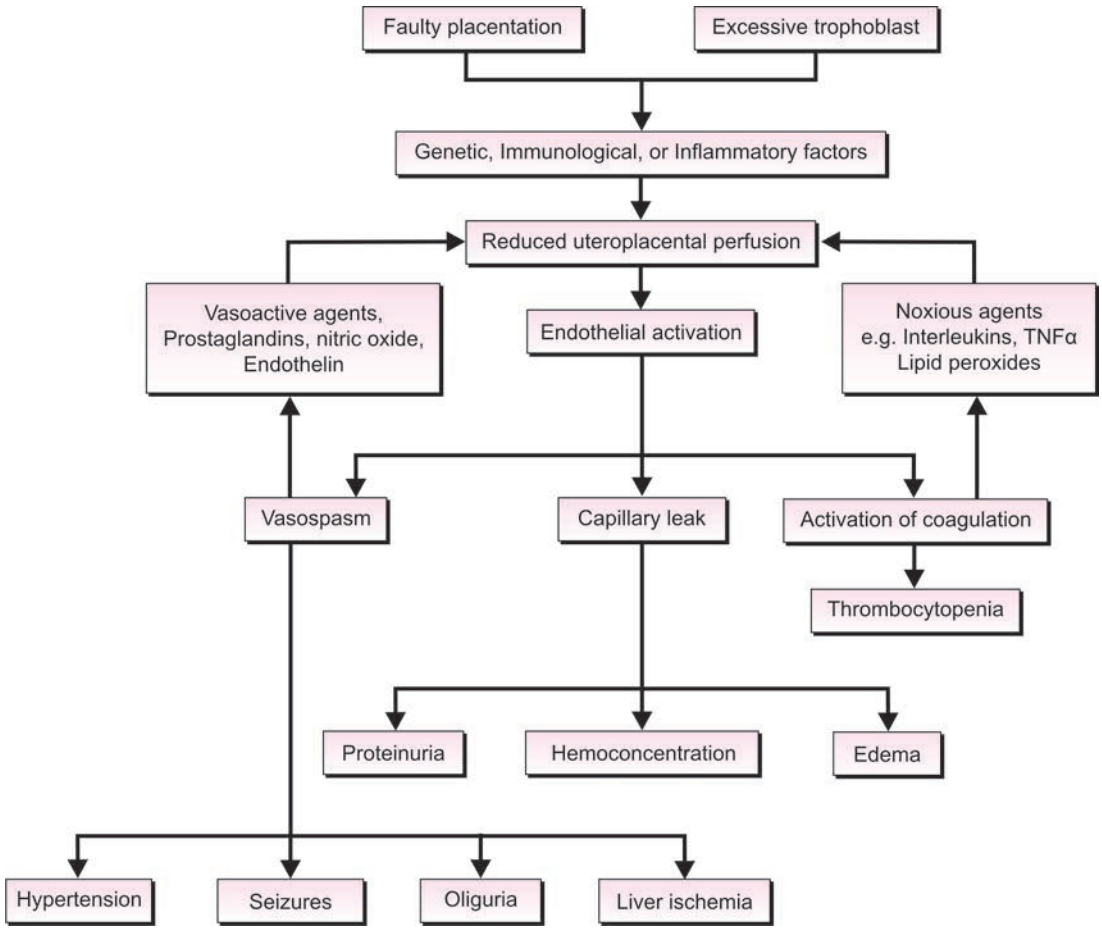

Fig. 6.1: Pathogenesis of hypertension in pregnancy

However, the diagnosis of gestational hypertension can be confirmed only 12 weeks after delivery when the blood pressure returns to normal.

If proteinuria (defined as the urinary excretion of 300 mg/L or more of protein in a 24 hour urine collection or > 30 mg/dl or 1+ by qualitative assessment using reagent strips) is present, it is preeclampsia, therefore proteinuria should be ruled out by testing for urine albumin.

If patient gives history of pre-pregnancy high blood pressure, or has history of high blood pressure before 20 weeks of gestation during this pregnancy, the diagnosis is chronic hypertension.

If blood pressure comes to normal 6 hours later by rest, patient should be observed carefully as there is high possibility of developing gestational hypertension later on in pregnancy. Also, if she gives history of hypertension in earlier pregnancy, she is likely to develop hypertension in this pregnancy suggestive of susceptibility of chronic hypertension later on in life.

It is a mild variety as blood pressure of ≥ 140/90 mm of Hg to <160/110 mm of Hg is considered as mild or non-severe. If it is more than 160/110 mm of Hg persistently, it is severe hypertension.

Q.2. Elaborate the points in the history of hypertensive patients in pregnancy which would help in the diagnosis and management

Ans:

1. Age and parity: Preeclampsia often affects young and nulliparous women; whereas older women >35 years of age are at greater risk for chronic hypertension with superimposed preeclampsia.
2. History of hypertension in family, in earlier pregnancy or prepregnancy high blood pressure: If there is history of gestational hypertension in earlier pregnancy, there are more chances of developing hypertension in this pregnancy, the incidence being 70%.[5] The risk of developing preeclampsia is 20-40% for daughters of preeclamptic mothers; 11-37% for sisters of preeclamptic women; and 22-47% in twin sisters.
3. Race and ethinicity: Africans are more susceptible than caucasians
4. History of diabetes, thyroid disorder, anemia: These are related disorders. Both hypo-thyroidism and hyperthyroidism are associated with hypertension. In India, hypothyroidism is more common than hyperthyroidism.
5. History of twins, hydramnios, H.mole: would cause earlier hypertension in this pregnancy.
6. Smoking reduces the risk of preeclampsia.

Q.3. What are the important points in examination?

Ans: Besides vital parameters like pulse, blood pressure, respiratory rate, temperature, urine output, pallor, pedal edema, other important points in examination are:

- Height, weight and BMI of the patient: obesity is more commonly associated with preeclampsia. The relationship between maternal weight and the risk of preeclampsia is progressive. It increases from 4.3% for women with BMI<20 kg/m^2 to 13.3% in those with BMI>35 kg/m^2.[3]
- Thyroid swelling: Any obvious fullness is to be noted and investigated.
- Cardiovascular system: signs of congestive cardiac failure like basal crepitations, raised JVP, dyspnea and tachypnea have to be ruled out.
- Obstetric examination: Fundal height should correspond to the period of gestation. Fundal height more than period of gestation suggests twins, hydramnios, molar pregnancy and these conditions are more commonly associated with hypertension in pregnancy. Fundal height less than period of gestation is suggestive of fetal growth retardation and also may be associated with hypertension or antihypertensive therapy, particularly atenolol.

Q.4. How will you manage the above patient?

Ans: First we will like to confirm the diagnosis of gestational hypertension . To rule out severe hypertension hospitalization is advisable at least initially for 48 hours. During this period 4 hourly blood pressure measurements with other investigations are performed. They are as follows:

- Complete blood count including platelet count
- Urine albumin 4 hourly by dipstix method or 24 hour urinary protein
- Liver function test including enzymes aspartate transaminases (AST) and alanine transaminases (ALT) levels.
- Kidney function tests including serum creatinine and uric acid levels. Protein/ creatinine ratio and creatinine clearance in severe cases is also advisable.
- Lactate dehydrogenase (LDH) for the diagnosis of HELLP syndrome
- PT and PTTK-Only if platelet count is abnormal
- Fundus examination to rule out severity of the disease.

Urine albumin should be done daily by dipstick method. If the patient is confirmed to be mild hypertensive after investigation without any organ dysfunction, she may be allowed to go home. However, those who don't understand the implications of the disease and have no help at home or no access to nearby hospital would remain hospitalized.

All investigations are repeated once a week or fortnightly depending on the severity except urine albumin and blood pressure measurement which should be done daily.

In addition to maternal investigations, fetal monitoring is also required. Fetal assessment includes daily fetal movement count by the patient which should be more than 10 in 24 hours or more than 3 in one hour three times a day, non-stress test (NST), biophysical profile, umbilical artery and cerebral artery Doppler. These investigations are performed between 28-30 weeks of gestation initially and the biophysical profile/NST is repeated at least once a week till patient delivers. The frequency may increase if hypertension becomes of a severe variety or Doppler shows changes suggestive of fetal growth restriction.

Q.5. How to follow up the patient once she is diagnosed to have mild hypertension and discharged after investigations?

Ans: Patient will be discharged if all the above parameters are found to be normal and blood pressure is below 150/100 mm of Hg. These patients can be managed on outpatient basis, if they understand the seriousness of disease and implications. They should also have the facility of daily blood pressure measurement at home and if necessary should be able to come to the hospital or nearby center in one hour time. Patient is followed every weekly in ANC OPD with blood pressure record of one week, and urine albumin. The weekly assessment of patients with gestational hypertension must include a systematic review of maternal and fetal status. From the maternal side the review includes the levels of blood pressure at home, the presence or absence of symptoms suggestive of end organ damage (blurred vision, epigastric pain) and the presence of proteinuria. Fetal monitoring includes daily charting of fetal movements by the patient and antenatal growth charting (weight gain of the patient, fundal height, abdominal girth measurement). Other investigations for fetal monitoring have already been mentioned.

Proteinuria (≥2 +) in random urine sample is diagnostic of preeclampsia, when proteinuria is trace or 1+ it is necessary to send the random sample to the lab for the determination of the protein/creatinine ratio. A protein/creatinine ratio of >0.30 is indicative of preeclampsia and a value less than 0.20 rules out significant proteinuria. Normally in our hospital, 24 hour urinary protein is estimated even though it is cumbersome to collect 24 hour urine.

The development of proteinuria, elevation of the blood pressure above 150/100 mm of Hg threshhold, decreased fetal movements, abnormal fundal growth or development of maternal symptoms suggestive of end organ damage require admission to the hospital for further evaluation and perhaps for the termination of pregnancy.

Patients with negative findings for abnormality in their weekly assessment may continue with the pregnancy until they reach 38 weeks of gestation. At this time labor induction is performed with the help of cervical ripening agents like dinoprostone/oxytocin/artificial rupture of membrane or cesarean section offered to the patient depending on obstetric indication.

Pregnancy complicated by gestational hypertension is managed according to severity, gestational age and presence of preeclampsia. The management of severe variety of hypertension in pregnancy with or without proteinuria is on the same line and is discussed later.

Termination of pregnancy is the only cure for preeclampsia. Headache, visual disturbances, or epigastric pain is indicative that convulsions may be imminent, and oliguria is another ominous sign. Severe preeclampsia demands anticonvulsants and usually antihypertensive therapy followed by delivery. The prime objectives are to prevent convulsions and serious end organ damage and also to deliver a healthy infant. When the fetus is preterm, the tendency is to temporize in the hope that a few more weeks *in utero* will reduce the risk of neonatal death or serious morbidity from prematurity. Assessment of fetal well being and placental function are performed using NST and biophysical profile, especially when the fetus is immature. With moderate or severe preeclampsia that does not improve after hospitalization, delivery is usually advisable for the welfare of both mother and fetus. Labor induction is carried out, using usually preinduction cervical ripening with a prostaglandin. Whenever it appears that induction almost certainly will not succeed, or attempts have failed, cesarean delivery is indicated for more severe cases.

Q.6. What is the role of elective cesarean delivery?

Ans: Patients with mild disease are generally allowed vaginal delivery unless there are obstetric indications for cesarean sections. Once severe preeclampsia is diagnosed, labor induction and vaginal delivery have been considered ideal. Temporization with an immature fetus is considered subsequently. Several concerns, including an unfavorable cervix, a perceived sense of urgency because of severity of preeclampsia, and the need to coordinate neonatal intensive care, have led some obstetricians to advocate cesarean delivery.

Q.7. What is the role of antihypertensive drugs in mild hypertension in pregnancy?

Ans: Most obstetricians would like to start antihypertensive drugs after blood pressure reaches 150/100 mm of Hg thinking that these will prevent the progression of mild disease into severe disease and also prevent the complication like severe hypertension, abruptio placentae, IUD, cardiac failure, pulmonary edema, cerebral hemorrhage. However, there are studies showing that the use of antihypertensive drugs like labetalol in pregnancy is associated with intrauterine growth retardation of the fetus [6]. The initial dose of labetalol is 100 mg twice a day. This dose may be increased according to patient's response and the maintenance dose is usually 200-400 mg twice daily.

Calcium channel blocker like nifedipine is also being used. The usual dose is 10-30 mg orally every 6-8 hourly(20-80 mg in divided doses). It has no deleterious effect on utero placental blood flow. The most common side effects of nifedipine are facial flushing and headache.

Methyldopa (aldomet) has been the most widely used antihypertensive drug during pregnancy and longest followed up. It is found to be safe from the point of view of development of children later on in life, whose mothers were administered this drug during pregnancy. It has been submitted to many controlled trials during pregnancy and has been shown to have beneficial effects.[7] The usual starting dose is 250 mg of methyldopa three times a day. This amount may be increased up to a total of 2 gm /day according to the patient's response. Higher dose of more than 2 grams indicates severity of hypertension, though up to 4 grams of methyldopa can be used. The common side effects are postural hypotension, excessive sedation and depression. Positive Coombs' test and abnormal liver test are also reported.

CASE 2

Q.8. A 32-years old multiparous woman with 32 weeks of period of gestation has come to the

casualty with blood pressure of 160/110 mm of Hg and complains of headache and urine albumin on dip stix is 2 +. What is the diagnosis?

Ans: The diagnosis of this patient is more likely of severe preeclampsia with impending eclampsia. The diagnosis may also be that of severe pre-eclampsia superimposed on chronic hypertension if the patient gives history of chronic hypertension in the interval between pregnancy or before 20 weeks of the pregnancy.

Q.9. What are the additional points in the history and examination to be looked for?

Ans: Important points to be noted in the history are:

1. history of excessive weight gain
2. history of headache/visual disturbances like blurring of vision, scotoma, bright or black spots: suggestive of impending eclampsia
3. history of epigastric pain/ right upper quadrant pain
4. history of decreased urinary output
5. any history of convulsion
6. any history of intake of antihypertensive drugs
7. any history of breathlessness/chest pain/ ghabrahat etc: suggestive of impending cardiac failure/pulmonary edema
8. any history of renal disease

In addition to examination points discussed in the case1 of mild hypertension mentioned earlier, following points to be noted:

1. Reflexes: Brisk deep tendon reflexes are also common and result from central nervous system irritability. In some cases clonus and twitching of digits may also occur. It is unusual for preeclamptic patients to have seizures without first showing signs of nervous system irritability.
2. Fundus examination: Most common findings on fundus in severe preeclampsia are: (1) increase in a vein to artery ratio and segmental vasospasm (2) The presence of hemorrhage, exudates or extensive arteriolar changes suggest chronic hypertension. (3) Papilledema is not a common finding in preeclampsia. it suggests the possibility of a brain tumor, causing increase in intracranial pressure and secondary hypertension. Rarely, papilledema is found suggestive of fulminating nature of disease with raised intracranial tension where termination of pregnancy is required.

Q.10. What are the main objectives of the management?

Ans: The basic management objectives for any pregnancy complicated by preeclampsia are:

1. Termination of pregnancy with the least possible trauma to mother and fetus. As of now only cure for preeclampsia is the termination of pregnancy. At best, it may be controlled only when it is of mild variety. It is dangerous to continue pregnancy in severe preeclampsia for more than 1-2 weeks.
2. Birth of an infant who subsequently thrives
3. Complete restoration of health to the mother

Q.11. What are the points of severity of the disease?

Ans: Table 6.1 describes the differences in 'nonsevere' and 'severe' variety of hypertension in pregnancy.

Q.12. What is the immediate management of this patient?

Ans: Our aims for the immediate management of this patient are:

- To bring down the blood pressure to safe levels (from severe variety to moderate variety)
- Assess general condition for presence of immediate risk factors for convulsions (headache, altered sensorium, drowsiness, agitation, patients having premonitory symptoms).

Table 6.1: Characteristcs of 'nonsevere' and 'severe' variety of hypertension in pregnancy

Abnormality	*Non-severe*	*Severe*
Diastolic blood pressure	<110 mm Hg	≥110 mm Hg
Systolic blood pressure	<160 mm Hg	≥ 160 mm Hg
Proteinuria	≤2+	≥3+
Headache	Absent	Present
Visual disturbances	Absent	Present
Oliguria	Absent	Present
Upper abdominal pain	Absent	Present
Convulsions	Absent	Present
Serum creatinine	Normal	Elevated
Thrombocytopenia	Absent	Present
Serum transaminase elevation	Minimal	Marked
Fetal growth restriction	Absent	Obvious
Pulmonary edema	Absent	Present
Papilledema	Absent	Present
Hyper-reflexia	Absent	Present
Signs of CCF	Absent	Present
Signs of multi organ dysfunction	Absent	Present

- With the help of investigations and monitoring of urine output we will like to assess the patient for presence or absence of multiorgan involvement and HELLP syndrome.
- Assessment of the fetal wellbeing and reasonable maturity (which is more than 32 weeks ≥ 1 kg of weight, as in our hospital where baby can survive better). It may depend on the individual nursery and neonatology facility. Therefore, one must do the following:
  1. Use of antihypertensive drugs, importantly intravenous labetalol or oral nifedipine. Intravenous labetalol is used in the doses of 20 mg→40 mg→80 mg→80 mg repeated every 10-20 minutes till a maximum dose of 220 mg. Oral nifedipine in the doses of 10 mg→20 mg→20 mg→20 mg→20 mg may also be used upto a maximum dose of 90 mg,with blood pressure monitoring every 10-20 minutes.[8] Once the blood pressure control is achieved (blood pressure < 160/ 110 mm of Hg) maintenance dose in the form of oral labetalol 100 mg twice a day (maximum up to 1200 mg) or methyldopa 250 mg thrice a day (maximum up to 2000 mg/day) or nifedipine 10 mg twice to thrice a day (maximum up to 80 mg) may be started. The dose of oral drug can be titrated according to the blood pressure levels.
  2. Use of magnesium sulphate: It is the most commonly used drug for the prevention and treatment of eclampsia. Magpie trial (2002) proved that magnesium sulphate has a definite role in the treatment of severe preeclampsia. In this trial, the incidence of eclampsia was (2.7%) in the placebo group versus 1.1% in the magnesium sulphate group. Magnesium sulphate is used as 4 gm (20% solution) of loading dose intravenously followed by 5 gm of 50% solution intramuscularly in each buttock. Maintenance dose is 5 gm in alternate buttock 4 hourly till 24 hours after delivery.
  3. Send investigations as discussed earlier with immediate urine albumin examination
  4. Monitoring: blood pressure should be measured every 15 minutes till it comes down from severe to moderate variety and

then every one hourly. Urine albumin charting should be done every 4 hourly. Urine output monitoring preferably by catheterization should be done.

5. USG and Doppler examination to asses the maturity of the fetus if not done earlier to be done after patient settles down.
6. Decision regarding termination of pregnancy, if the fetus has achieved viable maturity has to be taken after counseling the relatives.

Q.13. What is the expectant management in the case of severe preeclampsia?

Ans: Most obstetricians would like to terminate the pregnancy if reasonable maturity of fetus is present (>32 weeks or >1 kg). Patient has to be treated only in a tertiary care center where facility of expert neonatologists, anaesthesiologists, senior obstetricians, O.T facility,and blood bank facility are available. In a rare case, when period of gestation is less than 28 weeks, to gain 1 or 2 weeks more, patient would be observed by extremely close monitoring that is done every 2 hourly blood pressure, urine output, general conditions (tachypnea, dyspnea, crepts in chest) monitoring and if necessary, everyday monitoring by investigations like hemogram with platelet count, Liver function test, kidney function test, PT and PTTK. The dangers are:

1. Patients throwing convulsions
2. HELLP syndrome (40% mortality)
3. Unannounced abruption and IUD
4. DIC
5. Cardiac complications like pulmonary edema
6. Fetal complications like intrauterine growth retardation, absent or reversed umbilical artery Doppler, intrauterine death, neonatal death. However, neonatal death may occur even after termination of the pregnancy.

Q.14. How do we manage a patient with eclampsia?

Ans: Management includes following:

1. Check vitals
2. Place patient in lateral decubitus position to prevent aspiration. The bed rails should be elevated to prevent maternal injury. Padded tongue blade should be inserted between teeth to avoid injury to the tongue.
3. Quick history and examination.
4. Keep airway clean and patent by frequent oral suctioning.
5. Give oxygen by mask at 8-10 litres/minute, if convulsion occurs or pulse oximetry shows hypoxia
6. Prevent convulsions further by keeping silence, dim lights, and minimal noise
7. Give loading dose of magnesium sulphate, 4 gm of 20% solution intravenously slowly over 5 minutes and 5 gm of 50% solution intra-muscularly in each buttock followed by a maintenance dose of 5 gms IM in alternate buttocks every 4 hourly till 24 hours after delivery.
8. Intravenous labetalol or oral nifedipine to bring down the blood pressure to moderate level.
9. Pulse oximetry: There is possibility of help from anesthetists if patient is not maintaining oxygen saturation on pulse oximeter or is having frequent convulsions.
10. After the patient is stabilized, do per vaginum examination and decide termination, preferably vaginal delivery by instilling dinoprostone gel if cervix is too unfavorable or oxytocin augmentation in higher concentration to prevent fluid overload (for primi patients 5 units in 500 ml of Ringer lactate @ 5 miliunits/minute and to be titrated according to the contractions.)
11. It should be noted that cesarean section in eclampsia has higher morbidity and mortality

than vaginal delivery. However, indications of cesarean in eclampsia sometimes can be, though rarely (1) obstetric indication like transverse lie, malpresentation, placenta previa, cephalo pelvic disproportion (2) uncontrolled fits not responding to the anticonvulsants treatment and for termination of pregnancy if there is no immediate prospect of vaginal delivery inspite of induction of labor.

Q.15. What are the causes of death in eclampsia?

Ans: Death in eclampsia may result due to following conditions:

- Intracranial hemorrhage, cerebrovascular accidents
- Pulmonary edema
- Status eclampticus
- Congestive cardiac failure
- Acute renal failure/hepatic failure
- Hypertensive encephalopathy
- Acute tubular necrosis or cortical necrosis
- Disseminated intravascular coagulation (DIC)
- Hyperpyrexia due to pontine hemorrhage
- ARDS
- Aspiration pneumonitis
- All above conditions either singly or in combination.

Q.16. What are the other organ systems involved?

Ans: Organ systems involved are:

- *Cardiovascular changes:* Women with preeclampsia initially have increased cardiac output (CO) and normal peripheral vascular resistance (PVR). However, with worsening of the disease there is a hemodynamic crossover to low CO and elevated PVR. The most serious hematological complication is the HELLP syndrome that is a form of severe preeclampsia with hemolytic anemia with thrombocytopenia with elevated liver enzymes.
- *Renal changes:* The distinctive renal lesion in preeclampsia is "glomerular endotheliosis". It consists of swelling, vacuolization, and deposits of osmophilic material resulting in the obliteration of the capillary lumen. Rarely, preeclampsia alone causes acute tubular necrosis and thus acute renal failure. Although mild degrees are encountered in neglected cases, clinically apparent renal failure is invariably induced by coexistent hemorrhagic hypotension.
- *Liver involvement:* The characteristic lesions commonly found were regions of periportal hemorrhage in the liver periphery. Hepatic hemorrhage from areas of infarction may extend to form a hepatic hematoma. These in turn may extend to form subcapsular hematoma which may rupture. There may also be moderate to severe pain in right upper quadrant or epigastric region.
- *Cerebrovascular changes:* Important neuro-anatomical lesions in the brain are intracerebral hemorrhage, cortical and subcortical petechial hemorrhage, subcortical edema, multiple non-hemorrhagic areas of "softening" throughout the brain and hemorrhagic area in the brain.

Q.17. What is the prognosis of the disease?

Ans: The seizure characteristics of eclampsia are acute and transient and long-term neurologic deficits are rare in patients adequately treated. However, 35% of patients who develop eclampsia will have preeclampsia in a subsequent pregnancy. However, recurrence of eclampsia is 1.4%.

- In women with preeclampsia in first pregnancy, the probability of recurrence in second pregnancy is about 30% and is in inverse relation to the gestational age at which the patient developed the disease.
- The incidence of chronic hypertension was significantly increased 5.2 fold in those who

had gestational hypertension, 3.5 fold after mild preeclampsia and 6.4 fold after severe preeclampsia.
- The risk of developing preeclampsia is 20-40% for daughters of preeclamptic mothers; 11-37% for sisters of preeclamptic women; and 22-47% in twin sisters.

CASE 3

Q.18. A 35-year old lady with first trimester pregnancy with history of hypertension being treated with combination of drugs like atenolol and enalapril (ace inhibitor), comes to ANC OPD. How will you manage?

Ans:

1. First of all, enalapril being fetotoxic should be stopped. Enalapril belongs to angiotensin converting enzyme inhibitors group and is known to cause abnormal renal development in the fetus. They also cause growth restriction, limb shortening and maldevelopment of the calvaria. Atenolol should also be stopped as it is associated with intrauterine growth retardation.
2. Patient should be admitted for initial work up and blood pressure monitoring. Since there is spontaneous reduction in blood pressure in early second trimester, this patient may not require any antihypertensive drugs. However if the blood pressure is still high, this patient can be switched over to other antihypertensive agents which are safe in pregnancy like methyldopa or labetalol.

Q.19. What are the complications expected in this patient and what modified management besides those discussed earlier is needed?

Ans: Maternal complications are:
- Super imposed preeclampsia (incidence being 25%)
- Development of severe hypertension.
- Placental abruption

Fetal complications are:
- Fetal growth restriction
- Preterm delivery and perinatal mortality
- Prone to developmental anomalies due to exposure to fetotoxic drugs like ACE inhibitors in early pregnancy.

Modified treatment includes searching for confounding medical diseases like obesity, diabetes mellitus, and hypothyroidism. These associated medical conditions must be controlled. One must also look for structural defects in fetus if mother has been exposed to fetotoxic drugs early in pregnancy. USG at 14-16 weeks and then repeat at 18-20 weeks must be done to rule out gross congenital anomalies.

Aspirin and antioxidants like vitamin C and vitamin E have also been used for the prevention of superimposed preeclampsia. However, the benefits of these drugs have not been established yet.

Q.20.What are the complications in neonates of mother with hypertension in pregnancy?

Ans: The complications are:
- Intrauterine growth restriction
- Prematurity and perinatal morbidity
- Low birth weight
- Hypoglycemia
- Gross congenital anomalies if mother exposed to fetotoxic drugs in early pregnancy
- Long-term sequel: Risk of development of hypertension in later life

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7 Heart Disease in Pregnancy

CASE 1

Mrs X, 32-yr-old female, married for 10 years, G2P1+0+0+1, last child birth 7 years ago, full term normal vaginal delivery, known case of Rheumatic heart diseases with mitral stenosis for last 8 years was admitted in labor room at 30 weeks with chief complaints of dyspnea, productive cough and palpitations for last 2-3 days.

Q.1. How will you elaborate the history in the above mentioned case?

Ans:

Cardiac history

- Age at diagnosis of cardiac problem, any history of previous surgery/intervention.
- Results of previous investigations for comparison as ECG, ECHO
- History of previous cardiac events (arrythmias, ischemic events, etc.)
- Medication(previous/current)
- Exercise tolerance (and pre-pregnancy comparison), with reference to NYHA classification
- History of palpitations, dyspnea, orthopnea, paroxysmal nocturnal dyspnea and easy fatigability, syncope, chest pain, hemoptysis
- History of recurrent chest infection, cough, fever, urinary infection, periodontal infection

Obstetric history: Any significant history related to cardiac problem in previous pregnancy and in postpartum period, any obstetric complications.

Past history: History of tuberculosis, diabetes mellitus, hypertension, hypercholestrolemia, pulmonary embolus or deep vein thrombosis, blood transfusion, allergy to any drug, any history of previous cardiac surgery or cardiac event.

Family history: History of tuberculosis, diabetes mellitus, hypertension, thromboembolic disease, genetic problems, congenital anomalies, any history of congenital heart disease.

Personal history: History of cigarette smoking, alcohol and illicit drug use and domestic violence. Bowel and bladder habits, history of contraceptive practice prior to pregnancy.

Dietary history: Total caloric intake with reference to carbohydrates, protein and fat intake. Dietary advice is given for adequate protein intake (80-90 gm/day) and to restrict sodium intake.

Treatment history: Details of taking cardiac drugs as digoxin, diuretics, beta-blocker, injection penicillin/3 week, syrup potassium chloride, etc.

Socioeconomic and occupational history: Occupation of the patient should be noted to interpret symptoms due to fatigue or occupational hazards and occupation of the husband to know about socioeconomic condition of the patient and per capita income. This helps to anticipate and treat complications associated with low socioeconomic status like anemia, preeclampsia, prematurity etc. Also enquire about the educational status of the patient to judge her understanding of the disease and explain her about the treatment.

Q.2. How will you examine this case?

Ans:

General physical examination

Built
Nutrition
Height: in cms
Weight: in kg
Body mass index (BMI = wt.in kg/Ht^2 [m])
Gait
Pallor: note in lower palpebral conjunctiva, dorsum of tongue and nail beds
Cyanosis/clubbing
Jaundice
Tongue, teeth, gums and tonsils: look for stomatitis, glossitis or any evidence of infection in mouth
Neck: JVP, thyroid gland and lymph nodes
Pedal edema
Pulse: rate, mention if regular or irregular, volume, note if radiofemoral delay (to rule out coarctation of aorta)
Blood pressure - mm Hg in right arm supine position
Temperature
Respiratory rate

Systemic examination

Cardiovascular

Inspection—JVP raised or not, any visible cardiac impulse
Palpation—Apex beat, heave, thrill,
Auscultion—mention type and grade of murmur, specify area where murmur is best heard over the chest (Benign soft ejection systolic murmurs are present in about 80% of pregnant women and those of low grade are unlikely of clinical significance, however diastolic murmurs are considered abnormal).

Chest examination

- Air entry
- Breath sound, any adventitious sounds
- Basal crepts indicating left ventricular failure

Per abdomen

Hepatomegaly/splenomegaly
Fundal height/lie and presentation, whether corresponding to period of gestation
Comment on liquor and fetal growth, uterine activity, fetal heart rate

In the above patient on cardiac examination pulse rate was 130/min irregularly irregular, JVP raised, mid-diastolic murmur heard at apex, S_1 loud, opening snap following S_2 at apex. Chest auscultation revealed fine crepts at bases.

Q.3. How will you investigate this case?

Ans:

Base line investigations

Hemogram, liver function test, kidney function test, serum electrolytes, coagulation profile is to be done if patient is on anticoagulants. PT/INR is an important marker if patient is on warfarin, aPTT if patient is on unfractionated heparin, ECG and ECHO.

In the above mentioned patient:

ECG (12 long lead): Rate 130/minute, no discernible P wave, variable RR interval, findings suggestive of atrial fibrillation.

Echo – RHD/Severe MS (0.7 $cm^{2)}$/severe TR/Mild AR/trivial MR/Left ventricular ejection fraction 60%, right ventricular systolic pressure = 50 mm Hg [secondary pulmonary artery hypertension].

Q.4. What is the diagnosis and how will you manage atrial fibrillation (AF) in this case?

Ans: The diagnosis is Rheumatic heart disease, severe mitral stenosis (MS), moderate pulmonary arterial hypertension (PAH), atrial fibrillation with fast ventricular rate, CHF, NYHA class IV, without infective endocarditis.

Atrial fibrillation with fast ventricular rate is a medical emergency in a patient of severe MS as there is risk of embolism and hemodynamic deterioration. A patient of MS cannot tolerate increased heart rate associated with atrial fibrillation well because of further compromise in diastolic filling. In rheumatic MS patients atrial fibrillation is usually chronic and is associated with chronically enlarged left atria, cardioversion by

electrical or pharmacotherapeutic means may not lead to sustained sinus rhythm so heart rate control becomes a priority. Ventricular rate should be controlled with beta blockers, calcium channel blockers or digoxin in that order of preference. Target heart rate should be 60-70 beats/minute. Antithrombotic therapy is recomemended for all AF patients to prevent embolic complications including pregnant women.

Q.5a. How will you manage heart failure in this case?

Ans: This patient needs immediate admission and management of CHF which consists of the following.

1. Multidisciplinary team of senior obstetrician, anesthetic, cardiologist.
2. Bed rest to reduce the cardiac work
3. Decreasing the preload with diuretics
   - Propped up position
   - Oxygen by mask, vital charting
   - Diuretics—furosemide 20-40 mg I/V 8 hourly
   - In any patient of critical MS heart rate control is must. Beta blockers, calcium channel blockers or digoxin can be used IV in that order of preference to achieve target heart rate of 60-70 beats/minute.

Note: There is maximum chance of cardiac failure during pregnancy around 30 weeks, during labor and soon following delivery.

Q.5b. If any pregnant patient has acute pulmonary edema, how will you manage her?

Ans: This is a life threatening condition that occurs frequently during pregnancy. It should be managed in intensive care unit. It can occur any time during pregnancy.

The basic pathology of pulmonary edema is

Fluid accumulation in alveolar space

↓

Impaired gas exchange

↓

Oxygen desaturation

↓

Retention of CO_2. It leads to generalized tissue hypoxia, acidosis and death.

Apart from cardiac diseases, fluid overload, preeclampsia, eclampsia, CHF, chorioamniotic infection, use of beta agonist can lead to pulmonary edema.

Apart from diuretics, pharmacological management of pulmonary edema is dependent on the underlying cardiac condition. In case of **critical mitral stenosis** where the left ventricular ejection fraction is usually normal the treatment of choice is rate control by beta blockers, calcium channel blockers or digoxin in that order of preference.

In case of ***regurgitant lesions like MR, AR*** afterload reduction is needed to increase the cardiac output. Nitroglycerine and sodium nitroprusside are the chief afterload reducing agents.

In patients with ***dilated cardiomyopathy with low ejection fraction***, avoid fluid overload, give diuretics (preferably IV), morphine, dobutamine to increase contractility of heart and decrease the after load resistance by nitroglycerine.

Q.6a. How will you treat mitral stenosis in this case?

Ans: This is the most common lesion during pregnancy. It may lead to pulmonary edema, atrial fibrillation, thromboembolic complications and severe PAH. The normal mitral valve area is 4-6 cm^2. Stenosis is graded as mild, moderate and severe according to MVA of >1.5 cm^2, 1 -1.5 cm^2 and <1 cm^2 respectively.

In this case mitral valve area is 0.7 cm^2 that is critical mitral stenosis and this needs to be corrected by balloon mitral valvotomy (BMV).[1] BMV should be done in the second trimester (20-24 weeks) with adequate shielding of abdomen to avoid radiation risk to the fetus.

Open heart surgery and valve replacement is indicated when valvotomy fails or valve is not suitable for valvotomy. ***Heavily calcified valves, severe associated regurgitation and left atrial thrombus are not suitable candidates for BMV.***

Q.6b. How will you manage a patient of mild-moderate mitral stenosis?

Ans: Patient with mild to moderate MS (valve area >1 cm^2 and mean gradient less than 10 mm Hg) who is asymptomatic or mildly symptomatic can almost always be managed with judicious use of diuretics and beta blockers. Diuretics are given to relieve pulmonary and systemic venous congestion. Beta blockers (cardioselective as atenolol or metoprolol) are given to attenuate the increase in heart rate (maintain rate between 60-70 beats per minute) and optimize diastolic filling.

Q.7. How will you monitor this patient in ward after stabilization and post-BMV?

Ans: Enquire about symptoms such as breathlessness, palpitations and chest pain. Examine pulse, blood pressure, heart sounds and chest examination. Carefully monitor for any signs of pregnancy induced hypertension and/or pre-eclampsia. Anemia and hyperthyroidism need to be recognized and treated promptly. Infections like chest, urinary, dental etc, needs to be recognized and treated promptly.

Q.8. What is the role of tocolytics in pregnancy with heart disease?

Ans:

- Most of them are contraindicated in pregnancy
- Safest tocolytic is *atosiban* (oxytocin antagonist)
- Beta agonist is contraindicated in cardiac arrthymias, valvular disease and cardiac ischemia because of their sympathomimetic side effects such as tachycardia, palpitation and hypotension.[2]
- Nifedipine is contraindicated in conduction defect, left ventricular failure due to side effects as tachycardia, hypotension, etc.

Q.9a. What are the ECG and ECHO findings in a *normal pregnant* female?

Ans:

ECG:

Sinus tachycardia
Decrease PR, QRS and QT intervals
Left axis deviation
Small Q wave and negative P wave in lead III
T wave flattening and small ST depression
Atrial and ventricular premature contractions

Echocardiography

Mild left atrial and left ventricular enlargement
Trivial pulmonic and tricuspid valvular regurgitation
Physiological MR.

Q.9b. What are Hemodynamic changes in *normal pregnancy* and labor and their effect on a cardiac patient?

Ans: The hemodynamic changes during pregnancy are:[3]

- The plasma volume by second trimester approaches 50% above normal.
- The heart rate increases to about 20% above baseline.
- There is fall in peripheral vascular resistance.
- The venous pressure in lower extremity rises.
- In normal pregnant females there is rise in cardiac output. It increases by 30-50% above baseline.

So ***volume load*** compromises a patient who has impaired ventricular function (e.g. Patient of dilated cardiomyopathy).

Stenotic lesions like AS and MS are less well tolerated during pregnancy as compared to regurgitant valvular lesions **like AR or MR.** Decrease in peripheral vascular resistance during

pregnancy increases the gradient and severity of AS. Since regurgitant lesions regurgitate less in the presence of decreased afterload they are better tolerated.

Mitral stenosis patients cannot tolerate rapid ventricular rate because when heart rate increases it is the diastolic time which is decreased so left ventricle cannot fill and thus eject properly. Ventricular rate control is must in an MS patient.

During labor and delivery the hemodynamic changes are abrupt. There is increase in cardiac output and blood-pressure. The cardiac output during 2nd stage of labor is often 50% above normal. So conditions like Marfan' syndrome with dilated aorta is not tolerated well and there may be acute aortic dissection or rupture.To avoid abrupt increase in blood pressure (during second stage of labor) cesarean section is indicated in a compromised Marfan's patient.

Q.10. What is the effect of cardiac disease on pregnancy?

Ans: Maternal mortality is maximum in patient of severe pulmonary arterial hypertension of any cause (specially Eisenmenger's syndrome). Maternal complications of heart disease include congestive heart failure, pulmonary edema, arrythmias and sudden cardiac arrest.

In fetus: There is risk of

- IUGR
- Prematurity
- Abortion
- Inheriting congenital heart lesion.

There is high risk of inheriting a congenital heart disease in the child of a mother with congenital heart disease (3% in TOF and 10% in ASD, coarctation of aorta and aortic stenosis). Since Marfan syndrome is an autosomal dominant condition, it has a 50% recurrence rate in offspring. A fetal echo is indicated if the mother has congenital heart disease.[4, 5]

Q.11. What are the predictors of cardiac events during pregnancy?

Ans: Potential for an adverse cardiac event in a pregnant female as pulmonary edema, sustained arrhythmia, stroke, cardiac arrest or cardiac death can be estimated by following parameters.[6]

N New York Heart Association (NYHA) class >2
O Obstructive lesions of the left heart (Mitral valve or aortic valve area <1 cm^2).
P Prior cardiac event before pregnancy—Heart failure, arrhythmia, transient ischemic attack, stroke
E ejection fraction <40%

The risk of cardiac complications is 3%, 30% and 60% when none, one or more than one of these complications are present.

NYHA classification[7] (revised 1979)

Class I: No limitation of physical activity
Class II: Slight limitation of physical activity
Class III: Marked limitation of physical activity
Class IV: Dyspnea at rest.

Q.12a.What is the risk of cardiac events during pregnancy in women with heart disease?

Ans: The risk of cardiac events during pregnancy are:[8]

Low risk:

- Small left to right shunts such as ASD, VSD and PDA
- Repaired lesions with normal cardiac functions
- Mild to moderate pulmonic or tricuspid lesions
- Marfan's syndrome with normal aortic roots
- Homograft or bioprosthetic valves
- Bicuspid aortic valve without stenosis

Intermediate risk:

- Uncorrected cyanotic heart disease
- Large left to right shunts
- Uncorrected, uncomplicated aortic stenosis
- Mechanical valve prosthesis
- Severe pulmonic stenosis
- Moderate to severe left ventricular dysfunction

- Previous left ventricular dysfunction now resolved (such as peripartum cardiomyopathy)
- Previous myocardial infarction

High risk:

- Pulmonary hypertension
- Marfan's syndrome with aortic valve involvement
- Cardiomypathy
- Complicated aortic coarctation.

Q.12b. What are the indications for admitting a patient with heart disease in pregnancy?

Ans: Patients with NYHA class I and II need regular frequent follow up in OPD whereas patients with NYHA III and IV need hospitalization. Heart disease patient require emergency admission whenever there is deterioration of functional grading, appearance of sign/symptoms of failure or any pregnancy complications as anemia, toxemia etc.

Q.13. What are the recommendation of American College of Cardiology/American Heart Association for endocarditis prophylaxis regimens (AHA 2007)?

Ans: The American Heart Association recently updated its guidelines regarding which patients should take a precautionary antibiotic to prevent infective endocarditis (IE).[9]

Prophylactic antibiotics are ***no longer recommended for gastrointestinal or genitourinary tract procedures***. This recommendation follows from the observation that most cases of IE result from bacteremia caused by routine activities such as chewing food, brushing teeth, and flossing. Moreover, no published data clearly indicate that prophylaxis prevents IE from invasive procedures.

It is recommended that IE prophylaxis may be given during labor in the following subgroups of patients who carry substantially high mortality from IE

- Prosthetic cardiac valve
- Previous IE
- Unrepaired congenital heart disease (including palliative shunts and conduits)
- Completely repaired congenital heart defect with prosthetic material or device, during the first 6 months after the procedure.
- Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or device.
- Cardiac transplantation recipients who develop cardiac valvulopathy.

Q.14. What antibiotic regimen for IE prophylaxis is recommended?

Ans: Only a few regimens are recommended by the American College of Obstetricians and Gynecologists (2008)[10] for prophylaxis which is given preferably 30-60 minutes before the procedure. Either ampicillin, 2 gm, or cefazolin or ceftriaxone, 1 gm, is given intravenously. For penicillin sensitive patients, one of the later regimen is given, or if there is history of anaphylaxis, then clindamycin, 600 mg is given intravenously.The recommended oral regimen is 2 gm of amoxicillin. If *Enterococcus* infection is of concern, vancomycin is also given.

Q.15. How will you plan delivery in above case?

Ans: The plan will be to await spontaneous labor if maternal condition is stable and there is no evidence of fetal compromise. With careful monitoring vaginal delivery poses fewer risks.

Q.16. What is the role of induction in labor?

Ans: This has little role in management of heart disease. It may lead to prolong time between induction and delivery interval which results in infection, failure and increase in cesarean section rates.

However if there is obstetric indication there is no contraindication for induction.

The method of induction which is preferable is concentrated syntocinon. During syntocinon infusion precaution should be taken to avoid fluid overload. The concentration of syntocinon infused should be doubled compared with the standard dilution and infusion rate should be halved.[2] *Prostaglandin can be used but with caution as it may lead to pulmonary edema if it is associated with preeclampsia.*

Q.17. What are the indications of elective cesarean section in heart disease?

Ans: In pregnancy with heart disease usually ***cesarean section is indicated for obstetrical reasons*** only.

Exceptions to this rule are:

1. Coarctation of aorta with valvular involvement.
2. Marfan's syndrome with aortic involvement.
3. If there is abrupt hemodynamic deterioration.
4. Some authors recommend cesarean section in women with severe pulmonary hypertension or severe aortic stenosis.[11]
5. A patient who is fully anticoagulated with warfarin at the time of labor needs to be counseled for cesarean section because the baby is also anticoagulated and vaginal delivery carries increase risk to the fetus of intracranial hemorrhage.

Q.18. How will the management differ if the valvular lesion is aortic stenosis (AS) in this patient?

Ans: AS during pregnancy mostly has congenital etiology (bicuspid aortic valve). Rheumatic AS is less common and occurs in association with mitral valve disease. Most patients with mild to moderate AS have a favorable outcome. However those with severe AS (valve area < 1cm^2 or mean gradient > 50 mm Hg) should be counseled not to have pregnancy as the maternal mortality is as high as 17%.[11] The decrease in peripheral resistance during pregnancy will exaggerate the gradient and may precipitate heart failure. Severe heart failure symptoms may necessitate early delivery. Cesarean is considered in severe AS in view of abrupt hemodynamic changes.

- Abrupt fall in afterload when the baby is delivered vaginally may lead to maternal collapse.
- AS patients are critically dependent on preload volume for maintenance of cardiac output as increase in preload will cause pulmonary edema and decrease in preload due to blood loss at the time of parturitation can also lead to maternal collapse. Epidural anesthesia is not preferred in these patient's due to same reasons.

Asymptomatic patients should be managed by bed rest and beta blockers. Diuretics and potent vasodilators should be avoided as these patients are dependant on preload. In case of severe AS percutaneous aortic balloon valvuloplasty may be done especially if the valve morphology is suitable.

Q.19. What will be the management of 1st stage of labor?

Ans:

- Patient should be in lateral decubitus position
- Vital charting (pulse and respiratory rate every 15-30 minutes and BP monitoring 2 hourly)
- Intermittent chest auscultation
- Adequate pain relief
- Restrict IV fluid to 75 ml/hr, avoid bolus oxytocin
- Antibiotic prophylaxis
- Strict input output charting
- Intermittent/continous electronic FHR monitoring
- Per vaginum examination under strict aseptic precautions and only when indicated
- Avoid or delay artificial rupture of membranes
- Pulse oximetry especially in NYHA III and IV
- With highly compromised patient Swan-Ganz catheter facilitates maintenance of optimal hemodynamics.

Q.20. How will you manage 2nd stage of labor?

Ans:

- Lateral decubitus position
- Oxygen by mask
- Pulse oximeter
- Intermittent chest auscultation
- Pain control (I/M tramadol, IV morphine 2-4 mg)
- Anesthesia of choice (Epidural block, or epidural narcotics)
- IV fluid 75 ml/hour
- Vaginal delivery is the better option
- Cut short the second stage (Either vacuum or forceps may be used for operative vaginal delivery if required)

Q.21. How will you manage 3rd stage of labor?

Ans:

- Injection methergin should be avoided
- Injection frusemide 20-40 mg IV to be given to avoid postpartum pulmonary edema
- Sedation
- Intermittent chest auscultation.

Q.22. What will you monitor in the immediate postpartum period?

Ans: In the immediate postpartum period (initial 24-72 hours) there is abrupt increase in venous return not only because of autotransfusion from uterus but also due to removal of vena caval compression post-delivery. So women is vulnerable for pulmonary edema.

- W/F signs and symptoms of CHF
- W/F bleeding per vaginum
- Input output charting
- Vital charting
- Intermittent chest auscultation.

Q.23. What will be the differential diagnosis in this case?

Ans: Normal pregnancy changes, anemia and respiratory problems need to be differentiated from cardiovascular disease in pregnancy.

The normal pregnant patient has a faster resting heart rate, bounding pulse, widened pulse pressure, low blood pressure and warm extremities.

a. Features suggestive of severe anemia:

History: Enquire about socioeconomic strata, dietary history in detail and history of regular antenatal iron intake

Look for other factors as:

Multigravida, multiple pregnancy, chronic illness as UTI, worm infestation, bleeding piles, dysentery, lethargy, palpitations, breathlessness on exertion, history of menorrhagia, blood transfusions

Examination:

- Pallor ++, edema feet +, chelosis, koilonychia
- Pulse regular good volume
- Maintained BP
- Soft systolic murmur
- JVP not raised (unless in failure)
- Hepatosplenomegaly

b. Features suggestive of respiratory disease:

History: Fever with chills and rigors, cough with sputum, pleuritic chest pain, hemoptysis

Examination: Tachycardia, temperature, conducted sounds on chest examination

c. Features suggestive of heart disease

Symptoms:

- Progressive dyspnea
- Orthopnea
- Nocturnal cough
- Hemoptysis
- Syncope
- Chest pain
- Palpitation on ordinary activities
- Easy fatigability

Signs:

- Irregularly irregular pulse
- JVP raised
- Diastolic murmur/systolic murmur gr>III
- Cadiomegaly
- Persistent arrhythmia
- Persistent split S2
- Pulmonary hypertension

CASE 2

Mrs Y, 30 years old female, married for 5 years, Primigravida, known case of Rheumatic heart disease undergone double valve replacement prior to pregnancy has presented in OPD at 6 weeks of pregnancy.

Q.24. How will you manage this patient with prosthetic valve *in situ*?

Ans: It is important to enquire whether patient has mechanical or bioprosthetic valves *in situ*. Women who have undergone valve replacement or had a congenital lesion surgically corrected prior to pregnancy, should be considered for anticoagulants if they have mechanical valve. Bioprosthetic valve or homograft valve do not require any treatment but these valve have shorter half-life of six to eight years which is further shortened by hemodynamics changes of pregnancy.

Management of patient with mechanical valve in situ is:

The patient should be admitted at 6 weeks to switch over from warfarin to heparin. Up to 12th week-heparin to be given (Unfractionated heparin UFH or subcutaneous low molecular weight heparin LMWH) UFH should be given in dose which maintains aPTT twice as high as control.

12th to 36 week—warfarin (Dose should maintain an INR between 2.5-3.5).

36 weeks onwards—omit warfarin, restart heparin. Stop heparin when patient goes in labor and should be started 6 hours after delivery and 24 hours after cesarean section. This heparin may be omitted after overlapping with warfarin therapy once the target INR is achieved.

Low molecular weight heparin may be used in place of conventional unfractionated heparin (Enoxaparin, Therapeutic dose 2 mg/kg body weight).The advantages of LMWH includes less thrombocytopenia, longer half life which permits once or twice daily doses, less incidence of osteoporosis, lower risk of bleeding and need for lab monitoring. ***LMWH should be used only if facility of monitoring anti Xa level is available.***

Q.25. What are the recommendations of American College of Chest Physicians for Anticoagulation of Pregnant Women[12] with mechanical prosthetic valves?

Ans: For pregnant women with mechanical heart valves, any one of the following is recommended:

- Adjusted-dose LMWH twice daily throughout pregnancy. The doses should be adjusted to keep manufacture's peak anti-Xa level 4 hours after subcutaneous injection.
- Adjusted dose UFH administered every 12 hours throughout pregnancy. The doses should be adjusted to keep the midinterval aPTT at least twice control or attain an anti-Xa heparin level 0.35 to 0.70 U/ml.
- LMWH or UFH until 13 weeks gestation with warfarin substitution until close to delivery when LMWH or UFH is resumed.

In women judged to be at very high-risk of thromboembolism and in whom concerns exist about the efficacy and safety of LMWH or UFH as dosed above—some examples include older-generation prosthesis in the mitral position or history of thromboembolism. In these patients Warfarin is suggested throughout pregnancy with replacement by UFH or LMWH (as above) close to delivery. In addition, low-dose aspirin-75 to 100 mg daily should be orally administered.

Q.26. How will you manage if a fully anticoagulated patient on warfarin goes into labor?

Ans: If the patient is still on warfarin and goes into labor, injection vitamin K should be given and fresh frozen plasma should be arranged. In a patient who is on heparin and goes into labor or there is excessive bleeding, protamine sulphate should be arranged (dose is 1 mg/100 units heparin if required).

Q.27. What are the cardiac conditions in which the maternal risk is very high and even termination of pregnancy is indicated?

Ans: Conditions in which risk to mother and fetus is exceptionally high are:

- **Pulmonary artery hypertension (PAH)**[13]: Pulmonary hypertension (PA systoic > 50 mm Hg or 2/3 systemic) regardless of the cause, carries a high mortality when associated with pregnancy. Causes include thrombo-embolic disease, anorexic drugs, valvular heart disease and idiopathic primary pulmonary hypertension. Pregnancy is poorly tolerated, with a risk of worsening cyanosis and hypoxia, arrythmias, heart failure and death.. Maternal mortality rate is as high as 50% in PAH.
- **Dilated cardiomyopathy** with ejection fraction < 40% due to volume overload of pregnancy
- **Symptomatic obstructive lesions** as AS, MS, Coarctation of aorta.
- **Marfan's syndrome with aortic root > 40 mm**, as patient is vulnerable to progressive aortic dilatation, dissection and rupture. This occurs because of increased stroke volume in pregnancy and due to hormonal changes in pregnancy which adversely affect aortic changes. Estrogens interfere with collagen deposition within media of large and medium muscular arteries. Circulating elastase breaks the elastic lamellae and relaxin decreases collagen synthesis and predisposes to aortic dissection. Beta blocker should be used. Hypertension should be avoided to prevent aortic dissection.
- **Cyanotic lesions**: As peripheral vascular resistance falls in pregnancy, right to left shunt increases and hence maternal hypoxia increases and affects fetal growth and survival. Only 12% of such pregnancies result in live born fetus if oxygen saturation is < 88%. Apart from this erythrocytosis of cyanotic lesions and hypercoagulable state of pregnancy may lead to venous thrombosis which may lead to paradoxical embolism.
- **Mechanical prosthetic valves:** Already described.

Termination of pregnancy is indicated in following conditions

- *Eisenmenger's syndrome:* Patients with this syndrome have pulmonary hypertension with shunt (R to L) through an open ductus, an ASD or VSD. Maternal mortality is about 50%. Termination of pregnancy should be seriously considered. Heparin should be used through out the pregnancy as there is risk of systemic and pulmonary thromboembolism. Epidural anesthesia is contraindicated. Inhaled nitric oxide or IV prostacycline is used as a pulmonary vasodilator.
- Primary pulmonary hypertension.
- Marfan's syndrome with aortic involvement
- Uncorrected coarctation of aorta especially when associated with other anomalies as aneurysm of circle of willis.

CASE 3

P2L2 patient, 3rd postoperative day of cesarean develops sudden cardiac failure.

Symptoms: Weakness, shortness of breath, palpitation, nocturnal dyspnea and cough.
Sign: Tachycardia, arrhythmia, peripheral edema, pulmonary rales. S3 present and no murmur

She had been a booked patient with regular antenatal check-ups and with no prior heart problem and uneventful prior obstetric history.

Q.28. What is the probable diagnosis and how will you confirm it?

Ans: The diagnosis of peripartum cardiomyopathy should be kept in mind.

The criteria for diagnosis are[14]

1. Cardiac failure within last month of pregnancy or within 5 month postpartum.

2. No determinable cause for failure (may be immunological or nutritional).
3. No previous heart disease.
4. Left ventricular dysfunction (Echocardiography) as evidenced by ejection fraction < 45%
5. Left ventricular end-diastolic dimension > 2.7 cm/m^2.

Predisposing factors

- Multiparous
- Young 20-35 years
- Twins pregnancy
- Chronic hypertension pre-eclampsia
- Prolonged tocolytic therapy.

Investigation

Chest X-ray: Enlarged heart and pulmonary vascular redistribution.

Echo: Enlargement of all chambers of the heart (predominantly left heart).

Left ventricular global hypokinesia with decreased ejection fraction.

Treatment:

- Salt restriction
- Bedrest
- ACE inhibitors
- Beta blockers
- Diuretics
- Digitalis

Risk of recurrence is high in women in whom there is persistent left ventricular dysfunction.

Q.29. What will be the contraceptive advice to women with heart disease?

Ans: Steroidal contraception is contraindicated as it may precipitate thromboembolic phenomenon. Intrautetrine device is avoided for fear of infection. Barrier method of contraceptive (condom) is safely recommended. Sterilization should be considered with completion of the family at the end of first week in the puerperium preferably through abdominal route by minilap technique. If the husband is willing vasectomy should be advised.

Q.30. What are the cardiovascular drugs used during pregnancy and their side effects?

Ans:

Amiodarone: Goiter, hypothyroidism and hyperthyroidism, IUGR.

Angiotensin-converting enzyme inhibitor (contraindicated): IUGR, oligohydramnios, renal failure, abnormal bone ossification;

Beta blocker (relatively safe): IUGR, neonatal bradycardia, hypoglycemia.

Calcium channel blocker (relatively safe):

Digoxin (safe); no adverse effects.

Lasix (safe): Caution regarding maternal hypovolemia and reduced placental blood flow.

Warfarin: Fetal embryopathy, placental and fetal hemorrhage, central nervous system abnormalities.

Q.31. What is the role of preconceptional counseling in case of heart disease?

Ans: Pre-pregnancy counseling has a major preventive role in ensuring an optimal pregnancy outcome. The assessement is best performed by the obstetrician and the cardiologist. The topics for discussion are[15]:

- Characteristics of the heart condition, functional and risk classifications.
- Effects of cardiac conditions on pregnancy.
- Effects of pregnancy on cardiac conditions.
- Fetal and neonatal complications associated with specific heart condition.
- Need for multi disciplinary care.
- Frequency of prenatal visits and need for maternal and fetal testing.
- Need for anticoagulation, hemodynamic monitoring.
- Timing of birth, type of hospital facility required for childbirth.
- Pain control and type of anesthesia required during labor and delivery.
- Potential need for cesarean delivery.

- All potential source of infection should be looked for and eliminated by clinical examination and laboratory investigation.
- Women who are receiving warfarin should be considered for switch over to heparin therapy.
- Genetic testing if the patient is suffering from heritable congenital heart disease.

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Chandan Dubey

8 Fetal Growth Restriction

A fetus that has been unable to achieve a specific biometric or estimated weight threshold by a specific gestational age is called a small-for gestational-age [SGA] fetus. The most commonly used threshold is the tenth centile for abdominal circumference and estimated fetal weight.[1] This is an arbitrary selection. A more rigorous criterion like the third or fifth centile would be more specific but less sensitive thus resulting in many at risk fetuses being missed from crucial surveillance.

SGA fetuses comprise:

- Fetuses with growth restriction.
- Constitutionally small and healthy fetuses. (50-70% of SGA fetuses.)[2]

Classification of fetal growth restriction [FGR]: Clinical relevance of earlier classification as symmetric or asymmetric based on concordance of growth of head and abdomen as measured on ultrasound is now controversial as studies have shown significant overlap.[3,4] Early onset growth restriction is defined as growth compromise clinically recognizable before 28 weeks of gestation.[5]

Fetuses with FGR are at increased risk of stillbirth, asphyxia, prematurity, neonatal complications, impaired neurodevelopment and possibly type 2 diabetes and hypertension in later life.

CASE 1

Mrs R, a primigravida with 31 weeks pregnancy is suspected to have fetal growth restriction because her fundal height corresponds to 26 weeks only.

Important points in history

- Determining the period of gestation with accuracy is crucial for diagnosing FGR.
- Date of last menstrual period, sure of dates with regular cycles or any history of prolonged cycles.
- History of using hormonal pills like oral contraceptives just prior to conception.
- An ultrasound done in the first trimester with pregnancy dated by CRL between 8-14 weeks would help to date the gestation most accurately.

First trimester

- History of fever with or without rash to rule out infections like rubella, herpes, chickenpox, malaria which can lead to FGR if transmitted to the fetus *in utero*.
- History of exposure to drugs or radiation.

Second and third trimester

- History of poor weight gain, or excessive weight gain as in preeclampsia with swelling of feet and tightening of rings suggesting edema.

- History of pain abdomen, bleeding or leaking per vaginum to rule out chronic abruption and preterm premature rupture of membranes.
- History of perceiving fetal movements.

Obstetric history

- In a multiparous patient details of previous outcomes regarding birth weights, mode of deliveries.
- Any complications like preeclampsia, abruption, miscarriages, growth retricted babies, intrauterine deaths or stillbirths may suggest APLA syndrome.

Past history

- History of hypertension, renal disease, diabetes mellitus, heart disease, asthma, autoimmune diseases like SLE.
- History of clots in blood vessels suggestive of thrombophilias.

Personal history

- Smoking, alcoholism and drug abuse especially cocaine as all these can cause FGR.

Dietary history

- Diet adequate in calories and proteins with iron and calcium supplementation or not.

Socioeconomic history

- Poor socioeconomic status and maternal malnutrition may be contributory to FGR.

Family history

- Family history of genetic disorders or syndromes.
- History of thalassemias or thrombophilias.

Examination

General Physical Examination

General build and nutritional status.

Height and weight – A constitutionally small mother may have a healthy small-for-gestational-age fetus.

Pulse: Rate, rhythm, volume, peripheral pulses and any radiofemoral delay

Blood pressure.

Respiratory rate

Pallor, cyanosis or icterus.

Thyroid swelling

Cervical lymphadenopathy

Jugular venous pulsations

Pedal edema

Systemic Examination

Detailed CVS and Respiratory system examination.

Abdominal examination:

Inspection- Distended uterine ovoid, any visible scars, hernial sites.

Palpation-Liver and spleen may be enlarged in chronic malaria.

Renal angle tenderness. Renal angle tenderness may be present in recurrent upper urinary tract infections and chronic pyelonephritis which may be the causes of FGR.

Fundal height in weeks and symphysiofundal height [SFH] in cms.

Fetal lie, presentation, amount of liquor. Decreased liquor may be clinically apparent and is often associated with FGR.

Auscultation- Fetal heart rate.

Q.1. How do you measure SFH?

Ans: Patient should be empty bladder and lying supine with legs straight. Start the measurement by first identifying the variable point the fundus and then measuring to the fixed point the symphysis pubis, with the centimeter values hidden from the examiner to avoid observer bias.[6]

Q.2. What is the accuracy of SFH measurement in detecting SGA fetuses?

Ans: SFH has limited diagnostic accuracy in predicting SGA fetuses, with a sensitivity of only 27% and specificity of 88%.[7]

Serial measurements and use of customized SFH charts may improve sensitivity and specificity.[8]

Q.3. What are the causes of FGR?

Ans: Maternal factors:

- Preeclampsia, chronic or essential hypertension, secondary hypertension.
- Renal disease
- Diabetes with vasculopathy
- Autoimmune syndromes-APLA, SLE.
- Thrombophilia
- Severe or cyanotic heart disease
- Asthma
- Hemoglobinopathy
- Smoking, alcoholism and substance abuse like cocaine
- Therapeutic agents like anti-cancer drugs
- Malnutrition

Fetal Factors:

- Aneuploidies- Trisomy 13, 18, 21 or triploidy
- Genomic imprinting and uniparental disomy
- Malformations-heart disease, diaphragmatic hernia, gastroschisis, omphalocele
- Multiple gestation
- Fetal infections-malaria, cytomegalovirus, herpes, toxoplasmosis

Placental factors:

- Confined placental mosaicism
- Placenta previa
- Abruptio placenta
- Infarction
- Placenta accreta
- Hemangioma
- Circumvallate placenta.

Investigations

Q.4. What investigation would you like to do for this patient, Mrs R ?

Ans:

Routine

Hemogram

Blood group and Rh type

VDRL

Glucose challenge test

HIV

HBsAg

HPLC (High Performance Liquid Chromatography) for HbA2 estimation Fetal Hemoglobinopathy may cause FGR.

Urine routine, microscopy, culture and sensitivity.

Others:

TORCH test. (Toxoplasma Rubellla CMV, herpes and others).

Screen for Anti-phospholipid Antibodies (LAC, ACL both IgG and IgM)

Thrombophilia screen.

KFT(Kidney Function Test)

LFT(Liver Function)

Thyroid function tests (Thyroid disorders may be a part of autoimmune diseases.)

A detailed level II ultrasound for:

- Fetal anatomic survey to rule out congenital anomalies as anomalies may be a cause of FGR
- Fetal biometry to confirm FGR, repeated every two weeks, to assess for fetal growth
- Abdominal circumference (AC) and estimated fetal weight (EFW) specifically.
- Fetal echocardiography to rule out congenital heart disease.
- Doppler flow studies of the umbilical artery, repeated weekly if normal or twice a week if compromised blood flow.
- MCA and venous Doppler only if umbilical artery Doppler is showing compromise.

Amniocentesis is indicated and may be offered in cases where:

1. Fetat karyotype is needed to rule out aneuploidies as in early onset FGR. Chromosomal anomalies may be found in 19% of fetuses with AC and estimated fetal weight (EFW) less than fifth centile.[9] This risk increases with the presence of anomalies and normal AFI and Doppler parameters on ultrasound.[9]
2. Gene probes for specific genetic disorders.

3. PCR for fetal viral infections in early onset FGR, with normal AFI and Doppler studies, maternal TORCH positive, calcifications in fetal brain and liver on ultrasound.

Screening for anomalies and aneuploidies is important because presence of severe anomalies with poor prognosis for fetus or aneuploidies will indicate avoidance of fetal surveillance for growth and well being and unnecessary interventions like LSCS for fetal indication.

Biophysical tests of fetal well being:

Biophysical Profile [BPP]

Non-stress test [NST]

Amniotic fluid assessment by amniotic fluid Index (AFI) or single deepest pocket

Cardiotocography [CTG]

These will be performed weekly or more frequently as the severity of the case demands.

Q.5. Are there any newer investigations that you know of ?

Ans: Transverse cerebellar diameter has been shown to correlate well with gestational age in FGR.[10] It's advantage over bony parameters is controversial.[11]

3-D ultrasound[12,13] and MRI[14] are being evaluated for diagnosis and management of FGR.

Q.6. Dating a pregnancy is crucial to arrive at a diagnosis of FGR. What is the reliability of various parameters for the same?

Ans:

	Parameter	*Error[95%]*
History	LMP(excellent history)	14 to 17 days
	LMP(poor history)	>28 days
	IVF	1 day
	Ovulation induction	3 days
Physical examination	First trimester PV	14 days
	Second trimester fundal height	28 days
	Third trimester fundal height	28 to 36 days
Investigations	Crown rump length {CRL) first trimester	5 to 7 days
	Gestational sac diameter first trimester	7 days
	BPD (<28 weeks)	5 to 7 days
	BPD (third trimester)	14 to 28 days

Crown rump length (CRL) is the most accurate method of dating a pregnancy in the first trimester[15] follwed by BPD in the second trimester.

Q.7. What is the reliability of various biometric parameters in the diagnosis of FGR?

Ans:

	Fetal weight	*AC*	*HC/AC*	*AC/FL*	*Doppler UA*
Sensitivity(%)	65.8	62.2	49.1	28.9	66.7
Specificity(%)	88.9	90.7	83.7	47.8	68.5
Positive predictive value (%)	63.6	67.3	47.1	47.8	38.4
Negative predictive value (%)	89.8	89.8	84.8	81.3	87.5
False positive (%)	8.6	7.2	12.6	7.2	24.4
False negative (%)	7.8	8.0	11.6	16.2	7.8

AC-Abdominal circumference, HC- Head circumference, FL- Femur length, UA- umbilical artery

- Abdominal circumference (AC) and estimated fetal weight (EFW) show the best specificity, positive and negative predictive value and the lowest false positive and negative values. They are the most accurate in predicting SGA fetuses.[1]
- Combining AC or EFW with umbilical artery (UA) Doppler studies improves the accuracy of diagnosing FGR.[16]
- An individual test alone may not be predictive of FGR, but a combination of abnormal findings

such as a small fetus for dates on ultrasound with reduced liquor and/or abnormal umbilical artery Doppler, may indicate pathology.

- A threshold of tenth centile for AC and EFW is better for diagnosing SGA than other centiles.[1]
- Customized EFW charts adjusted for physiological variables like maternal weight, height, ethnic group and parity have better sensitivities for identifying SGA fetuses.
- Serial scans every two weeks to measure AC and EFW are superior to single estimate of AC or EFW in the prediction of FGR and poor perinatal outcome.[17, 18]

Q.8. What is the role of Doppler in diagnosis and followup of pregnancies with FGR?

Ans: Use of umbilical artery Doppler in managing pregnancies with FGR decreases the risk of perinatal mortality by 38%.[19]

The identification of abnormal UA flow pattern occurring as a result of fetal adaptation to impaired utero-placental blood flow, is a very useful diagnostic and surveillance tool for FGR fetuses.[20]

It helps to distinguish constitutionally small fetuses from growth restricted ones.

Doppler indices used for estimation are:

Systolic-to-diastolic ratio (S/D ratio)

$$\frac{\text{Systolic peak velocity}}{\text{Diastolic peak velocity}}$$

Pulsatility index (PI)

$$\frac{\text{Systolic – end diastolic peak velocity}}{\text{Time averaged maximum velocity}}$$

Resistance index (RI)

$$\frac{\text{Systolic – end diastolic peak velocity}}{\text{Systolic peak velocity}}$$

A relative decrease in end-diastolic velocities elevates each of the indices and usually reflects increased downstream resistance. With absent end diastolic velocity (AEDV), the S/D ratio approaches infinity and the resistance index becomes 1

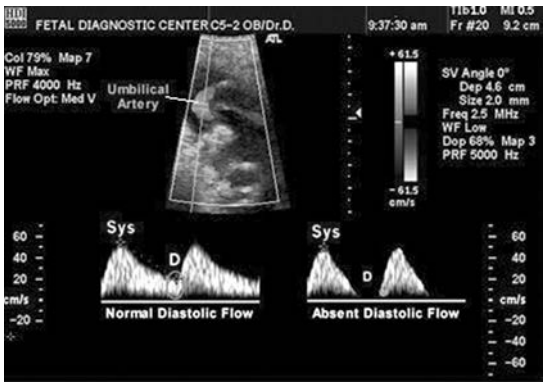

Fig. 8.1: Doppler of umbilical artery showing normal and absent end diastolic flow

(Fig. 8.1). The PI has the advantage of smaller error and can be numerically analyzed even with absent end diastolic velocity.[21]

Q.9. Why and how do these changes in Doppler indices occur?

Ans:

- In the normal fetus Doppler of umbilical artery shows presence of diastolic flow by 15 weeks gestation. As the placental resistance decreases with advancing gestation due to trophoblastic invasion, diastolic flow increases. This is manifested as decrease in S/D ratio or PI. Thus the UA shows a waveform with continuous flow during systole and diastole.
- In a growth restricted fetus with decreased placental perfusion and increasing resistance to flow due to atherosclerotic like process with local ischemia and necrosis, the UA Doppler shows an increasing S/D ratio, RI and PI as the diastolic flow decreases. Gradually the diastolic flow ends (AEDV-absent end diastolic velocity) and then reverses (REDV- reversed end diastolic velocity) (Fig. 8.2).[22]
- AEDV and REDV are associated with increased perinatal morbidity and mortality [23] and if identified, urgent intervention with steroid

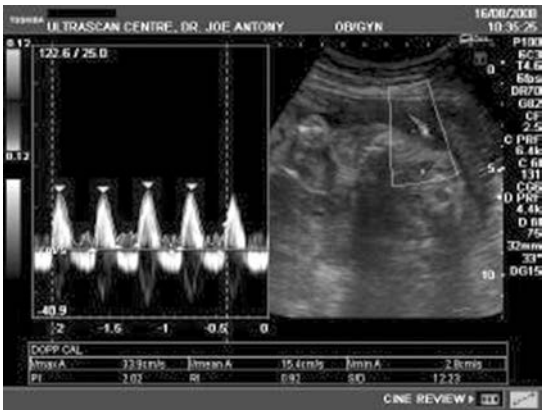

Fig. 8.2: Doppler of umbilical artery showing reversed end diastolic flow

administration for fetal lung maturity and delivery is required even in a preterm fetus.

Q.10. What is the role of middle cerebral artery (MCA) Doppler in follow-up of a pregnancy with FGR?

Ans: In the normal fetus MCA is characterized by higher impedance to flow as compared to umbilical artery and hence it exhibits a low amplitude of diastolic flow in the normal circumstances. The flow increases in a hypoxic fetus due to cerebral vasodilation which occurs as an adaptive mechanism, resulting in a decreased PI value. This is usually a later change in a hypoxic fetus and occurs after the UA shows AEDV.

Q.11. What is the role of venous Doppler in monitoring a fetus with growth restriction?

Ans: Venous Doppler changes usually occur late in fetuses with growth restriction when there is fetal acidosis with cardiac function compromise. Increased preload manifests as:

- Pulsations in umbilical vein (UV).
- Increased reversed flow during atrial contraction in the inferior vena cava (IVC).
- Absence or reversal of flow during atrial contraction in the ductus venosus (DV).[24,25]

Doppler assessment of UV, IVC and DV may be used as back up tests in fetuses with umbilical artery Doppler showing AEDV [26] at less than 34 weeks. Presence of such pre-terminal changes may indicate urgent delivery.

Q.12. What is the importance of amniotic fluid assessment in pregnancies with fetal growth restriction?

Ans:

- Decreased amniotic fluid may signify placental insufficiency or fetal anomalies like renal agenesis or dysplasia, urethral obstruction, bilateral polycystic/multicystic kidneys. Oligohydramnios may also be a feature of congenital viral infections.
- Both amniotic fluid index (AFI) and single deepest pocket measurement are equally good for liquor assessment according to current evidence when used as a part of biophysical profile.[27]
- Antepartum AFI ≤ 5 is associated with increased risk of cesarean section for fetal distress and an Apgar score of < 7 at 5 minutes.[28]
- A low or marginal AFI should be followed by more frequent surveillance. AFI ≤ 5 should prompt consideration for delivery.[29]

Q.13. What is the role of biophysical profile (BPP) in evaluating growth restricted fetuses?

Ans:

- BPP has a high false positive rate of 40 to 50% and a low false negative of 8 per 1000.
- BPP is a standard practice in management protocols of FGR pregnancies.
- It is rarely abnormal when Doppler of UA is normal.[30]
- It may be more useful when UA Doppler is abnormal as it has a high negative predictive value in high-risk cases.[31]
- Fetal death is rare in women with a normal BPP. Usually done once a week, and increased to twice weekly or daily in severe cases.

- Progessive fetal hypoxemia is associated with decline in AFV, fetal breathing, gross body movements, fetal tone and NST.[32,33] Fetal breathing is affected first followed by AFV, and then fetal heart rate variability decreases.
- Fetal movements and tone are lost with fetal acidemia,[34] and are late events
- Although originally all parameters were given equal importance, it has been shown that oligohydramnios has an independent risk and its presence requires reassessment of management plan.

Q.14. What is the role of NST in managing FGR pregnancies?

Ans:

- NST is a frequently used test of fetal well being with a false positive rate of 80% and a false negative rate of 2-3/1000. A reactive NST signifies that fetal compromise is remote and is reassuring, but a nonreactive NST may be associated with adverse perinatal outcome and fetal sleep cycle.
- NST may be used weekly in FGR pregnancies or increased to twice weekly or daily in severe cases.
- A modified BPP profile with just NST and AFI as it's components may be used to follow up FGR fetuses.

Q.15. Is there a role of uterine artery Doppler in management of FGR pregnancies?

Ans:

- Uterine artery Doppler has a role in the prediction of FGR.
- Deficient placentation is highly associated with gestational hypertensive disorders, FGR and fetal demise. Uterine artery Doppler resistance profile that is high, persistently notched, or both, identifies women who are at risk for pre-eclampsia and FGR. It has a sensitivity of 85% when done between 22 to 23 weeks.[35,36]
- Low dose aspirin initiated this late in pregnancy does not improve placental function.[37]
- First trimester is being explored in high risk patients with hypertension, thrombophilia, or a history of pre-eclampsia and FGR. Those with bilateral uterine artery notching at 12 to 14 weeks may benefit by low dose aspirin therapy.[38]

Treatment

Q.16. Is there a role of therapeutic measures in management of pregnancies with FGR?

Ans: Depending on the cause various therapies have been tried, but most etiologic factors are not amenable to therapy and do not benefit fetal growth.

- Antihypertensives used in hypertensive disorders of pregnancy do not help fetal growth.
- Lifestyle modifications like smoking cessation, or cessation of alcohol intake or illicit drug use may be helpful.
- Diagnosis of fetal viral and parasitic infections is important for prognosis and neonatal management. Maternal therapy in toxoplasmosis and malaria may prevent the spread of infection to fetus *in utero*. A thorough history, maternal blood antibody titres and amniocentesis or cordocentesis may help in detecting the infectious agent.
- There is no concrete evidence to evaluate benefits and risks of hospitalisation and bed rest, oxygen therapy to mother, nutrient therapy, betamimetics, calcium channel blockers, hormonal therapy and plasma volume expanders for treatment of FGR.[8]
- Combined aspirin and heparin therapy may benefit fetal outcome in women with APLA.

Q.17. How will you follow up the patient, Mrs R, further and when will you plan delivery?

Ans: Assume that there are no maternal complications, dates are excellent, diagnosis of FGR is confirmed by AC and EFW < fifth centile, there

are no anomalies on scan and UA Doppler and BPP are normal.

- Patient may be followed up on outpatient basis with weekly antenatal visit.
- Explained to keep a daily fetal movement record at home and report earlier in case of diminished movements.
- Check blood pressure, urine albumen, maternal weight gain and SFH on each visit.
- Fortnightly biometric scans to detect severity of growth lag.
- Weekly Doppler of UA is recommended as the primary modality for fetal well being. (Level 1 evidence).
- BPP or NST and AFI may be done weekly as a primary testing though they may be used as back up tests when UA Doppler starts showing abnormal changes.
- Admission will be needed if Doppler shows abnormal ratios.

If the UA Doppler shows present end diastolic flow delivery may be delayed till 37 weeks provided other surveillance findings are normal.[8]

Q.18. How will you plan the mode of delivery and what factors will you take into account?

Ans:

- The mode of delivery will be dictated by gestational age, Bishop's score, fetal presentation, fetal tolerance of labor depending on Doppler parameters and BPP and maternal complications.
- An elective cesarean delivery may be considered in the presence of pretem gestation with unfavorable cervix or serious fetal compromise like AEDV or REDV, BPP ≤ 4, ominous venous Doppler changes or any maternal medical or obstetric complications. If no such complications are present, a vaginal delivery is planned and patient is induced at 37 weeks if delivery is not indicated earlier.

Q.19. What are your concerns for labor and delivery and how will you prevent complications?

Ans:

- Consent for labor induction is taken from the patient explaining the increased likelihood of emergency cesarean for fetal distress. Presence of oligohydramnios increases the risk of cord compression and variable decelerations. Late deceleration may occur due to fetal asphyxia.
- Delivery should be conducted in a facility with optimal anesthesia and neonatology services.
- Antenatal steroids 48 hours prior to induction should be given if gestation is less than 34 weeks to reduce the incidence of respiratory distress syndrome.[39]
- Intrapartum fetal monitoring with continuous CTG is recommended.[8]
- If CTG is not available intermittent auscultation every 15 minutes in first stage and every 5 minutes or after every contraction in second stage is done.
- Secondary tests like fetal scalp blood sampling or scalp stimulation should be performed when indicated and if available.
- ST segment analysis of the fetal electrocardiogram has been shown by 2 randomized trials as an effective tool for fetal monitoring in labor.[40,41]
- In case of any signs of fetal compromise decision for cesarean section should be prompt as the fetus with growth restriction has poor capacity to tolerate labor.
- A skilled pediatrician should be present at delivery and a neonatologist should be present when gestation is extremely preterm or growth restriction is severe.[8]

CASE 2

Mrs X, a primigravida with proven FGR :AC < 5th centile and low AC growth rate at 32 weeks

pregnancy with Doppler of UA showing abnormally increased S/D ratio. How will you manage her?

- Needs admission, daily fetal movement record, weekly SFH, weekly weight check
- Weekly Doppler of UA
- Twice weekly BPP
- Steroid cover for fetal lung maturity
- Delivery is planned at 37 weeks if diastolic flow is present on UA Doppler and fetal well being tests do not show compromise unless indicated earlier for obstetric or maternal factors.

CASE 3

Mrs Y, G2P1L1 with 32 weeks pregnancy with proven FGR with no other complications shows AEDV on UA Doppler. Outline management plan.

- Admit.
- Give steroid cover.
- Doppler of UA, MCA, venous Doppler daily
- BPP daily.
- Deliver at 34 weeks or earlier if REDV occurs, BPP shows compromise, CTG shows decelerations or reduced variability, or there is reversed flow in ductus venosus during atrial contraction or umbilical vein pulsations.
- Mode of delivery is likely to be by cesarean section in these scenarios.
- Risk of prematurity and a compromised growth restricted fetus may result in an adverse perinatal outcome despite delivery and patient has to be counseled about the prognosis accordingly. Neonatologist should be involved in the decision making.

CASE 4

Mrs Z with 30 weeks gestation, with severe proven growth restriction of fetus with a normal fetal karyotype, no anomalies on scan and no maternal complications shows REDV on UA Doppler. How will you manage her?

- REDV is a preterminal event and needs admission, steroid cover and immediate delivery,which is most likely by LSCS[8] after careful counseling of parents and considering their wishes. Unfortunately, this may not ensure a favorable perinatal outcome.
- Patient has to be explained the high-risk of prematurity, with severe FGR and fetal compromise and high risk of perinatal morbidity and mortality despite LSCS. Neonatologist should also be involved in counseling.
- The option of no LSCS for fetal indication may be given to the patient in cases where there is very high risk of adverse perinatal outcome.

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9 Rh Alloimmunization

The introduction of Anti-D immunoglobulin in 1969 has led to a steep fall in the incidence of Rhesus red cell alloimmunization from 5% to 1.7 %. Consequently, there has been an increase in alloimmunizations attributable to non-D Rhesus red cell antigens like C and E and non Rhesus red cell antigens like Kell, Duffy and Kidd. However, Rhesus alloimmunization remains the most prevalent cause of Hemolytic disease of the fetus and newborn (HDFN) even today.

The Rhesus Blood group system consists of **5 antigens** C, D, c, E and e. There is no d antigen and Rh negative or D negative implies the absence of the D antigen. These antigens are codified by 2 genes, the RhD gene which encodes for the RhD antigen and the RhCE gene which encodes for the other 4 antigens (E, e, C, c). Both are located on the short arm of chromosome 1. The rhesus genotype is inherited according to Mendelian principles and the individual is either homozygous or heterozygous for each antigen represented in the genotype. The parental genotype may therefore be represented as, for e.g. CDe/cde, one set being inherited from each parent. Rh negative persons are homozygous for a complete absence of the Rh D gene. Rh positive persons may be homozygous (2 copies of D antigen) or heterozygous (1 copy of D antigen). This has practical importance. When a homozygous Rh positive male mates with a Rh negative woman, the offspring will be Rh positive in 100% of the cases whereas if the man is heterozygous Rh positive, the chances of the offspring being positive is 50%.

There are at least 40 Rhesus antigens other than D,C and E but the Rh D antigen is the most immunogenic followed by Rh c, E, e and C. A common antigenic variant is the Du antigen also known as weak D wherein the patient is Rh positive but the D expression is weak. These women are not at risk of developing Rh alloimmunization.

The e, E antigens as well as Kell, Duffy and Kidd antigens usually cause immunization through blood transfusion rather than through fetomaternal bleeds.

The incidence of Rh negative individuals varies with race and ethnicity, being as low as 1% in Asians, 15% in whites and as high as 100% in Basques. A Rh negative woman has a 60% chance of bearing an Rh positive fetus.[1]

CASE 1

A young primigravida at 24 weeks period of gestation attends the antenatal OPD. Her pregnancy till now has been smooth and uneventful. Routine investigations show her blood group to be B negative.

Q.1. What is the importance of the Rh factor during pregnancy?

Ans:

- The Rh factor is an antigen (protein) present on the red cell membrane which has the ability

to stimulate an immune antibody response when presented to an individual who does not possess one. This is the phenomenon of development of alloimmunization and therein lies the importance of an Rh negative pregnancy.

- About 75% of pregnant woman have fetal RBCs circulating in their blood sometime during pregnancy and delivery. If these fetal RBCs are Rh positive, they stimulate a maternal immune response against the non self Rh antigen. A primary exposure leads to the production of antigen specific IgM antibodies after 6 weeks to 12 months. These IgM antibodies are high molecular weight heavy antibodies which do not cross the placenta and therefore do not harm the fetus (Primary sensitizing pregnancy).
- A subsequent exposure of the mother to the antigen, as in her second pregnancy, produces an amnestic response and rapid production of large amounts of Ig G antibodies which actively cross the placenta and bind to the Rh antigens on the fetal red cells causing their sequestration and destruction leading to a spectrum of hemolytic disease in the fetus and neonate (First sensitized pregnancy).
- The first sensitizing pregnancy is therefore usually unaffected and only 1% of RhD negative mothers will have detectable RhD antibodies before delivery of their first RhD positive baby.[2]
- After birth of the first Rh positive baby, antibodies can be detected in 8% of at risk mothers 6 months after delivery.[2]
- By the end of the second Rh D positive pregnancy, in the absence of AntiD prophylaxis, 17% of Rh D negative mothers will have detectable antibodies.[2]

Q.2. On what factors does the development of alloimmunization depend?

Ans: Fetal red cells may gain access to the maternal circulation any time during pregnancy, delivery or in the immediate postpartum period. The amount of fetal blood entering the maternal circulation may vary from **less than 0.1ml to >30 ml.**[3] Both the frequency and magnitude of the bleed increases as pregnancy advances. In majority of the cases (15-50%) fetomaternal hemorrhage (FMH) sufficient to cause alloimmunization occurs at the time of delivery.

However, inspite of this, an immune response is mounted by only 10-15% of Rh negative women during delivery and by less than1% during pregnancy.

There could be varying reasons for this.

1. Maternal inborn responsiveness- 30% of Rh negative woman are immunogenic non-responders who do not become sensitized to the Rh positive antigen, a characteristic which is genetically controlled.[2]
2. Strength of the antigenic stimulus- Rh D is the most potent Rh antigen.
3. The volume of the fetomaternal hemorrhage, i.e. size of the inoculum- Greater the number of fetal cells entering the maternal circulation, greater is the possibility of maternal sensitization, though some mothers may become sensitized with as little as 0.25 ml of fetal red cells.
4. Co-existence of ABO incompatibility between mother and fetus reduces the risk of sensitization by 50-70% because of rapid clearance of ABO incompatible fetal cells from the maternal circulation or damage to the fetal Rh antigen rendering it non-immunogenic. This effect is especially seen when the mother is O and father is A, B or AB. Risk of Rh isoimmunization is 2-3% in ABO incompatible pregnancy as compared to 13-15% in ABO compatible pregnancy.
5. Bowman observed that longer the interval between primary and secondary sensitizations, greater is the quantity of antibodies produced and the avidity with which it binds to the red cells.

Q.3. Are there any specific investigations to be done?

Ans: The specific investigations required are the father's blood group and Rh and the maternal Rh antibody titre for the detection of maternal Rh alloimmunization.

If the husband is Rh negative, nothing further needs to be done.

All Rh negative pregnant women with Rh positive husbands should be screened for the presence of Rh antibodies on their first visit including those who have received Anti D in their first pregnancy (as postpartum administration of Anti D does not guarantee prevention of Rh alloimmunization) as well as–those who have a history of blood transfusion, unexplained fetal losses or infants with unexplained jaundice.

Q.4. How can you detect maternal alloimmunization?

Ans: The presence of Anti D antibodies in the maternal serum is diagnostic of maternal alloimmunization.

Determination of Rh titer: Previously used agglutination methods using saline or albumin are no longer used as they detect IgM which is of no clinical significance in Rh alloimmunization.

The Human Antiglobulin Titer (Indirect Coombs' Test)

- It is the most sensitive and reliable method used to determine the degree of isoimmunization. Here, maternal plasma is incubated with Rh positive erythrocytes. Agglutination of red cells on the addition of serum rich in antihuman globulin (AHG) antibody (Coombs' serum) indicates the presence of IgG Rh antibody in the mother's serum. (the IgG antibodies have a small molecular weight and are incapable of bridging the red cells which are repelled by their negative surface charge. Addition of Coombs' serum decreases this intercellular distance and facilitates agglutination of red cells).
- The concentration of Anti D antibody is determined by a titration procedure. The titre values are reported as the tube with the greatest dilution with a positive agglutination reaction. In most first sensitized pregnancies the concentration of antibody is very low and can be detected only in undiluted serum or after enzyme pretreatment (papain activated by cysteine hydrochloride is the most popular enzyme used). **A titre value of 1:4 indicates alloimmunization**. Titer values vary between laboratories, as also the critical titer level associated with significant risk for fetal hydrops; so the same laboratory should be used when repeat titers are done. For most labs the critical titer varies between **8 and 32, usually 1:16.**[4]

A direct relationship does not exist between antibody titre and severity of HDFN.

Quantitation of Rh antibody: In the UK, quantification of Anti D is done through the autoanalyser. Levels of < 4 IU/ml are rarely associated with HDFN. Between 4 and 15 IU/ml there is moderate fetal hemolysis warranting close monitoring by repeated levels every 3 weeks. Levels >15 IU/ml are associated with severe hemolysis requiring intervention.[5] Anti D Concentration can also be estimated by radioimmunoassay using I labeled AHG and enzyme-linked immunosorbent assay (ELISA).

Since measurement of maternal Anti D is a poor predictor of HDFN, *in vitro* bioassays have been developed which predict fetal disease by mimicking red cell destruction that occurs in the fetus. The commonly used ones are:

- The antibody dependent cell mediated cytotoxicity assay (ADCC)
- Monocyte monolayer assay
- The monocyte chemiluminescence test.

These tests are not used widely though some countries like Belgium routinely use ADCC. They are based on the premise that adherence of sensitized erythrocytes (target cells) to Fc receptor on monocytes or macrophages (effector cells) is the initial event which leads to erythrophagocytosis and the lytic potential of anti D can be assayed using lymphocytes, monocytes or cultured macrophages as effector cells.

Q.5. What is the objective of management of a Rh negative nonimmunized mother ?

Ans: The main objective in the management of a nonsensitized Rh negative pregnant woman is prevention of alloimmmunization through the passive administration of Rh immunoglobulin (termed antibody mediated immune suppression).

Q.6. What is Rh Immunoglobulin ?

Ans: Rh immunoglobulin (RhIg) is an antibody preparation used for the prevention of Rh alloimmunization. It could be polyclonal or monoclonal.

- Polyclonal RhIg is a sterile, concentrated solution of gammaglobulin that contains a measured amount of Rh antibody obtained from carefully screened, pooled and fractionated plasma of sensitized Rh negative donors. Screening for HIV, Hepatitis B and C is done but the potential risk of infection still exists. Polyclonal antibody is the standard recommended prophylaxis to prevent Rh alloimmunization.
- Monoclonal antibody is a synthetic antibody still undergoing clinical trials.

The exact mechanism by which RhIg prevents alloimmunization is not known. It could be partly due to masking of the Rh D antigenic sites and partly through a Fc dependent mechanism which causes down regulation of B lymphocytes.[4]

It should be given deep intramuscular in the deltoid muscle as injection in the gluteus muscle often only reaches the subcutaneous tissue and absorption is delayed.

A verbal/written consent should always be taken before administering RhIg as it is a blood product.

Anti D does not protect against the development of immunization by other antigens capable of causing HDFN.

Q.7. What are the standard recommendations for the prevention of Rh alloimmunization?

Ans: The current major recommendations for the prevention of Rh alloimmunization include:

- A systematic program of routine antenatal anti D prophylaxis (RAADP) at 28 weeks along with postpartum prophylaxis within 72 hours of delivery.[6]
- Apart from this, it is recommended that anti D should be given after potentially sensitizing events before delivery and after abortion.[6]
- For every 3 units of Rh positive platelets transfused 50 µg of Anti D should be given.[7]
- In the event of inadvertent transfusion of Rh positive blood, the dose of Anti D should be calculated on the basis that 500 IU of Anti D neutralizes 4 ml Rh positive blood.[7]

Q.8. What is Routine Antenatal Anti D Prophylaxis (RAADP)?

All pregnant Rh negative woman should be screened for Rh antibodies at the first antenatal visit.

- If negative, the screening should be repeated at 4 weekly intervals.
- As the incidence of Rh alloimmunization in the antenatal period is small (< 1%), antibody screening every 4 weeks is not universally accepted and a repeat test may be done at 28 weeks. However, testing every 4 weeks will detect those rare patients who do become sensitized before delivery.[4]
- It is recommended that RAADP should be given to all nonsensitized women at 28 weeks in a dose of 300 µg (1500 IU) which is sufficient to

neutralize a fetomaternal bleed of 15 ml of fetal red cells or 30 ml of fetal blood.[6] In some countries like the UK, 2 doses of Anti D, of 500 IU each, are given at 28 weeks and 34 weeks.[7]

- The rationale behind the use of RAADP is the prevention of antepartum sensitization by administering Rh antiglobulin before alloimmunization has begun. Once sensitization has occurred, drug therapy to suppress it has limited value.Thus, RAADP takes care of the silent bleeds that occur in the antepartum period.
- RAADP is not recommended before 28 weeks since the risk of sensitization is less than 0.1%. The cost-effectiveness of RAADP has also been questioned but is still recommended as it has been shown to reduce the incidence of antenatal alloimmunization from 2 to 0.1%.[5]
- After RAADP, the antibody screen may show anti D antibodies in the patients serum but the titre values do not go beyond 1:4. *A titer >1:4 probably results from alloimmunization rather than anti-D immunoglobulin administration.*
- The option for an informed choice for RAADP should also be given when RAADP is neither considered necessary nor cost effective like in the woman who has opted for sterilization after delivery or is certain that she will not have another child.[8]
- The administration of RAADP should not be affected by whether she has received Anti D prophylaxis for a potentially sensitizing event early in pregnancy.
- Since the half life of Anti D is **26 days**, this dose will provide protection for 12 weeks. A repeat dose of 300 µg may be administered if the woman does not deliver by 40 weeks but there is insufficient evidence to make a recommendation. If delivery occurs within 3 weeks of a full dose of Anti D and if FMH is not in excess of 15 ml of red cells, then administration after delivery can be omitted.[6,9]

Q.9. What is Postnatal immunoprophylaxis?

Ans:

- The dose used for postnatal prophylaxis varies in different countries. A standard postnatal dose of 1500 IU or 300 µg is used in USA, India and some European countries (except UK, France, Ireland) within 72 hours of delivery if the baby is Rh positive and Direct Coombs Test on umbilical cord blood is negative (which detects the presence of irregular antibodies in the fetal circulation), with no requirement for a routine Kleihauer test.[6]
- This prevents alloimmunization in more than 99% cases but does not take care of the those 0.3%, who may have a fetomaternal bleed of more than 15 ml fetal red cells which will not be neutralized by 1500 IU of Anti D. Ideally, therefore, fetomaternal hemorrhage should be quantified and postnatal prophylaxis must include a quantitative screening test for FMH when the possibility of a larger bleed exists.[6,7]
- The standard policy in the UK and some other European countries is to administer 500 IU or 100 µg of Anti D (which is sufficient for the 4 ml bleed seen in 99% of postpartum women) and obtain an anticoagulated blood sample within 2 hours after delivery to undertake the ***Kleihauer Betke screening test*** to identify women who need additional Anti D.[7]
- The MRC dosage trial has shown that 500 IU is as effective as 1500 IU.[2]
- Women with weak D should not receive anti D as they are genetically Rh positive and are at low risk of producing Anti D and at very low risk of having an affected fetus.
- Though the maximal protective effect occurs if Anti D is given within 72 hours, it may be given any time upto 4 weeks after delivery and treatment should not be withheld if > 72 hours have passed postpartum.[4,6]

Postnatal prophylaxis reduces the incidence of Rh sensitization from 15 to 1-2%.

Q.10. What are the risk factors for excessive postpartum FMH?

Ans: These include:[2]

- cesarean delivery
- manual removal of placenta
- intrauterine manipulations
- multiple gestation
- antepartum hemmorrhage
- abdominal trauma in third trimester
- still births and intrauterine death
- unexplained hydrops.
- However, *the majority of cases of excessive FMH occur after uncomplicated, vaginal delivery.*

Q.11. What are the other antepartum events requiring Anti D? What are the doses used?

Ans: In 1-2% of women, antepartum events may cause alloimmunization without disruption of the choriodecidual junction.[2]

- First trimester spontaneous/induced abortion-50 µg.

  A first trimester spontaneous complete abortion without any surgical evacuation does not need Anti D.

  Anti D is not considered necessary in women with first trimester threatened abortion with a viable fetus and cessation of bleeding. It may be required when bleeding is continuous or repeated.[6,7]
- Ectopic pregnancy/partial molar pregnancy-50 µg.

  A complete mole does not need Anti D.[6]
- Chorionic villus biopsy-50 µg
- Second trimester spontaneous/induced/threatened abortion-300 µg

  A threatened abortion with persistent bleeding may require Anti D at 6 weeks intervals.
- Amniocentesis/fetal blood sampling-300 µg
- External cephalic version/abdominal trauma-300 µg
- Antepartum hemorrhage-300 µg

Anti D should preferably be given **within 72 hours** of the sensitizing event but may be given **upto 10 days.**[2,6,7]

Q.12. How can fetomaternal hemorrhage be detected?

Ans: Fetomaternal hemmorrhage can be detected through tests which either detect cells with fetal hemoglobin or RhD antigen.

- The test most commonly used to detect HbF is the **Kleihauer Betke test**. It is sensitive and cost-effective but difficult to standardize and false positives can occur. It is an *acid elution test*. The maternal RBCs are rendered colorless or ghost like on the addition of an acid solution (citric acid phosphate buffer) because the adult hemoglobin is more soluble and gets eluted out leaving only the red cell membrane. Fetal hemoglobin is more resistant to elution and so fetal RBCs retain their color. The maternal blood is then examined on a counting chamber after fixation with 80% ethanol and hematoxylin-eosin staining. The number of fetal cells per 1000 ghost cells are counted under the light microscope.

  Amount of fetal bleed is calculated by the following formula:

$$5000 \times \frac{\text{No. of fetal cells}}{\text{1000 adult cells}} = \text{ml of bleed}$$

  False-positives can occur –HbF also elutes if left too long in the eluting solution.
  - some women may have high HbF levels
  - genetic hemoglobinopathies
- The other quantitative test used for FMH detection is **Flow cytometry**. The results of flow cytometry are more accurate and reproducible and since it detects Rh D positive cells, it is helpful in patients with high Hb F levels.
- **Rosetting test** is another simple serological qualitative test where Rh positive fetal cells

coated with anti D form rosettes with Rh positive indicator cells.

CASE 2

G2P1L1 with 28 weeks pregnancy comes to you for antenatal care. Her previous pregnancy was uneventful. Her Blood group is B negative and ICT positive in titre 1:8. She has not received Anti D in her previous pregnancy.

Q.13. What specific history would you like to know from her?

The important points to be noted in history are:

Present pregnancy

h/o any bleeding p/v, when, how much, how long
h/o associated pain abdomen
h/o undergoing any procedure like CVS, amniocentesis
h/o abdominal trauma
h/o receiving Anti D after any such event

Previous Obstetric History

This plays an important role. In the first sensitized pregnancy, the risk of fetal anemia is low. After an affected pregnancy, risk to the subsequent fetus increases and anemia occurs at an earlier gestation. ***If hydrops has occurred in a previous pregnancy, it is likely to occur at an earlier gestation.***
History of:

- any abortion/ectopic in the past
- any sensitizing event in the previous antenatal period
- any intrauterine blood transfusion being required
- development of polyhydramnios/pre-eclampsia
- gestation at delivery/presentation at delivery
- mode of delivery-induced or spontaneous/ vaginal or cesarean
- intrauterine manipulation/manual removal of placenta
- baby being born with jaundice/developing jaundice after birth
- severity of jaundice/h/o phototherapy/exchange transfusion
- receiving antepartum or postpartum Anti D

Q.14. Is the fetus at risk of developing anemia?

This is the first sensitized pregnancy of the woman and the risk of development of fetal anemia can be determined by performing serial anti Rh antibody titres. As long as the titre remains below the critical level of 1:16 or antibody concentration on immunoassay remains < 2.5 IU/ml., the risk of anemia in the fetus is low. Severe erythroblastosis or perinatal death does not occur if antibody levels remain below 1:16.

Q.15. What is the goal of management in this patient?

In Rh negative pregnant women who are already sensitized, the objective of management is early detection and adequate treatment of fetal anemia. Once maternal antibody quantification has been done the next step would be to find out paternal and fetal blood group phenotype and genotype.

Q.16. What is the importance of paternal genotyping?

Ans: If the father is Rh negative, the fetus will also be Rh negative and hence no further tests are required.

If the father is Rh positive, his genotype is determined indirectly by serological testing for the antigens produced by the RhD and RhCE genes and comparing the results with genotype frequency tables. If the father is homozygous, the fetus will be Rh positive and further testing for fetal Rh is unnecessary. If the father is heterozygous, then testing for fetal Rh becomes necessary to avoid unnecessary testing in the 50% fetuses that are Rh negative.

Q. 17. Why is determination of fetal blood group important?

Ans:

1. When the father is heterozygously Rh positive, half of the fetuses may be D negative and no further testing is required.
2. The presence of maternal Rh antibodies does not necessarily mean that the fetus is Rh positive and affected. This could occur because of:
   - A previously sensitized women may produce high levels of antibodies in a subsequent pregnancy even with a D negative fetus through an "amnestic response".
   - Many women sensitized to non D red cell antigens become immunized after a blood transfusion and the antigen may not be present on paternal erythrocytes.

Q.18. How is fetal blood group determined?

Ans: Chorionic villus sampling and **fetal blood sampling** to determine fetal genotype have been replaced by **amniocentesis** which has a lower risk of miscarriage and fetomaternal hemorrhage and can be easily performed under ultrasound guidance. The amniocytes obtained are cultured to obtain an adequate amount of DNA which is then amplified by PCR to identify the Rhesus gene locus on chromosome 1.

Free **fetal DNA** or DNA extracted from fetal red cells in maternal plasma is now being used as a noninvasive method for the detection of fetal RhD gene sequence by using highly sensitized fluorescence based PCR.

Q.19. If the antibody titre remains below the critical level, what will your management be?

- If the antibody titre remains below the critical level on 4 weekly repeated titre testing, the patient can be followed up with serial ultrasound scans till term
- Labor can then be electively induced at 40 weeks, if she does not go into spontaneous labor by then and if no other indication for early termination exists.
- The pediatrician should be notified in advance so that evaluation and treatment of the newborn can be started without delay.
- The cord blood should be collected for Rh typing, direct Coombs test, hemoglobin, reticulocyte count, red cell morphology and serum bilirubin.

Q.20. How does ultrasound help in the management of such a patient?

Ans: Ultrasound plays a key role in the management of the alloimmunized patient.

- **Accurate dating of pregnancy** is important for the interpretation of gestation dependent fetal assessments.
- 1-3 weekly assessment for **fetal growth and surveillance**.
- **Detection of fetal anemia** (defined as fetal Hb < 5 gm%) by[10]
  - Measurement of liver length and spleen circumference. Both are sites of extra-medullary erythropoiesis and an increase in size indicates fetal compensation for developing anemia.
    The liver length is measured from diaphragm to the tip of the right lobe in the parasagittal plane. A length > 95th percentile is predictive of fetal anemia.
    The spleen circumference (L + B × 1.57) is measured at the level of the fetal stomach in a transverse view. A perimeter more than 2 SD is predictive of severe fetal anemia.
  - Measurement of placental thickness and intraperitoneal volume. Placenta may increase 3-4 times in size. There is an overall increase in echogenicity with a characteristic ground glass appearance.
  - Changes in liquor volume—The common presentation is polyhydramnios which may occur because of increased renal blood flow

due to hyperdynamic circulation or the release of Atrial Natriuretic factor from an enlarged right atrium which suppresses ADH and increases diuresis. Sometimes liquor may be normal or reduced. Oligohydramnios in a sensitized pregnancy is a sign of grave prognosis.

- **Identification of fetal hydrops**—High resolution ultrasound allows a clear visualization of fetal structures and early diagnosis of fetal hydrops. However, USG detected hydrops should not be used as the main criterion for the evaluation of fetal anemia since fetal hydrops develops when severe hemolysis has already set in and fetal hematocrit has gone below 20%. Besides, the onset of fetal hydrops in many patients is sudden.
- **Doppler ultrasound** correlates blood velocity in different fetal vessels to the level of hemoglobin. It is best measured as peak systolic velocity in the middle cerebral artery (MCA PSV) and umbilical vein maximal velocity (UV V_{max}). Increased flow in the portal vein is reflected in the ductus venosus which appears prominent. The intrahepatic portal venous waveform may show a saw-toothed appearance which indicates a need for intervention. This appearance disappears after transfusion.

Q.21. What is Hydrops fetalis? What is the pathophysiology behind it?

Ans: Hydrops fetalis is a condition characterized by abnormal collection of fluid in the fetal extravascular compartments and serous body cavities. Rh alloimmunization is one of the major causes of immune hydrops.

- Severe and prolonged hemolysis occurs as a result of sequestration of fetal RBCs after the transplacental passage of maternal IgG antibodies. Severe fetal anemia sets in. There is marked erythroid hyperplasia as well as extramedullary hematopoiesis in the liver and spleen leading to hepatosplenomegaly and hepatic dysfunction. Normal hepatic protein synthesis is impaired and the portal venous pressure is increased leading to formation of fetal ascites.[11]
- Umbilical venous hypertension develops with the placenta showing hydropic changes and consequent enlargement. This impairs normal placental diffusion of aminoacids and this in combination with decreased protein synthesis results in fetal hypoproteinemia. Combination of decreased colloid oncotic pressure and increased capillary permeability with consequent increase in volume load and accumulation of fluid in the extravascular spaces predisposes to cardiac failure. These changes usually set in when fetal hemoglobin falls below 4 gm%. Weiver and coworkers evaluated umbilical venous pressure during antenatal transfusions in isoimmunized pregnancies and found that elevated pressure normalized within 24 hours of transfusion suggesting that elevated pressure was a result of hypoxic myocardial dysfunction which was reversed by transfusions.
- The hydropic fetus may die *in utero* from severe anemia, cardiac and circulatory failure. A sign of severe anemia and impending death is a sinusoidal fetal heart-rate pattern on CTG.

Q.22. How can hydrops be diagnosed on ultrasound?

Ans: Ultrasound features of hydrops are:[10]

- Hepatosplenomegaly demonstrated by increase in measurement of abdominal circumference.
- Increased blood flow through umbilical vein causing an increased diameter of umbilical vein and intrahepatic portal vein to > 5 mm.
- Presence of fluid in serous cavities indicates severe anemia. The first site of fluid collection is the pericardial space and abnormal pericardial effusion should be diagnosed when the thickness of the fluid is >2 mm.

- The earliest sign of fetal ascites is a clear delineation of the small bowel due to fluid in between the loops. Ascites could be minimal and seen as a rim of fluid around the abdominal circumference. This has to be differentiated from pseudoascites. True ascites covers the portal vein and outlines the bowel loops whereas pseudoascites is seen only in the periphery of the abdomen in between the abdominal wall and liver (Fig. 9.1).
- Pleural effusion and diaphragmatic elevation from ascites and hepatosplenomegaly may compress the lungs with consequent hypoplasia.
- Skin edema may be localized to the scalp and face or may extend to the entire body. Diagnosis is made when skin thickness is > 5 mm. The ideal site of measurement is the forehead.
- Right atrium of the heart is the first chamber to enlarge followed by Right ventricular enlargement. A dilated nonpulsatile IVC with exaggerated flow reversal is seen on Doppler. Finally the left heart enlarges. Cardiomegaly is diagnosed when the cardiac circumference to thoracic circumference ratio is > 50%.

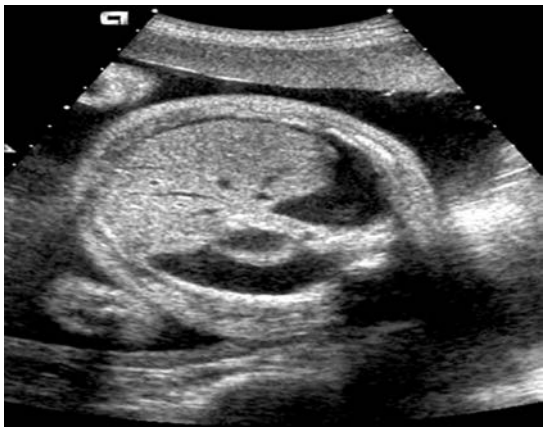

Fig. 9.1: USG picture showing gross fetal ascites

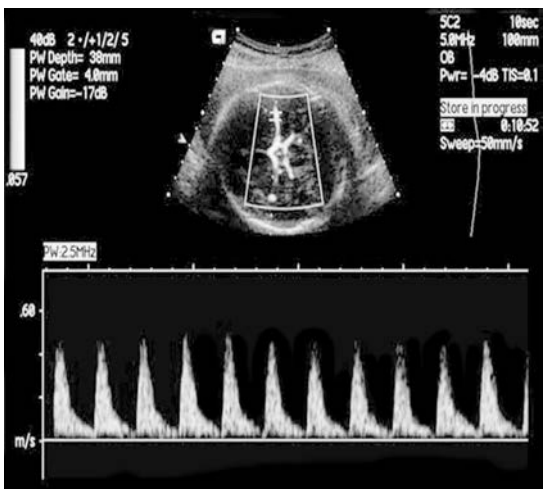

Fig. 9.2: Doppler velocimetry of the middle cerebral artery

Q.23. How does management change if the antibody titer rises above the critical level?

Ans: If at any point of time, the antibody titre exceeds the critical level or there is a significant rise in titre (two tube dilution) between two consecutive samples, further evaluation is done by Doppler velocimetry of the middle cerebral artery (MCA PSV) as antibody titres are no longer helpful.

Q.24. What role does Doppler ultrasound play in the management of such patients?

Ans: Middle cerebral artery Doppler has revolutionized the management of the Rh sensitized woman by minimizing the need for invasive testing by 70%. The sensitivity of MCA PSV for the prediction of moderate to severe anemia in the fetus at risk of anemia is 100% with a false positive rate of 12% (Fig. 9.2).[5]

The physiology behind this is: Fetal anemia is associated with decreased oxygen carrying capacity, low hemoglobin and albumin levels resulting in decreased blood viscosity. The compensatory hemodynamic changes that ensue lead to increased cardiac output and increased blood flow velocity. Though these changes are generalized and seen through out the entire fetal circulatory system, the

middle cerebral artery depicts these changes very accurately because of its sensitivity to hypoxemia.

Technique of measuring MCA PSV

To view the MCA, a transverse view of the fetal brain,which is adequate for the measurement of the BPD is used. The vascular structures are identified with color Doppler. The MCA of the cerebral hemisphere closer to the US transducer is identified at its origin from the internal carotid artery and the US probe placed over it such that the angle of insonation is as close to 0-degree as possible. The fetus should be resting as activity will falsely elevate the PSV.

The distal part of the MCA should not be used as it leads to a false depression of the real PSV. If it is difficult to identify the proximal part, then the MCA of the other cerebral hemisphere should be used.

Once the typical waveform is obtained, the highest point on this waveform is measured. At least 3 consistent waveforms are measured and averaged.

Interpretation of MCA-PCV [5,12]

In the initial report by Mari and coworkers, nomograms for MCA PSV values for different gestational ages was established and a value equal or greater than 1.5 multiples of median (MOM) for that gestational age was used as threshold value for the diagnosis of moderate to severe fetal anemia (Table 9.1).

Deti and coworkers (2002) studied the trend of MCA PSV and proposed the following protocol for use of MCA Doppler in detecting fetal anemia.

- Three consecutive weekly MCA PSV Doppler values are determined and a slope of the regression line is calculated (the slope can be determined using the SLOPE function in Microsoft excel) (Fig. 9.3).
- If the MCA PSV is less then 1.5 MOM and the slope is less than 1.95, studies are repeated at 2 week intervals.

Table 9.1: Values of middle cerebral artery peak systolic velocty (cm/s) based on multiples of the median between the 23rd and 35th gestational weeks.

	Multiples of the median for MCAPSV			
Gestational age (weeks)	*1.0*	*1.29*	*1.50*	*1.55*
23	35.44	45.72	53.16	54.93
24	35.48	45.77	53.22	55.00
25	35.81	46.20	53.72	55.51
26	36.45	47.03	54.68	56.50
27	37.43	50.01	56.15	60.09
28	38.77	50.01	58.15	62.75
29	40.49	52.23	60.73	62.75
30	42.61	54.97	63.91	66.04
31	45.16	58.26	67.74	70.00
32	48.17	62.13	72.25	74.66
33	51.65	66.62	77.47	80.05
34	55.63	71.76	83.44	86.22
35	60.13	77.56	90.19	93.20

MCAPSV, middle cerebral artery peak systolic velocity.

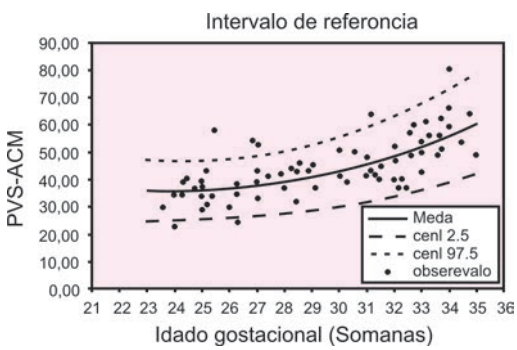

Fig. 9.3: Behavior of the middle cerebral artery peak systolic velocity (median, 2.5th and 97.5th percentiles) as related to the gestational age. [X: gestational age (weeks); Y: MCA-PSV].

- If the MCA PSV is less than 1.5 MOM and the slope is 1.95, studies are repeated at weekly intervals.
- If the MCA PSV is equal to or more than 1.5 MOM, further evaluation is required.
- MCA PSV should not be used after 35 weeks gestation as the number of false-positives is very high.

Q.25. If the MCA PSV in this patient, who is 28 weeks pregnant, exceeds 1.5 MOM what will you do?

Ans: If the MCA PSV is 1.5 MOM or more, and if there are other ultrasound features consistent with fetal anemia, amniocentesis for bilirubin levels should be done.

If there are no ultrasound features of fetal anemia, the MCA Doppler should be repeated within 24 hours to confirm the elevation and if found to be persistent, amniocentesis should be performed.

Fetal blood sampling and Intrauterine Transfusion will then be limited to fetuses showing abnormally elevated MCA PSV plus elevated AF bilirubin.

Q.26. If this patient was more than 34 weeks, what would you have done?

Ans: If lung maturity has been achieved, the pregnancy can be terminated. Otherwise, glucocorticoids can be given to achieve lung maturity. Glucocorticoids decrease OD450 values, so it is necessary to avoid a false sense of security and deliver the fetus 24 hours after the last dose of steroid.

Q.27. What help is amniocentesis in the management of the Rh alloimmunized patient?

Ans: In the Rh alloimmunized patient amniotic fluid assessment can help in the

Detection of lung maturity
Detection of fetal genotype
Detection of fetal anemia

Q.28. How does amniocentesis detect fetal anemia?

Ans: 50 years ago, amniocentesis was the traditional method to indirectly estimate the severity of fetal anemia. Today, it is used in conjunction with MCA PSV.[4]

- Assesment of ammiotic fluid for fetal hemolysis is based on the fact that spectrophotometric analysis of amniotic fluid bilirubin correlates well with the severity of fetal anemia.
- Grossly, a yellow colored amniotic fluid suggests the presence of bilirubin.
- Bilirubin is a byproduct of fetal red cell hemolysis and is excreted in the AF through pulmonary and tracheal secretions and by diffusion across the fetal membranes and umbilical cord. Since the amount of bilirubin in AF is low, spectrophotometry is used and is demonstrated as a change in absorbance at 450 nm –this difference is referred to as Δ OD 450. The curve of optical density of normal amniotic fluid when plotted on a semilogarithmic graph is approximately linear between wavelengths 375 nm and 525 nm. Bilirubin causes a shift in the optical density with a peak at a wavelength of 450 nm. The amount of shift from linearity at 450 nm (Δ OD 450) is used to estimate the degree of fetal red cell hemolysis (Fig. 9.4).

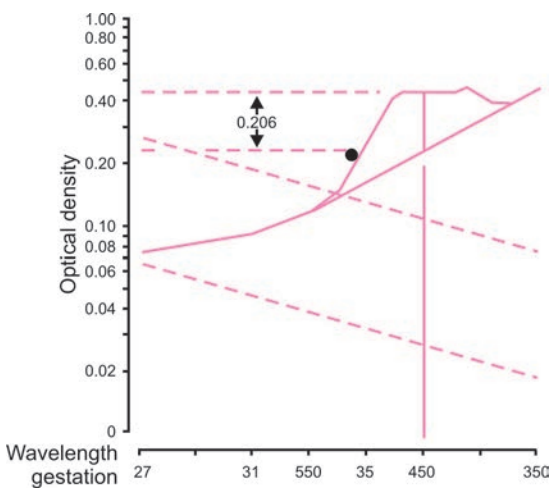

Fig. 9.4: Curve of optical density of amniotic fluid at different wavelengths

Q.29. How is amniotic fluid optical density interpreted in terms of fetal anemia and neonatal outcome?

Ans:

- William Liley correlated ΔOD 450 values with neonatal outcome. For this, he plotted a graph of gestational age from 27-40 weeks versus ΔOD 450 and divided it into 3 zones.
- Unaffected fetuses and those with mild anemia had ΔOD 450 values in zone 1, (lowest zone). Severely affected fetuses (Hb below 8 gm%) with the possibility of developing hydrops within 7 days, had ΔOD 450 values in zone 3 (highest zone). Zone 2 indicates that moderate anemia is present. In lower zone 2, the anticipated Hb is 11-14 gm%, whereas in upper zone 2, Hb ranges form 8-11 gm%.
- The boundaries of the zones slope downward as gestational age increases because AF bilirubin decreases with gestational age (Fig. 9.5).

Q.30. How is the procedure performed?

Ans: A 3.5-7 inches long 22 G disposable needle is inserted under aseptic precautions under ultrasound guidance to the desired depth so that the tip of the needle is in the center of the fluid pocket. 5 -10 ml is aspirated, kept in a brown bottle to protect it from sunlight, centrifuged at 4000 rpm for 20 minutes and analysed by spectrophotometry.

Q.31. What are the complications that can occur?

Ans:

Preterm labor pains

Amnionitis

Bloody tap- there is gross visible contamination with maternal or fetal blood and the procedure should be postponed for 1 week (A small button of red cells may even be found after centrifugation of a clear tap. This is not termed bloody).

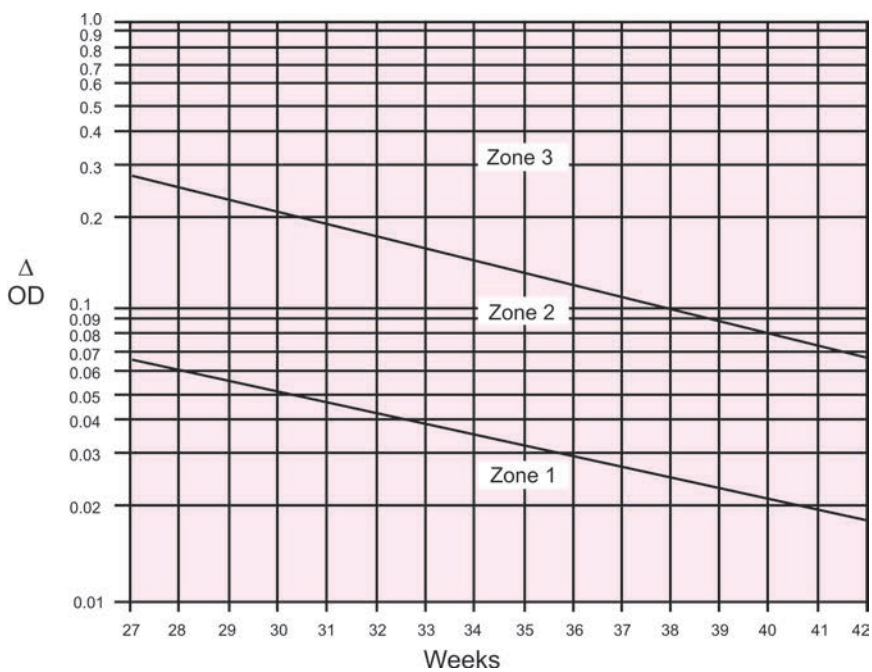

Fig. 9.5: Liley graph

Q.32. What are the limitations of the Lileys zones?

Ans: Since the Lileys graph begins at 27 weeks gestation and extrapolation of the graph backwards is inaccurate, OD450 levels in the second trimester are less reliable predictors of true fetal anemia.

The Liley graph was modified by Queenan et al who developed a curve from 14-40 weeks (Fig. 9.6). OD450 values above 0.15 indicate severe immunization and need for cordocentesis and transfusion. Values below 0.09 indicate mild disease. Values between 0.09 and 0.15 require repeat amniocentesis in 1 week. Because of the naturally high bilirubin levels in amniotic fluid at midpregnancy, a large indeterminate zone is created where bilirubin levels do not accurately predict fetal Hb.[4] Therefore, when severe fetal anemia or hydrops develops before 25 weeks, cordocentesis is a better method of fetal assessment than amniocentesis.

Q.33. What will the management be if AF OD450 lies in zone 1?

Ans: Management depends upon serial amniocentesis to determine the trend of ΔOD450 values over time.

If OD450 value is in zone 1, amniocentesis should be repeated in 4 weeks. If it remains in zone 1 throughout in amniocentesis repeated 4 weekly, the fetus will be mildly affected or unaffected and can be induced at 38 weeks in the absence of any alarming ultrasound features.

Q.34. How will you manage the patient if OD450 value lies in zone 2 or 3?

Ans:

- If OD450 values are in zone 2, amniocentesis should be repeated in 1 week.
- If the repeat value shows a horizontal trend, the test is again repeated in 1 week and if the horizontal trend continues, cordocentesis with evaluation of fetal hematocrit is indicated if lung maturity has not been attained.The patient should be induced if she is beyond 34 weeks or if lung maturity has been achieved.
- If the repeat value shows a decreasing trend, the test may be repeated in 2-4 weeks.
- If the repeat value has gone up to a higher level in zone 2 or to zone 3 or if the original OD450 value was in zone 3, cordocentesis with evaluation of fetal hematocrit is indicated.[4,11]

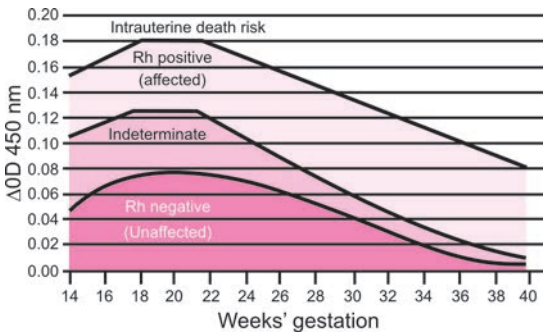

Fig. 9.6: Queenan curve for Δ0D450 values

Q.35. What are the principal disadvantages of amniocentesis?

Ans:

- It is an invasive test and serial tests have to be carried out.
- It is only an indirect predictor of fetal anemia. 9% of predictions based on a zone 2 ΔD450 may be erroreous. In a series of 11 fetuses with OD450 in zone 3, who Liley followed for several weeks, 30% had a clinically acceptable hematocrit at birth. Hence, the experience and judgement of the individual assessing the AF findings is important.
- It is not accurate for second trimester assessments because of the naturally high bilirubin content of AF. The trend of several amniocentesis findings or finding of a very high OD450 value is more predictive.
- Presence of meconium causes a rise in bilirubin values

- It is a poor predictor of Kell alloimmunization. Anti Kell antibodies cause severe fetal anemia and HDFN by erythroid suppression rather than direct fetal red cell hemolysis. Amniotic fluid bilirubin concentration, therefore, correlates poorly with fetal hematocrit, being much lower for the degree of anemia present.[3]

Q.36. What is the role of cordocentesis/fetal blood sampling?

Ans: Ultrasound guided fetal blood sampling has an established role in the management of Rh alloimmunization as it allows precise measurement of fetal Hb and hematocrit and the need for intrauterine blood transfusion. It requires expertise and is technically difficult before 20 weeks.

The main indications of FBS are:

- MCA PSV >1.5 MOM and DOD450 in upper zone 2 or zone 3.
- Rising trend of AF DOD450 and ultrasound features of fetal anemia.
- Picture of hydrops fetalis on ultrasound.
- It may be the preferred choice when there is severe polyhydramnious with diluted bilirubin concentration or early onset hydrops.

Site for Sampling

The umbilical vein at the site of placental insertion of umbilical cord is the commonly used site though the preferred site is the intrahepatic portion of the umbilical vein as it provides a pure fetal venous sample, avoids injury to the umbilical arteries and is associated with a reduced rate of fetal bradycardia.[5]

A 20 G spinal needle is inserted under ultrasound guidance and adequate blood withdrawn for Hb, Hematocrit, blood grouping and typing, Direct Coombs test and Reticulocyte count.

Q.37. What are the complications that can occur?

Ans: Umbilical artery spasm and fetal bradycardia
Cord tamponade.
Bleeding from puncture site is usually transient but may be severe enough to cause fetal death.
Thrombosis of umbilical vessels.
Amnionitis.
Fetomaternal bleeding with worsening hemolysis
Fetal loss rates vary from 1.5 % after 24 weeks to 5% before 24 weeks.

Q.38. When is intrauterine transfusion performed?

Ans: The goal of intrauterine transfusion is to correct anemia and reduce extramedullary hematopoiesis leading to a fall in portal venous pressure with improved hepatic function. The main indication for intrauterine transfusion is a hematocrit below 25% before 26 weeks gestation and below 30% after 26 weeks gestation as indicated by fetal blood sampling IUT can be started earliest at around 20 weeks..

Q.39. How is the procedure performed?

Ans: The routes of approach could be:

- **Intravascular (IVT)** (Fig. 9.7)
- Intraperitoneal (IPT)
- Combined intravascular and intraperitoneal
- Intracardiac

Fresh O negative, CMV negative blood which has been cross matched against the mother and leucocyte depleted, irradiated and double packed to a hematocrit of 70-80% is used.[8]

Q.40. What are the steps of an intravascular transfusion?

Ans:

- An informed consent is mandatory. The parents should be informed about the fetal status, the justification of the transfusion and the possible risks involved.
- The procedure is performed in a sterile room or O.T under asepsis, tocolysis and antibiotic cover. Fetal lie and attitude should be confirmed by real time ultrasound before starting the procedure.

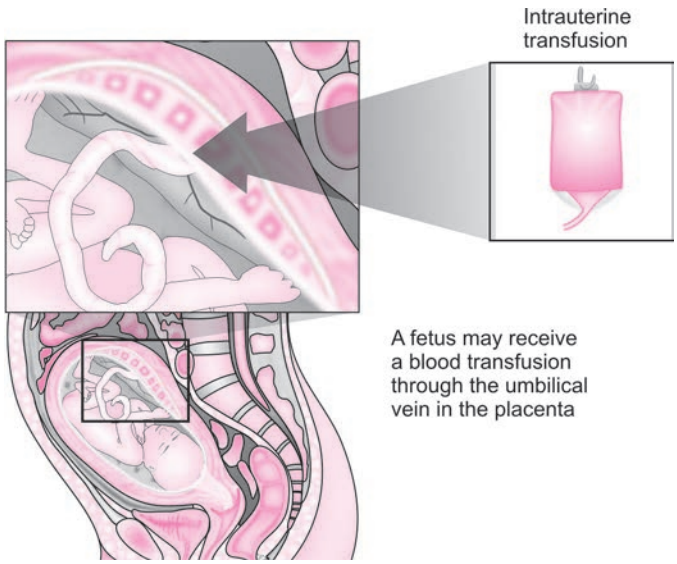

Fig. 9.7: Site of intrauterine transfusion

- A threeway stop cock with an extender tube along with a transfusion set is assembled. A 20/22 G needle is introduced into the amniotic cavity and fetal paralysis is achieved with pancuronium (0.25 mg/kg) or vencuronium bromide, injected into the fetal thigh, deltoid or gluteal region.FBS is performed and hematocrit obtained. During the procedure fetal heart is checked intermittently.
- The threeway stop cock is connected to the needle and packed cells transfused at the rate of 1-2 ml/min. Volume of blood needed for transfusion is calculated according to the Nicolaides chart or Macgehan guideline where,[10]

Volume of blood needed is

$$\frac{\text{(Desired hematocrit-actual hematocrit)} \times \text{estimated fetoplacental blood volume} \times \text{estimated fetal weight in kg}}{\text{Donor hematocrit.}}$$

Q.41. At what level should hematocrit be maintained?

Ans:

- At the first IVT aim is to raise hematocrit a little above the physiological range of 35-40% before 24 weeks, 45-50% after 24 weeks and 50-55% after 28 weeks.
- Hematocrit falls at the rate of 1% per day after the first IVT.The second IVT is therefore performed after 1-2 weeks thereafter, rate of fall decreases and subsequent IVTs are performed at 3-4 week intervals depending on post IVT hematocrit. The aim is to maintain a hematocrit at 40-45% with adult Rh negative red cells at a physiological level and suppress fetal Rh positive red cell production.
- The fetus can tolerate large transfusion volumes because of the capacity of the placental vasculature to dilate However, a stepwise correction should be done in severe anemia < 24 weeks as the fetus is less able to adapt to the

acute correction of IVT. Therefore, in the severely anemic fetus, post transfusion hematocrit should not be more than 25% or more than 4 times the pretransfusion value after the first IVT. The 2nd IVT is done after 48 hours, then after 7-10 days. Thereafter, repeat transfusions are based on hematocrit and KB stain.[5]

- Non invasive MCA PSV can be used to monitor and predict anemia after transfusions. However, there are currently no data on the accuracy of fetal MCA PSV for the prediction of fetal anemia after the 2nd IVT.
- In severely hydropic fetuses with cardiac decompensation, an exchange transfusion is another option to reduce the load on the fetal heart.
- Prior to every IVT a fetal platelet count should be done as it may decrease since only packed cells are being transfused.

Q.42. What is the response rate of IVT?

Ans: Survival after IVT varies with the experience of the performer and the the presence of hydrops. Overall survival is 84% in nonhydropic fetuses and 70% in hydropic fetuses. Mild hydrops is reversed in 88% fetuses and severe hydrops is reversed in 39% fetuses.[5]

Q.43. What are the complications of IVT?

Ans: Same as FBS

Q.44. If umbilical vein access is not possible, is there any other alternative?

Ans: Intraperitoneal transfusion

A 20 G needle is introduced into the flank of the fetus and donor blood transfused into the peritoneal cavity at the rate of 5-10 ml/min from where it is absorbed via the subdiaphragmatic lymphatics over 7-10 days.

Indications

Fetus is smaller than 18 weeks and umbilical vein is too thin.

Fetus lies with spine anterior and umbilical vein is inaccessible

Abnormal cord insertionm e.g. velamentous insertion.

Failed IVT with cord hematoma/thrombosis.

It is used as a supplement to IVT to prolong intervals between IVTs.

IPT is not helpful in hydropic fetuses as blood is not well-absorbed from the abdominal cavity.

Combined IVT and IPT

This approach achieves a more stable hematocrit, with a decline in hematocrit of only 1.01% per day. It also achieves a larger interval between transfusions.

Intracardiac transfusion

It is used only when urgent transfusion is required and no other route is available. The needle is placed in the right ventricle.

CASE 3

A Rh negative G4 P3 with 24 weeks pregnancy comes with an obstetric history which includes a first live born healthy child followed by the birth of a jaundiced baby who died within 24 hours followed by an intrauterine death at 8 months gestation. She did not receive Anti D at any time. Her Anti D titre is positive 1:32

Q.45. Outline your management.

Ans:

- The woman is severely sensitized to Rh antigen. Since the incidence of still birth before 37 weeks in a sensitized woman with high titres and a previously affected baby is 32%, investigations should be started straight away.
- She should also be assessed for the developmentof pre-eclampsia placentomegaly of hydrops may cause pre eclampsia. The pre-

eclamptic mother may also develop severe edema mimicking that of the fetus, referred to as the *mirror syndrome*).[11]

Investigations should include:

- Complete hemogram, renal and liver function tests
- Serial ultrasound for evidence of hydrops, fetal viability, fetal growth
- MCA PSV every 2 weeks. The general rule is to start MCA PSV 10 weeks before the gestation of intervention or bad outcome in the previous affected pregnancy. As the fetal reticulo-endothelial system is too immature to filter and hemolyse antibody coated erythrocytes, hydrops does not develop before 18 weeks. So monitoring of at risk fetuses is not started before 18 weeks.
- If MCA PSV remains below 1.5 MOM, 2 weekly estimations are continued till 35 weeks, steroids administered for lung maturity and patient delivered by 36-37 weeks.
- Amniocentesis for OD 450 should be done as soon as MCA PSV ≥ 1.5 MOM. In women with high titres and a h/o hydropic or stillborn fetus, the first amniocentesis may be done at 16-20 weeks.
- A rising trend of ΔOD450 or a picture of hydrops on ultrasound is an indication for FBS and intravascular transfusion if hematocrit is < 25%.
- The primary objective is to allow pregnancy to complete 34-35 weeks, which is the time that the last transfusion should be scheduled around, so that delivery can be aimed at by 36-37 weeks. The risk of continued invasive sampling and transfusions should be weighed against the neonatal morbidity and mortality associated with prematurity.[5].
- Labor should be induced at 36-37 weeks with appropriate blood in hand.
- Careful intrapartum monitoring is required as these babies are prone to intrapartum hypoxia and acidosis. Early involvement of the neonatologist is essential.
- The preterm baby may be safely delivered by cesarean.

Q.46. How can a neonate with Rh incompatibility present?

Ans: There is a wide spectrum of clinical manifestations[8]

- Normal baby who develops mild jaundice and responds to conservative treatment.
- Normal baby who develops rapid jaundice and requires exchange transfusions.
- Baby with hydrops fetalis, anemia with hepatosplenomegaly, generalized edema, ascitis, pleural effusion. The severely affected infant may suffer perinatal asphyxia, acidosis, hypothermia, may develop disseminated intravascular coagulation with leucopenia and thrombocytopenia. Hypoglycemia in the first 24 hours is due to hyperplasia of islet cells.
- In extreme cases there may be a still born baby or early neonatal death due to difficulty in establishing ventilation and perfusion.

Q.47. How should the baby be monitored?

Ans:

- Cord blood should be sent for hematocrit, blood grouping and typing, direct Coombs test, bilirubin level and reticulocyte count.
- Cord stump should be maintained such that catherization is possible.
- In severely affected babies, S. Bilirubin should be done every 6-12 hours depending on rise of bilirubin. The serum bilirubin is plotted on charts based on gestational age and need for phototherapy/exchange transfusion decided accordingly. If required, Double volume

exchange transfusion with 170 ml/kg of fresh O negative blood is recommended.

- Tests done for suspected kernicterus are:
  Serum albumin
  Serum bilirubin to albumin ratio
  Carboxyhemoglobin levels
  Bilirubin saturation index
  Bilirubin reserve binding capacity
- Early indications for exchange transfusion in such babies are;
  Cord Hb < 10 gm%
  Cord bilirubin > 5mg%
  Unconjugated bilirubin of 10 gm% within 24 hours or 15 mg% within 48 hours or rate of rise > 0.5 mg%

Q.48. What complications can the new born have?

Ans: The new born is at risk of prematurity, anemia, jaundice (as bilirubin is no longer cleared across the placenta into the mothers circulation), disseminated intravascular coagulation, severe thrombocytopenia, necrotizing enterocolitis, bronchopulmonary dysplasia and kernicterus if unconjugated bilirubin exceeds 310 µmol/l.

Q.49. What are the other treatment modalities in a severely immunized Rh negative patient?

Ans: Several methods have been used to suppress the maternal antibody concentration or its effect on the fetus. Of them, only few appear to have limited potential.

Plasmapheresis is indicated only when there is h/o hydrops before 20-22 weeks. The exchange transfusion is begun at 12 weeks, removing about 2 liters of blood per week. This reduces antibody concentration by 80% although transiently.

Immunoglobulins; intravenous immunoglobulin therapy may be used as an adjunct to plasmapheresis. An IV infusion of 400-500 mg/kg maternal weight is used to reduce the severity of hemolysis.

Chemotherapeutic agents like promethazine interfere with the ability of human fetal macrophages to phagocytize red cells coated with Anti D cells.

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Devender Kumar

10 Multiple Gestation

Multiple gestation refers to a pregnancy in which two or more fetuses are present in the womb. The response to their conception till birth has ranged from awe to fear. It can occur when two or more ovas are released from the ovary and fertilized in the same cycle or single zygote divides at an early stage of development. It is important to diagnose a multiple gestation to ensure proper care of the mother and fetuses.

Q.1. Why should we worry about multiple gestation?

Ans:

- Although multifetal births account for only 3% of all live births, they are responsible for a disproportionate share of perinatal morbidity and mortality.[1-3]
- The fraction of multiple pregnancies due to ART has increased from 28% in 1986 to almost 60%.[3]
- There is a higher risk of low birth weight babies and preterm labor. Multiple pregnancies are commonly associated with moderate to severe anemia, gestational hypertension mal-presentation, polyhydramnios, cord prolapse, abruption or placenta previa.[3-7]
- It's also associated with abnormalities like discordance, twin reversed arterial perfusion (TRAP) or conjoint twins.[8]

Q.2. What is the incidence of multiple gestation?

Ans:

- Twin pregnancy occurs in the proportion of about 1 in 80 to 1 in 90 births. An accepted formula of incidence is (Hellin's law) twins 1 in 80, triplets 1 in 80^2, quadruplets 1 in 80^3, and so on.[3]
- Uniovular is fission of single fertilized ovum.
- Uniovular twins are always of the same sex and are identical in appearance, resembling each other both physically and mentally, and even at times showing the same pathological tendencies.
- Binovular is fertilization of two ova. Binovular may occur from the fertilization of two distinct follicles which rupture at the same time of ovulation.
- Binovular twins are more frequent than uniovular (3:1). They may be of the same sex or opposite sexes and show a degree of resemblance no greater than that of brothers and sisters from different births. For this reason they can be referred to as "fraternal twins".

Q.3. What are the complications unique to multiple gestation?

Ans: The incidence of malformations is increased in twin and higher order compared to singleton. Congenital abnormalities reported in multiple

gestations vary from 6.86% to 17.4%.[4,5] Monozygotic twins are at greater risk due to following reasons[8]

1. Defects due to division of zygote.
2. Defects resulting from vascular interchange between monochorionic twins.
3. Defects that occur as the result of crowding.

CASE

35 years age Primi gravida came to ANC opd with 16 weeks amenorrhea. She had moderate pallor and 18 to 20 weeks size uterus. How will you manage the case?

In this case period of amenorrhea is not corresponding to clinical examination of uterus. So we have to consider the clinical conditions where uterus is larger than amenorrhea.

1. Wrong dates
2. Multiple gestation
3. Large for gestation
4. Trophoblastic diseases
5. Anomalies of the fetus or hydramnios
6. Associated fibroid uterus or adnexal mass

So history and examination must include or exclude the above mentioned causes or their complications, diligently.

Q.4. What should be elaborated in the history and examination?

Ans:

Present obstetric history

1. Age of the Patient:
   a. Increasing maternal age and parity have been shown to increase the incidence of twinning independently in all populations studied.
   b. There is growing proportion of older women undergoing fertility treatment.
   c. The ovarian stimulation increases with age. The rise in serum FSH is observed consistently with reproductive aging.
   d. Higher maternal age is also associated with congenital malformations like trisomies.
2. The Last Menstrual Period (LMP) and Expected Date of Delivery (EDD) should be noted. Try to ascertain the reliability. The following criteria are for excellent dates
   a. Patient had regular cycles and is sure of dates.
   b. Gestational age by LMP and clinical examination should correspond.
   c. The first and/or second trimester USG gestation age estimation corresponds to dates by LMP and clinical examination.
3. Hyperemesis is quite common in theses cases.
4. History of bleeding or blood stained discharge should be asked. It may be due to fetal loss or improper implantation.
5. Edema is quite common in these cases. It may be associated with hypoproteinemia or anemia. Breathlessness and easy fatiguability is common in these cases due to anemia and hydramnios. In fact unexplained anemia is often associated multiple gestation.
6. Hypertensive disorders are quite common in multiple gestation. It is significant to know how much weight she gained during this pregnancy and blood pressure records during regular antenatal care. History related to complications of hypertensive disorder should be asked.
7. Increased carbohydrate intolerance is seen in these cases. History of diabetes or glucose challenge or tolerance test should be asked.
8. History of abdominal discomfort/labor pains/ discharge or bleeding per vagina.

Menstrual history

- The history of previous menstrual cycles is significant. History of oligomenorrhea may indicate underlying Polycystic Ovarian Syndrome (PCOS). PCOS is associated with anovulation which is commonly treated with ovarian hyperstimulation in women who desire pregnancy. This can lead to multiple gestation.

- Use of oral contraceptive pills (as contraception or management of Dysfunctional Uterine Bleeding) can be a cause of multiple gestation.

Past obstetric history

- These cases are associated with similar condition (multiple pregnancy) in the previous pregnancies.
- Multiparous women have higher chance of multiple gestation.[9]

Past history

- History of anovulatory cycles or subfertility period prior to this conception can hint on the dependability of dates.
- Knowledge of ovulation or ART provides a strong clue.

Family history

- Racial variation is observed in multiple gestation and is associated with increase in FSH levels.
- Family history of mother is more important than father. It is explained that these cases have tendency to release multiple ova, in same cycle.
- Autosomal dominant genes are reported in dizygotic twinning.[3]

General examination

- The built and nutrition status should be recorded and BMI should be calculated with weight and height. PCOS is common in obese cases.
- The pallor, icterus, and edema should be recorded.
- Thyroid disorders are associated with anovulation. Thyroid dysfunction should be checked. Note any swelling in thyroid gland.
- Pulse rate and blood pressure should be recorded.
- Observe the hair distribution over face and body hyperadrogenism (Hirsuitism). This is associated with hyperandrogenism which is commonly observed in PCOD.
- Examine the cardiac and respiratory system to rule out any associated disorder complicating the present pregnancy.

Per abdomen examination

- Over-distended abdomen may or may not be associated with stretched shiny skin depending upon the amount of liquor.
- Fundal height (in weeks) and symphysio-fundal height (in cms) should be recorded.
- The feel of more than two fetal poles can clinch the diagnosis. Palpation of three poles is diagnostic.
- The presence of more than one fetal heart sounds with difference of at least 10 beats per minute and at a distance of 10 cm (auscultated by two persons simultaneously) will confirm the clinical diagnosis.
- Abdominal girth should be recorded to monitor the growth of pregnancy.
- Hydramnios is not rare in these cases. Sometimes it's difficult to make out the fetal parts which may feel smaller, multiple fetal poles and excess amount of liquor raises the clinical suspicion of multiple gestation.

Per speculum examination

- It should be performed on first visit and cervix and vagina should be examined.
- Subsequent examination depends on the complaints like labor pains or discharge per vagina.
- Multiple gestation is associated with abortion, fetal losses or preterm labor.
- Vaginal infection can be treated if present.

Per vaginum examination

- It should be done to notice the cervical length and os.
- In the first trimester its mandatory to assess uterus size otherwise there may be delay in the diagnosis.

Q.5. How do we measure fundal height?

Ans: Explain the procedure to the patient and take informed consent. Ask the patient to void completely and lie down supine. Flex the hip and

knee joint about 45 degrees to lax the abdominal wall. The abdomen is exposed from anterior superior iliac spines to xiphisternum but cover the lower extremities. Correct the dextro (or levo)-rotation (with right hand) to bring the uterus in midline and just feel the max height of the uterus by sliding the other hand (left) over the uterus or starting from the xiphisternum and where the first resistance is encountered without indenting or altering the position of the uterus. Express the position in weeks.

Q.6. How do we express the fundal height?

Ans: Fundal height is expressed in weeks. The number is determined by the position.

When the fundus of uterus is just palpable above symphisis pubis, it corresponds to 12 weeks gestational age by LMP.

At the lower border of umbilicus, the gestational age is 20 weeks.

At the upper border of umbilicus, the gestational age is 24 weeks.

Close to xiphisternum, it is 36 weeks.

Above umbilicus, the part of abdomen is divided into three equal parts, 24 to 28, 28 to 32, and 32 to 36 weeks. The 32 weeks gestation lies at the level of subcostal margin.

Q.7. When do we suspect multiple gestation?

Ans: Whenever the fundal height is more than expected for that gestational age we should suspect multiple gestation. If three or more fetal poles are palpable it means multiple gestation. The pole means either head or breech. The localization of two or more fetal heart rates is also diagnostic of multiple gestation. Many of these cases are associated with hypertension, anemia and/or significant edema. This condition is more common in ART cases so all the cases should undergo assessment once they are pregnant.

Q.8. How do we confirm our suspicion?

Ans: An early USG should be performed in all suspected cases. Trans-vaginal sonography is preferred technique. Routine 16 to 24 weeks USG examination detects 99% of the cases whereas just 62% if done for a specific indication. Currently, there is no better method than USG. The 3D/4D may provide better fetal sacs orientation.[10]

There are pitfalls in USG like sac appearing later or due to fetal demise. Prediction is more accurate from 6 weeks to 10 weeks. Less than 6 weeks, it may undercount in 15% of cases.[11]

Q.9. What are the clinical problems in examination of these cases?

Ans: Sometimes it may be difficult to identify twins by abdominal palpation, especially if one twin overlies the other, obese mother or hydramnios.

Q.10. What are the investigations routinely done in multiple gestation?

Ans: Hb, PCV, Urine examination, Blood group and type (ICT if Rh incompatible), VDRL, HIV, HBsAg, GCT, and USG. In third trimester NST is integral part of investigation for fetal well being. Other investigations like LFT, doppler and Amniocentesis/PUBS, etc. depends on associated complications.

Q.11. What is the role of doppler in multiple gestation?

Ans: Doppler study provides a measure of fetal well being and helps in the management of IUGR fetuses. Doppler values are same and used in similar manner as in singletons. It was reported that velocimetry alone was not consistently useful in identifying twin discordancy but absent end diastolic flow in the umbilical artery was associated with low birth weight and perinatal mortality.[14,15,21]

Q.12. What is zygocity?

Ans: It means whether the pregnancy developed from single or multiple ova fertilization. Zygocity determines the chorionicity and amnionicity of the multiple gestation. Monochorionic twin means uniovular pregnancy. As chorion develops before the amnion so it helps in determination of amnionicity. The counting of gestation sacs before 10 weeks, accurately predicts chorionicity. The rate of monozygotic twins is 1 in 250 births and is apparently constant through out the world.[9, 10]

Q.13. How do we determine the chorionicity and amnionicity?

Ans: In early gestation, amnion is closely applied to embryo, so fluid filled gestational sac is predominantly chorionic fluid and represents chorionic cavity. As the pregnancy progresses, the amniotic cavity enlarges until it obliterates the chorionic cavity by 10th gestational week, approximately.

The amnion develops after the chorion, so dichorionicity implies diamnionicity. Identification of two gestational sacs with a single embryo or embryonic heartbeat in each sac confirms dichorionic and diamniotic. Single gestational sac with two embryos can be either monoamniotic or diamniotic which require repeat USG assessment after 10 weeks of pregnancy to confirm the amnionicity.[10-13]

Q.14. How do we determine the chorionicity in pregnancy beyond first trimester?

Ans: Sonographically, criteria shifts to "twin peak sign", fetal gender, number of placentas, and thickness of inter-fetal membrane to assess chorionicity. "Twin peak sign" is seen in dichorionicity, and has 94% sensitivity and 88% specificity. In dichorionic gestation, the membrane is composed of two layers of chorion and two layers of amnions. Triangular portion of placenta extending into the intertwin membranes can be seen where the membranes attach to placenta (Fig. 10.1). In monochorionic diamniotic twin, the layer is composed of two layers of amnions only and there is no extension of placental tissue in between the membranes.[16]

Q.15. What is the role of membrane thickness in prediction of chorionicity?

Ans: Prediction of chorionicity based on membrane thickness is more reliable before 26 weeks pregnancy as thinning of the membrane occurs with the progress of pregnancy. A membrane is considered thick if it is well defined, hyperechoic and has a finite measurable thickness greater than 1 mm. A thick membrane 2 mm or more (dichorionic diamniotic) was identified in 100% of cases before 12 weeks, 89% in 13th to 26th weeks and 36% in pregnancy of more than 27 weeks.[17, 18]

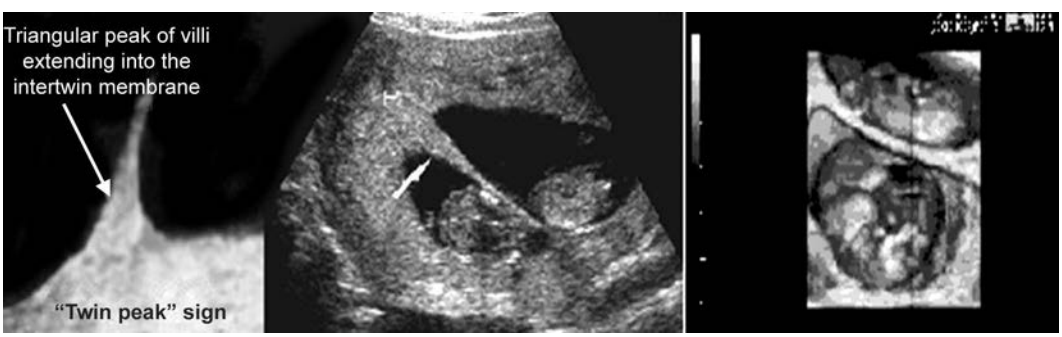

Fig. 10.1: Triangular portion of placenta

Q.16. How do we diagnose monoamniotic twins?

Ans: Monoamniotic twin pregnancy is rare (1 in 12500 births). This is associated with late division of the fertilized ovum. Sonography can directly confirm the monoamnionicity when entanglement of cords, conjoined twins, non-visualization of intertwine membrane or single umbilical cord containing more than three vessels is visualized.[19,20]

Q.17. Why do we worry about monoamniotic twin pregnancy?

Ans: The perinatal mortality is 50% and associated with Twin to Twin Transfusion Syndrome (TTTS), congenital malformations like acardiac, conjoint twins, or preterm deliveries.[19]

Q.18. What are the antenatal advices to women with multiple pregnancy?

Ans: ANC should be in referral center and should be once in two weeks in second trimester and weekly in third trimester. Dietary improvements should be advised as early as possible. She has to consume additional 300 kcal per day. Daily iron (100mg) and folic acid (1mg) requirement also increases. Early USG to confirm the zygocity and serial USG examinations are performed for growth and to rule out anomalies. In monoamniotic twins fetal surveillance should be done once in 2 weeks. Frequent fetal surveillance before 36 weeks is not mandatory in dichorionic diamniotic twins with concordant growth.

Q.19. How will you monitor the growth of the pregnancy?

Ans: Dizygotic twins have different genes so may vary in growth. Monozygotic twins have same genes, theoretically they should have identical parameters. The highest accuracy for growth prediction is obtained by estimated fetal weight and abdominal circumference. Significant discordancy means that one twin is average and the other is small. The difference in expected weight of 20%, AC 20 mm or more are most sensitive parameters of significant discordance. The growth monitoring with USG should be performed once in 3 to 4 weeks after 26 weeks of pregnancy and more frequently if there is discordance or IUGR.[21-24]

Q.20. What are the criteria to diagnose discordance postnatally?

Ans: Postnatal, the common criteria for discordance are birth weight discrepancy of >20% of the weight of heavier twin[23] and hemoglobin difference of >5 gm%.

Q.21. What are the causes of discordance?

Ans: The causes are diverse:

- Twin to Twin Transfusion Syndrome (TTTS)
- Abnormal karyotype
- IUGR

Q.22. What is TTTS?

Ans: The AV malformation in placenta leads to TTTS. It is always seen in monochorionic placenta. It's rare in dichorionic. In 35% of monochorionic pregnancies, one of the twins may have more amniotic fluid whereas the other will have less or nil liquor.

- In twin pregnancies, the combined presence of same sex twins, a single placenta with thin separating membrane, weight discordance and major difference in fluid volume between amniotic sacs with severe oligohydramnios in one sac has been termed as Twin Oligo-hydramnios/Polyhydramnios Sequence (TOPS).[28]
- In most of TOPS (Fig. 10.2) there is unbalanced shunting in the deep arteriovenous anastomoses within the placenta. In this true type of TTTS, there is gradual antepartum transfusion from the restricted or stuck twin into the vascular system of the other, the communication being from the umbilical arterial system of the "donor" twin to the umbilical vein of the "recipient".

- The donor twin is growth restricted, hypovolemic, and anemic. The recipient is larger, hypervolemic, and plethoric.
- The earlier the TOPS appears, worse will be the prognosis.
- TTTS is more common in female fetuses.
- By injecting O negative leukocyte poor washed RBC into the smaller (donor) twin and immediately removing the blood from the co-twin and testing it with Kleihauer-Betke stain, twin to twin transfusion can be confirmed. In a study they found 4 out of 6 cases with TOPS by this method while the Hb difference of >5% was present only in 1 of those 4 cases.
- Arterial supply from the donor twin drains into the venous system of recipient. Doppler can pick up the vessels from one twin's umbilical cord and then finding a continuing vessel with venous flow coursing towards the co-twin's umbilical cord.

Q.23. How do we manage TOPS?

Ans: The TOPS can cause TTTS, Preterm delivery, Polyhydramnios, IUGR or fetal demise.

- Amnioreduction has shown improvement in fetal survival in 65% of cases. When the amniotic fluid exceeds 40 cm, one liter of fluid is removed for every 10 cms rise above normal. This procedure takes care of polyhydramnios and fetuses are born later in gestation and weigh more than untreated cases with TOPS.[28-30]
- Amniotic septostomy can create artificial opening between the gestational sacs to produce in effect a monoamniotic pregnancy. TTTS is seldom seen in monoamniotic gestations. There is speculation that the donor twin has access to amniotic fluid via the opening so it can correct the oligohydramnios by oral rehydration.[29]
- The vessels on the placental surface can be ablated by neodymium:yttrium-aluminum-garnet laser (Fig. 10.3).[28]
- Some advocate ablation of all the vessels crossing the interwining septum, others recommend identifying the causative arteriovenous communications and ablation of those vessels.
- Severe twin–twin transfusion syndrome presenting before 26 weeks of gestation should be treated by laser ablation rather than by amnioreduction or septostomy.
- Finally, selective fetoreduction (SFR) can treat TTTS but this method is reserved for refractory cases to other forms of therapy or when *in utero* death of one of the twins is imminent.

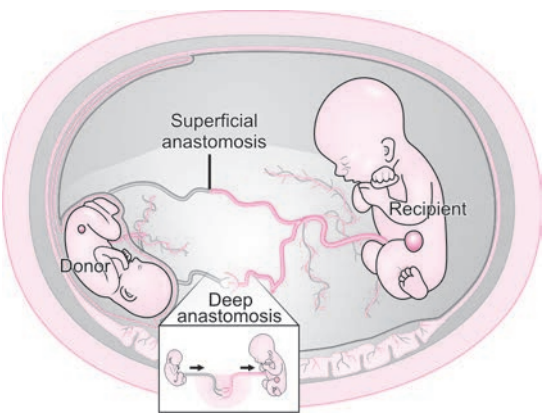

Fig. 10.2: Twin oligohydramnios/polyhydramnios sequence: An unbalanced shunting

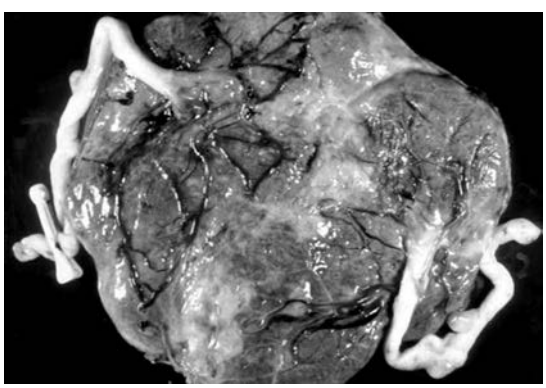

Fig. 10.3: The placenta was symmetrically shared by the twins. The laser surgery was performed at 20 weeks, with the 4 lb. 5 oz. and 3 lb. 14 oz. Twin boys born 12 weeks later

Q.24. How is the Twin-Twin Transfusion Syndrome (TTTS) classified?

Ans: Dr. Rubén Quintero is the director of the Fetal Therapy Center at the University of Miami Miller School of Medicine. He developed the field of operative fetoscopy to treat birth defects in utero via a minimally-invasive approach by designing surgical instruments and techniques. He pioneered the selective laser surgery technique to treat Twin-to-Twin Transfusion Syndrome (TTTS) and has proposed 5 stages of TTTS based on ultrasound findings:[32]

Stage I:

- This is the initial way TTTS is seen on ultrasound.
- There is oligohydramnios in the donor's sac with a Max Vertical Pocket (MVP) of 2 centimeters or less (3/4 inch) and polyhydramnios in the recipient's sac with a maximum vertical pocket of fluid of 8 centimeters or more (just over 3 inches).
- **The bladder of the donor baby is still seen.**

Stage II:

- As defined above, there is polyhydramnios and oligohydramnios but the **bladder is no longer** seen in the donor twin during the ultrasound evaluation.

Stage III:

- Blood flow in the fetus can be measured with doppler. In addition to the findings of Stages I and II, careful study of the blood flow in the umbilical cord and **fetal ductus venosus** (the large blood vessel in the fetus that returns blood to the heart from the placenta) **reveals abnormal patterns** in Stage III.
- These patterns can occur in either or both fetuses.
- In the umbilical cord, the diastolic flow is either absent or reversed. This pattern is usually seen in the donor twin.
- In the ductus venosus, the diastolic flow is either absent or reversed. This pattern is usually seen in the recipient twin due to early heart failure.
- The recipient twin can also exhibit leakage across the main valve on the right side of the heart – this is known as tricuspid regurgitation.

Stage IV:

- One or both babies shows signs of hydrops. This means there is excess fluid in parts of the baby such as swelling of the skin around the head (scalp edema), fluid in the abdomen (ascites), fluid around the lungs (pleural effusions) or fluid around the heart (pericardial effusion).
- These findings are evidence of heart failure and are typically seen in the recipient twin.

Stage V:

- One or both babies **are dead**.
- The survival of the twins is poorer when there is progression to a higher stage over time.
- It has been estimated that half of the patients will progress to a higher stage, 30% will remain at the same stage and 20% will improve to a lower stage II or III

Q.25. How do we manage multiple gestation if one fetus dies?

Ans:

- The first trimester estimation of multiple gestation is higher than incidence of births. One twin was lost (vanished) in as many as 20% of twin gestation diagnosed in first trimester.[12]
- The early loss is reported to have negligible effect on the pregnancy.
- Second and third trimester loss is associated with significant morbidity and mortality in the survivor. There is 20% probability of neurological damage which is difficult to predict. The surviving twin should be evaluated with USG and/or MRI. If no *lesions* are observed, the patient may be councelled and expectant management should be adopted.[33,34]

- The outcome is worse in monochorionic than dichorionic pregnancies. The lesions are infarction, necrosis in the brain (multicystic encephalomalacia), liver, and kidney (renal cortical necrosis) causing major neurological or renal impairment.[34,35]
- The reversal of blood flow from live to dead fetus, release of thromboplastin in circulation and/or necrotic emboli may pass from the dead to the live fetus are the main postulates for complications (hypotension, DIC, anemia necrosis or infarction).
- Delivery of the live fetus as soon as the survivor can be expected to live without undue adverse consequences of prematurity is recommended. Corticosteroid for lungs maturity can be given and fetus should be delivered by 34 weeks.

Q.26. What is selective fetal reduction?

Ans: From 8% to 20% of multiple pregnancies reduce spontaneously by the end of the first trimester. When the phenomenon of the "vanishing twin" occurs prior to 14 weeks' gestation, it has no adverse effect on the remaining fetus. If the higher-order gestation does not reduce spontaneously, selective multifetal reduction (SFR) or multifetal pregnancy reduction (MFPR) can be offered as an option. This is an abortion procedure where one or more babies are aborted in order to improve perinatal outcome for the remaining fetuses.[36-38]

Q.27. What are the principles of SFR?

Ans: Fetal reduction in multiple gestation has two principles.

- It should be done in higher order pregnancy (more than 3).
- Elimination of fetus with known serious anomalies to improve the outcome of the normal co-twin.

Q.28. When should we perform SFR?

Ans:

- Multifetal reduction is usually carried out in the first trimester. In 10 to 14 weeks, the fetus has very small amount of devitalized fetal tissue, spontaneous reduction (vanishing) occurs before this period and remaining fetuses are large enough to be evaluated by USG.
- The needle is introduced into the heart of the fetus and potassium chloride (0.4 to 1 ml) injected under USG guidance.
- The fetus most conveniently punctured is selected for reduction.
- There was no statistically significant difference in gestational age at delivery between control twins and twins obtained by reduction.[39]
- In cases of triplet gestations, however, this option remains controversial.

Q.29. What are the complications associated with SFR?

Ans:

- After fetal reduction, there is a 2-10% chance that the woman will lose the entire pregnancy prior to 20 weeks' gestation.
- The risk may be slightly higher if the presenting fetus is terminated.
- The original number of fetuses, the route of the needle as well as the number terminated may influence the likelihood and the rate of pregnancy loss.
- In monochorionic placenta the vascular anastomosis can cause death of both fetuses, so reduction of monochorionic gestation should be avoided.
- Periodic clotting studies should be done after selective reduction.

Q.30. What is the main advantage of SFR?

Ans:

- Every additional viable fetus present in the first trimester shortens the duration of gestation by about 3.6 weeks. [37-39]
- Each fetus reduced, either spontaneously or medically, can potentially prolong gestation by about 3 weeks.

Q.31. Is it ethically justified to do SFR?

Ans:

- Ethical justification was articulated by Chevernak and colleagues[40] in terms of three goals:
  - Achieving a pregnancy that results in a live birth of one or more infants with minimal neonatal morbidity and mortality.
  - Achieving a pregnancy that results in the birth of one or more infants without antenatally detected anomalies.
  - Achieving a pregnancy that results in a singleton live birth.
- Too often MFPR is assumed by the medical and research community to be what the parents want without obtaining true informed consent or giving them a choice about the number of fetuses to be kept alive.
- More research needs to be done into the effects of MFPR on couples and on their future family life with the surviving babies. This research should be carried out by investigators not already involved in performing and advocating this procedure.
- Parents' reactions to the loss of some of the fetuses conceived are similar to those experienced after abortion for genetic reasons viz: sadness, guilt, and depression.

Q.32. Is there any role of routine hospitalization, tocolysis or corticosteroid?

Ans:

- Routine hospitalization is not necessary to prolong multifetal pregnancy.
- Limited physical activity, early work leave, more frequent health care visits and USG examinations and structured maternal education on the risks of preterm delivery have been advocated to reduce preterm births.
- There is no role of prophylactic tocolysis.
- In fact tocolytics are associated with cardiovascular and pulmonary complications more in multiple gestation than singleton.
- Guidelines for corticosteroid therapy are not different for multiple gestation.
- Prophylactic cerclage does not improve the outcome.

Q.33. What are the malformations unique to multiple gestation?

Ans:

Conjoint twin
Fetal acardia

Q.34. What are conjoint twins?

Ans:

- Conjoint twins are a rare anomaly (1 in 50000 to 100000). It affects 1 of every 200 monozygotic twin pregnancies.[41-43]
- Most of them have preterm delivery and 40% are still born.
- They develop from single zygote and result from incomplete division of the embryonic disc 13 days after fertilization.
- 70% of them are female fetuses. Risk of recurrence is negligible.
- They are grouped under following types
  1. Craniopagus – head to head fusion
  2. Thoracopagus – chest to chest fusion
  3. Omphalopagus – abdomen to abdomen fusion
  4. Pyopagus – joined at buttocks
  5. Ischiopagus – joined at ischium

Q.35. How do we diagnose conjoint twins?

Ans:

- It should be suspected in monoamniotic twins, inseparable fetal bodies, no change in the relative position of the fetuses, or single umbilical cord with more than three vessels.
- Most of them are fused ventrally. The following USG findings increase the probability of conjoint twins
  - The fetal heads at same level and plane.
  - Both fetal heads hyperextended.

  - There is no change in the relative position of the fetuses with movement.
- If the sonogram and fetogram are suggestive of conjoint twins, the diagnosis may be confirmed by injecting 40ml of radiopaque material into the amniotic cavity. This is called Amniography and helps in location of fusion between the fetuses.[20, 42]
- Prenatal diagnosis of conjoint twins is now well-reported from the mid first-trimester, using B-mode ultrasound, Doppler, color Doppler and three-dimensional imaging techniques, with detailed assessment of cardiovascular anatomy important for determining prognosis and planning management.

Q.36. What should be the mode of delivery in conjoint twins?

Ans:

- MTP should be counseled if diagnosed before 20 weeks.
- Vaginal deliveries of conjoint twins have been reported in prenatally undiagnosed cases but most of them are associated with risk of dystocia and uterine rupture.
- If diagnosed late (in third trimester) then they should be delivered by elective cesarean section.[43]

Q.37. What is acardiac twin?

Ans:

- It is a rare anomaly that occurs in approximately 1 in 30000 of monozygotic twin pregnancies.
- Typically, the acardiac twin has a poorly developed upper body with a small or absent head and often absent or underdeveloped upper extremities.
- All cases are associated with placental arterial to arterial and venous to venous anastomoses. The blood flows from "normal" fetus referred as pump twin through vascular anastomoses to the acardiac twin via a single placenta.[44]
- The flow pattern leading to acardia has been described as twin reversed arterial perfusion (TRAP) sequence.

Q.38. Why caudal portion is mostly well developed in acardiac twin?

Ans:

- Caudal aspect of the perfused fetus receives blood with relatively more nutrients and oxygen than the upper torso, resulting in better development of the pelvis and lower extremities in the acardiac fetus (Fig. 10.4).
- Fully desaturated blood then flows in a retrograde fashion to the upper body and head, leading to mal-development of the heart, head, and upper torso, which are either completely absent or severely deficient. Therefore, on USG it appears as a heterogeneous mass, simulating a teratoma or intrauterine fetal demise.

Q.39. What are types of acardiac twins?

Ans:

- This condition mainly have the following presentations
  - Acardius anceps – when head is poorly formed

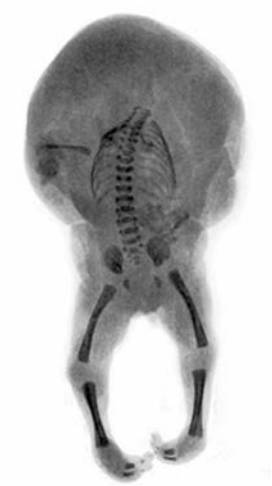

Fig. 10.4: Well-developed caudal portion in an acardiac twin

- Acardius acephalus – if the head is absent
- Acardius acormus – presence of head only
- Acardius amorphous – unrecognizable amorphous mass

Q.40. What are the other complications associated with acardiac twins?

Ans:

- Chromosomal anomalies may be present in up to 50% of cases of acardiac fetus.
- The acardiac twin usually has a dorsal cystic hygroma. If the head is formed, holoprosencephaly or other severe brain malformations may occur. The other structures may be absent, hypoplastic or severely malformed.

Q.41. How do we diagnose acardiac twin antenatally?

Ans: It's not simple and most commonly confused with anencephaly or fetal demise of one of the twins. It is easy to erroneously diagnose fetal death in these cases because of the absence of cardiac motion in one of the twins

- The pump twin is at great risk for high output congestive cardiac heart failure, polyhydramnios, and hydrops fetalis.
- The condition should be suspected when a severely malformed fetus is observed in a monochorionic twin gestation.
- In contrast to TTTS, upper extremities are not formed and diffuse edema and cystic hygroma are common.

Q.42. How do we manage acardiac twin pregnancy?

Ans:

- The acardiac twin should be terminated with intracardiac potassium chloride or radiofrequency ablation (Fig. 10.5) or umbilical artery occlusion.[45,47] Not all pregnancies with TRAP sequence require invasive treatment and this appears to be dependent on:

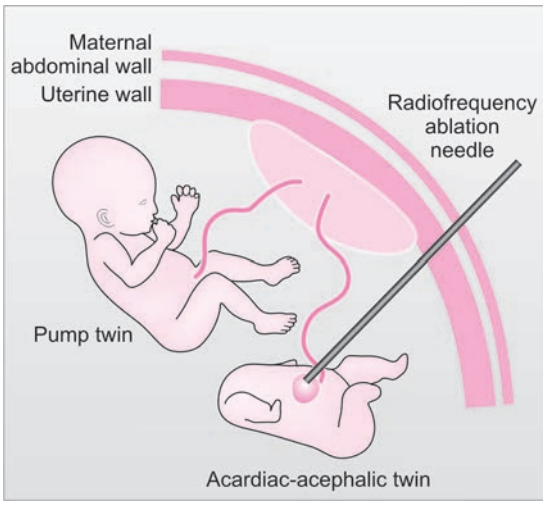

Fig. 10.5: Acardiac-acephalic twin

  - The relative size of the 'acardiac' twin to the pump twin
  - The presence of any cardiovascular impairment in the 'pump' twin.
- Careful monitoring and ultrasound surveillance is required. Mortality of the normal twin is approximately 50%.

Q.43. How do we manage a case of 36 weeks multiple gestation?

Ans:

- Fetal biophysical profile should be done twice a week at least.
- Wait for the spontaneous onset of labor. Twins are usually allowed vaginal delivery if there is no obstetric indication for LSCS like fetal distress, major degree placenta previa, contacted pelvis, malpresentation of the first fetus, or cord prolapse etc.
- Indication for Induction is similar to singleton pregnancy if planned for vaginal delivery.
- Higher order pregnancy (triplet or more) are delivered by LSCS if not extreme preterm or survival of fetus is doubtful.
- Monoamniotic twins should be delivered by elective LSCS at 34 weeks.

Q.44. How do we manage the Twin pregnancy in labor?

Ans: Multiple gestation should be delivered in a referral institution or a place where following facilities are available.

- An obstetrician, pediatrician and anesthetist
- Blood transfusion facility
- Operation Theater
- Ultrasonography
- CTG and Pulse-oxymeter

– Epidural analgesia is very effective in these cases.
– The labor is monitored with partograph.
– Augmentation of the labor of first of the twin should be done judiciously. Labor is allowed to progress spontaneously most of the time.
– Electronic fetal heart (CTG) monitoring is ideal. USG may be required in the management of second of the twin delivery.
– After first baby delivery, wait for progress of labor with spontaneous contractions and fetal heart rate monitoring. If contractions are not effective even after 10 minutes, augmentation may be done.
– Once the presenting part of the second of the twin is engaged, membrane may be ruptured. The delivery depends on the fetal heart rate, dilatation of cervix and station of fetal presenting part like any other case.
– ***Prophylactic methergin is always withheld after delivery of the first baby.*** Episiotomy can be made during first baby delivery if required.
– The placenta should be examined thoroughly after delivery. Indications for instrumental delivery are similar to singleton pregnancy.
– PPH should be prevented with continuous oxytocic infusion.

Q.45. What is the ideal interval between the deliveries of twins?

Ans: Soon after the delivery of the first baby, the second of the twin should be assessed for fetal heart rate, presenting part, expected weight and its relationship to birth canal carefully and quickly. USG is very useful at this stage. If the presentation is transverse and there is no CPD or fetal heart abnormality then ECV may be attempted.[45,46] Once the lie is longitudinal (cephalic or breech), the labor is allowed to resume. The safest interval is cited as less than 30 minutes. If CTG is available then interval can be longer but vigilance is mandatory.[50,51]

Q.46. What are the neonatal outcomes with different mode of deliveries?

Ans:

- Neonatal outcomes were same in the vaginal and LSCS delivery of 23 sets of triplets in a study.[52, 53] Malposition, premature separation of placenta causing hemorrhage, and manipulations required to deliver the babies (requiring skilled obstetrician) are more likely to complicate vaginal delivery so LSCS is preferred.
- The safety of neonates depends on obstetrician's skills.
- Monoamniotic twins or conjoint twins are direct indication for LSCS.
- The phenomenon of locked twin is rare, but if suspected, LSCS is the mode of delivery.
- Elective LSCS does not improve the neonatal outcome when both twins are cephalic.[54]
- Internal podalic version can be performed for second twin in second stage.
- Breech extraction was considered superior to external cephalic version for second of twin according to a study.[55]

Q.47. What is internal podalic version?

Ans: It is used only for the delivery of a second twin. It consists of the insertion of hand into the uterine cavity to turn the fetus manually by holding the feet. This procedure is performed under

adequate analgesia and aseptic conditions preferably in the OT. The obstetrician seizes one or both feet of the baby and draws them through the fully dilated cervix while using the other hand to transabdominally push the upper portion of the fetal body in the opposite direction. This is followed by breech extraction of the baby.

Q.48. When should we admit the patient in hospital?

Ans: The duration of gestational age, type of multiple gestation and associated complication determine the time of admission in the hospital.

- Any case that is associated with complications like moderate to severe anemia, hypertension, hydramnios causing respiratory distress, diabetes, bleeding per vaginum or labor pains should be admitted immediately.
- The patients are admitted for the procedures like fetal reduction, amnioreduction or surgical procedure like laser ablation.
- The patients with single fetal demise are admitted for investigation and psychological support.
- The suggested time of admission for twin pregnancy is 36 weeks or more, for triplet is 30 to 32 weeks and for higher multiple gestation it can be as early as 26 to 30 weeks. This is due to following reasons
  - Preterm delivery chances are higher in higher multiple gestation, so to prevent preterm birth and improve the perinatal outcome patient should get adequate bed rest.
  - Steroid has to be given for early fetal lung maturity.
  - The monoamniotic twins should be admitted at 30 to 32 weeks.
- The routine hospitalization is not required if patient compliance is good.

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Renu Tanwar

11 Pregnancy with Previous Cesarean Section

INTRODUCTION

Rising incidence of cesarean section worldwide has become a matter of concern to the obstetrician, the patient and the health care providers. This problem can be tackled by

1. The indication for primary cesarean section should be stringent and highly selective.
2. More trial of labor for nonrecurring conditions would result in fewer number of repeat cesarean section. The dictum ***once a cesarean, always a cesarean*** is no longer tenable.

CASE 1

Mrs X, 28-year-old G2P1L1 at 34 weeks pregnancy with previous cesarean section came to ANC OPD for her routine check-up.

Q.1. What history and examination would be required in this case?

Ans: For this the routine detailed history and examination is a must but more importance should be given to the following points.

Previous obstetric history

a. Number of vaginal deliveries
b. History of vaginal birth after CS
c. History of interdelivery interval.
d. Number of CS
   - Indication of CS, and at what period of gestation
   - Elective/Emergency CS
   - Stage of labor
   - Type of CS from history or pervious record/ notes if available.
   - History of puerpueral infection/wound infection
   - History of resuturing
   - Any blood transfusion.

Physical Examination:

General built and nutritional status
Height and weight
Pulse: rate, rhythm, volume, peripheral pulses and any radiofemoral delay
Blood pressure.
Respiratory rate
Pallor, cyanosis or icterus.
Jugular venous pulsations
Pedal edema

Systemic examination:

Detailed CVS and respiratory system examination.

Abdominal examination:

Inspection

- Distended uterine ovoid,
- Details of scar (type, length and healing of the scars)
- hernial sites

Palpation

Fundal height in weeks and symphysiofundal height [SFH] in cm.

Fetal lie, presentation, amount of liquor, estimated fetal weight.

Scar tenderness: Palpate the lower part of the uterus between the suprapubic region and the symphysis pubis and try to engage the patient in some conversation and look whether the patient winces in pain on palpation. This suggest scar tenderness. If the patient is in labor, then it should be elicited in between the contraction, when the uterus relaxes.

Auscultation: Fetal heart rate.

Per speculum examination: Look for vaginal discharge/leaking.

Per vaginal examination: Under aseptic precaution (hand washing and sterile gloves)

Done at 36 completed weeks

- Cervical dilatation and effacement
- Confirm the presentation, station of presenting part, position and degree of flexion
- Status of membrane
- Pelvic adequacy and rule out CPD

Q.2. What investigations are required?

Ans:

- Apart from the routine blood and urine investigations
- USG to rule out GCA (level II) at 16-18 weeks of gestation
- Placental localization, rule out placenta accreta and thickness of scar in the third trimester

Q.3. How should women be counselled in antenatal period?

Ans: Antenatal counselling should be documented in notes

- Plans for future pregnancy.
- Final decision for mode of birth should be agreed between the woman and the obstetrician (by 36 weeks of gestation) before the expected/ planned delivery date.
- Counsel about the maternal and perinatal risk and benefits of planned VBAC and ERCS (elective repeat cesarean section).
- Chances of successful planned VBAC are 72–76%.[1]

Q.4. Which patients would fit for VBAC?

Ans: Only women who meet specific criteria and who can deliver in appropriate facilities should be offered VBAC.

(Recommendations of ACOG useful for selection of candidates for VBAC)[2]

1. Patient consent
2. No more than one prior low transverse cesarean delivery
3. Clinically adequate pelvis
4. No other uterine scars or previous rupture
5. Physician immediately available throughout active labor who is capable of monitoring labor and performing emergency cesarean delivery
6. Availability of anesthesia and personnel for emergency cesarean delivery

Q.5. What are absolute contraindications to VBAC?[3]

Ans:

1. Prior classic, T-shaped incision or other transmural uterine surgery
2. Contracted pelvis
3. Medical or obstetric complication that preclude vaginal delivery
4. Patient refusal
5. Inability to immediately perform cesarean section because of unavailable surgeon or anesthesia personnel, inadequate staff or facility
6. Previous rupture or scar dehiscence
7. Non reassuring fetal status
8. Previous two LSCS

Q.6. What are the factors influencing VBAC?

Ans: The following are the factors for consideration when determining labor and delivery management of a patient with a prior cesarean.

a. ***Prior vaginal delivery***
Those women who have given birth vaginally atleast once are 9 to 28 times more likely to have a successful VBAC and the success rate is 83-95%[4]

b. ***Prior VBAC***
It is the single best predictor for successful VBAC and is associated with an approximately 87-90% planned VBAC success rate.[5]

c. ***Large for gestational age/Macrosomia***
Successful VBAC with suspected large for gestational age infants > 4000 gm often have a vaginal delivery rate of only 50-60%.[3] Elkousy et al (1) found a statistically significant increase in the rate of uterine rupture among women without a prior vaginal delivery when delivering an infant > 4000 gms. Absolute risk of 3.6% for uterine rupture. Discourage VBAC attempts in those gestations with estimated fetal weight of 4250 gm or greater.

d. ***Indication for prior cesarean delivery***
The success rate for a trial of labor depends to some extent on the indication of the prior cesarean delivery, i.e. Breech, fetal distress and in relation to cervical dilatation achieved before the original cesarean delivery. Success rate was less for dystocia, failure to progress and in the completely dilated group. The likelihood of vaginal delivery in the completely dilated group is as low as 13% and patient should be informed her low chance of a successful VBAC.[6]

e. ***Maternal obesity***
As the maternal weight increases (body mass index >30), the rate of VBAC success decreases.[7]

f. ***Other factors[1]***
- At or after 41 weeks of gestation
- Previous preterm cesarean birth
- Advance maternal age

Are associated with a decreased likelihood of planned VBAC success.

Q.7. What is the role of induction of labor in a patient with a previous CS?

Ans:

INDUCTION OF LABOR

Spontaneous labor is preferable to labor induction and augmentation of labor after previous cesarean delivery. Induction of labor may be either indicated or elective.

An **indicated induction** of labor implies that the maternal or fetal benefits of delivery will be greater than the benefits of continuing the pregnancy.

An **elective induction** of labor is in the absence of the medical or obstetrical indication.

Advantages

The elective timing of delivery allows for planning and organization of the remaining member of their family. It ensures an adequate core of labor and delivery staff as well as advances in the option of cervical ripening have led to increased rate of induction of labor.

Disadvantages

- Iatrogenic prematurity
- No randomized control trials available

The Bishop score has been useful in predicting the success of labor induction at term.

When the **Bishop score** exceeds 8, the likelihood of vaginal delivery after induction is similar to the rate associated with spontaneous labor.[8] Await spontaneous labor beyond 40 weeeks gestation in VBAC candidates. However, at 41 weeks in well dated patients, consider induction if there is favorable cervix (Bishop score > 8), adequate clinical pelvimetry and an estimated fetal weight of < 4000 gm. If these criteria cannot be met, a repeat cesarean section is recommended.[3]

Q.8. What are the different methods of labor induction and the risk associated with it?

Ans:

OXYTOCIN

- Can be used for induction or augmentation of labor if cervix is favorable with close monitoring in women with a prior cesarean delivery undergoing a trial of labor.
- Use of standard regimens of oxytocin is considered safe and efficacious and may in fact enhance the overall VBAC success rate.[9]

DOSE OF OXYTOCIN

- Start with 0.4 mu/ml and increase every 30 minutes till the patient has adequate contractions (3 contractions in 10 minutes and each lasting for at least 45 minutes) until a maximum dose of 22.8 mu/ml of syntocinon is reached.[10]
- Rate of uterine rupture in patient undergoing a trial of labor.[11]
  - Spontaneous 0.4%
  - Augmented 1%
  - Induced 2.3%

PROSTAGLANDINS-E2 (DINOPROSTONE)

Can be used for ripening (only one dose).[12] There should be a clear and compelling clinical indication. The potential increased risk of uterine rupture with prostaglandin use should be discussed with the patient and documented (ACOG 2003, 2004).

The rate of uterine rupture is 1.3%.[13]

MISOPROSTOL

ACOG has recommended a moratorium on misoprostol use in women undergoing a trial of labor. It is contraindicated because of an extremely high rate of disruption of the previous uterine scar. The incidence of scar rupture is 5.6%.[14]

MIFEPRISTONE

It is being studied as an agent for labor induction in France but data are sparse. Its potential use as a safe alternative in women with previous uterine scar will likely be investigated in the near future.[15]

Q.9. What are the other mechanical labor induction methods?

Ans: Membrane stripping results in a significant increase in phospholipase A2 actitvity and PGF2-alpha levels and hence greater frequency of spontaneous labor and fewer postdated inductions. It is done at 38 weeks and repeated at the following appointment, if the patient remains undelivered. The cervix should be at least 1 cm dilated.[16]

- If cervix is favorable (BS > 8), consider amniotomy and oxytocin augmentation.
- If cervix is unfavorable and one is unable to await labor onset, then Foley's bulb cervical dilatation [17] and amniotomy when possible and then oxytocin for induction/augmentation.

Q.10. How is the labor to be monitored in a patient with a previous cesarean section?

Ans: *The following points have to be kept in mind.*

- Establish IV line
- Blood for cross-matching to be sent.
- Clear fluids are to be allowed. Fluid replacement same as normal labor.
- Maternal monitoring – pulse rate every half hourly, BP- 2 hourly till she progresses to established labor.
- Oxytocin can be used for induction/augmentation after amniotomy. Titration of dose has to be done with careful fetal and maternal monitoring.
- Record electronic FHR continuously and in absence of this facility, intermittent auscultation of fetal heart rate half hourly in early labor, every 15 minutes in first stage of labor and after each pain during the second stage of labor.
- Record progress of labor on a partogram.
- Labor Analgesia – Epidural analgesia can be used and the fear that it would mask the signs

and symptoms of uterine rupture have not been substantiated.[18]

Injection Pethedine (50 mg) + Injection Phenargan (25 mg) IM.

Injection Tramadol (10 mg) IM 8 hourly. No sedation after 6 cm dilation.

- Watch for signs of scar dehiscence.
- During second stage of labor careful watch to be maintained.
- No mid cavity forceps to be applied. If second stage > one hour, outlet forceps/vaccum can be applied provided all criteria are fulfilled, as shortening the second stage reduces the strain on the cesarean scar.
- No routine digital exploration of scar.
- Patient to be kept under observation for 4 hours in the labor room after delivery.
- If condition is not stable (rising pulse rate, falling BP/pallor) prepare the patient for exploration in OT. Inform the senior consultant on call.

Emergency ceserean section is required in 30 to 40% of cases.

Q.11. What are the signs of scar dehiscence?

Ans:

1. Unexplained maternal tachycardia – if present/ rising, check temperature/hydration.
2. Pain at incision site
3. Deceleration of FHR on CTG – prolonged deceleration or variable decelerations that are persistent and severe is the most specific sign of uterine rupture. Deceleration of fetal heart rate to 60 to 70 beats per minute or less that lasts for more than a few minutes that does not return to baseline requires rapid intervention.
4. Meconium stained liquor
5. Scar tenderness
6. Fresh bleeding PV
7. Bladder tenesmus
8. Sudden cessation of uterine contractions or there is receeding of presenting part on PV examination
9. Fetal parts palpable superficial on Per abdomen examination
10. Hematuria

Q.12. What are the risk factor for uterine rupture during trial of labor after cesarean delivery?[18]

Ans:

1. Types of prior uterine incision

Prior uterine incision	*Estimated rupture (%)*
Classical	4-9
T-shaped	4-9
Low vertical	1-7
Low transverse	0.2-1.5

In about 1/3rd of the women, the classical scar will rupture before the onset of labor.

2. Interdelivery interval

   Shipp et al[19] hypothesized that, short interval between a cesarean section and subsequent trial of labor might increase the risk of uterine rupture because of inadequate time of healing. In inter delivery of interval of 18 months or less rupture rate was 2.3% compared with a rupture rate of 1% for women with longer interdelivery interval.
3. Postpartum fever after cesarean
   - Predisposed to poor wound healing.
   - Tend to have wider scars though clinical significance of this finding has not been assessed.
   - It is associated with threefold increase in the risk of uterine rupture during a subsequent trial of labor.
4. Uterine anomalies

   Includes bicornuate, unicornuate, didelphic and septate uterus. The rate of rupture in this group was 8% as compared with the rate of 0.6% for women without these anomalies.[20]

5. Closure of prior incision
   A review of studies published to date implies that the single layer uterine closure is not prone to uterine rupture than the traditional double layer closure.[21]
6. Current pregnancy characteristics
   a. Macrosomia – a small increase in risk is possible when fetus weighed 4 kg or more.
   b. Thickness of the lower uterine segment in late pregnancy (36-38 weeks).[22] It may be useful for screening high-risk population.

Thickness	*Risk of rupture*
>4.5 mm	0%
3.6-4.5 mm	0.6%
2.6-3.5 mm	6.6%
< or = 2.5 mm	9.8%

   c. Induction and augmentation of labor (as previously discussed): Additional large studies that distinguish between prostaglandins and oxytocin use are needed. Women with uterine rupture had a somewhat higher mean oxytocin dose and duration of oxytocin exposure but they were not statistically significant.

Emergency response time for vaginal birth after cesarean patients in labor.[13]

Emergent cesarean delivery is required in approximately 2% of labors regardless of whether the uterus is scarred. ACOG guidelines do not mention specific time interval.

Practice crash ceasarean **fire drills** with the goal of moving the patient to the operating room and having her ready for surgery in the shortest possible time interval.

Make a **crash** cesarean operative tray that includes only those instruments that are needed to deliver the baby.

Q.13. Can external cephalic version be attempted in a previously scarred uterus?

Ans: Role of VBAC with external cephalic version

Flamm et al[23] in his series suggested that this procedure is not likely to be associated with an extremely high rate of uterine rupture. But more studies are required.

Q.14. Can vaginal delivery be offered in twin pregnancy with previous one cesarean scar?

Ans: Role of VBAC in twins[1]

The safety of VBAC in women with twin gestation has been examined in small case series and found that the rates of successful VBAC and uterine rupture do not differ significantly between study subjects and women with singleton gestations who were attempting VBAC.

Role of VBAC with preterm birth[1]

It was found that planned preterm VBAC has similar success rate to planned term VBAC but with a lower risk of uterine rupture.

Q.15. What are the complications in pregnancy with previous cesarean sections?

Ans:

1. **UTERINE RUPTURE**
   Classification
   a. **Complete rupture** – When all layers of the uterine wall are separated. It includes extrusion of intrauterine contents into the abdominal cavity.
   b. **Incomplete or partial rupture or uterine dehiscence**
      Uterine muscle is separated but visceral peritoneum is intact. This includes extrusion of intra uterine contents into the broad ligament.

SYMPTOMS

- Pain in lower abdomen/incision site
  Ranging from mild to severe and sometimes as a tearing sensation
- Shoulder pain
- Uterine contraction often diminish in intensity and frequency

- Dizziness and weakness
- Gross hematuria

SIGNS

- As mentioned above (in the signs of scar dehiscence)
- If it is scar rupture
  - Tenderness over the whole abdomen
  - Distension of the abdomen
  - Uterine contour not well made out
  - Fetal parts more superficially palpated
  - Fetal heart sound absent
  - Bleeding per vaginum may or may not be present
  - Hematuria may or may not be present
  - Receeding of the presenting part on per vaginum

MANAGEMENT

Exploratory Laparotomy followed by repair or hysterectomy

- **Repair the uterine defect**–If it is technically feasible
  - Hemostasis can be achieved
  - If the patient wants to retain fertility
    The wound should be reapproximated followed by closure similar to that used for cesarean delivery.
- **Cesarean hysterectomy is required**
  - If extension into broad ligament vessels
  - Uncontrollable uterine hemorrhage
  - The presence of placenta accreta.

Q.16. Discuss role of both MRI and Doppler in the diagnosis of morbidly adherent placenta accreta?

Ans: The risk of placenta previa accreta in a patient with previous cesarean is as high as 30%.[12] Antenatal imaging can help to establish a diagnosis in such cases and techniques used include ultrasound imaging, power amplitude ultrasonic angiography, MRI and color flow Doppler. Doppler ultrasonography gives a sensitivity of 82.4% and a specificity of 96.8%. The positive and negative predictive values are 87.5 and 95.3% respectively.[24] MRI may be helpful in assessing deep myometrial, parametrial or bladder involvement but sensitivity is low. Hence, color flow Doppler is the investigation of choice until further experience or refinements occur with MRI. Patient should be consented for possible cesarean hysterectomy in these cases . Blood products should be immediately available and preferably should be done electively in day time with senior obstetrician and anesthesiologist. The maternal mortality rate is as high as 10%.

Q.17. How would you counsel the patient with the history of prior uterine rupture?

Ans: The rate of repeat rupture or dehiscence in labor is 6% if the site of ruptured scar is confined to the lower segment. If the upper segment is involved the rate of repeat rupture is 32%.[2] Hence, these patients with prior uterine rupture are best delivered by repeat cesarean as soon as fetus is mature or at 36 to 37 weeks of gestation. These patients should not be allowed to go in labor.

2. **PERINATAL MORTALITY AND MORBIDITY**

Planned VBAC carries a 2-3/10,000 additional risk of birth related perinatal death when compared with elective repeat cesarean section (ERCS). It is comparable to the risk for women having their first birth.VBAC is estimated with 10/10,000 risk of antepartum still birth beyond 39 weeks of gestation and 4/10,000 risk of delivery related perinatal death. Incidence of intrapartum HIE is significantly greater in planned VBAC (7.8/10,000) compared with ERCS (zero rate).[1]

VBAC reduces the risk that the baby will have respiratory problems like transient tachypnea of the new born and respiratory distress syndrome (TTN/RDS). After birth, the rates are 2-3% with planned

VBAC and 3-4% with ERCS. It can be reduced if ERCS is done at 39 weeks of gestation.[25]

3. MATERNAL MORTALITY AND MORBIDITY

The vast majority of maternal deaths in women with prior cesarean section arise due to medical disorders such as thromboembolism, amniotic fluid embolism, pre-eclampsia, surgical complications and uterine rupture. No statistically significant difference between planned VBAC (17/100,000) and ERCS (44/100,000).[1]

Maternal morbidity is higher in women with unsuccessful VBAC.

PENDING RELEVANT TRIALS

- BAC (Birth after cesarean)—Planned vaginal birth or planned cesarean section for women at term with a single previous cesarean birth, ISRCTN 53974531, Professor C Crowther, University of Adelaide, Australia.
- The twin study multicenter randomized controlled trials, Canada.
- DIAMOND. (Decison Aids for Mode of Next Delivery) UK.
- CAESAR (Ceserean Section Surgical Techniques) UK.

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12 Pregnancy with Previous Intrauterine Death of Fetus

Intrauterine death of the fetus is a difficult situation for both the couple as well as the treating obstetrician. Intrauterine death of the fetus (IUFD) is defined as the death of a fetus at any time after the 20th week of pregnancy.

CASE 1

Mrs A, 25-year old, G4P3LO, presented with 5 months amenorrhea and previous three intrauterine deaths. How would you manage this patient?

Pregnancy with previous recurrent IUDs is an important situation where we need to establish the cause for previous IUDs. History taking, examination and investigations are important in establishing the cause of previous IUFD and in management of this pregnancy.

History

In this particular case, since it is a case of recurrent IUFD, history of previous pregnancies in detail is very important to establish the cause.

Obstetric history: Following history is asked for each pregnancy:

- Was it a spontaneous conception?
- Any history of rash or fever.
- History of pregnancy induced hypertension, preeclampsia or eclampsia, gestational diabetes
- Any medical problem like hypertension, diabetes mellitus, asthma, thyroid disorders, jaundice or any other medical disorder
- Any history suggestive of abruption placentae
- When was IUFD diagnosed?
- How the deliveries took place?
- What was the weight and sex of the baby?
- Any congenital anomaly and whether autopsy was performed.

Personal history

- H/O smoking, alcoholism

Past history

- History suggestive of any thrombotic disorder in past like deep vein thrombosis or stroke

Family history

- H/o any such occurrence in family
- H/o birth of any congenitally malformed baby in the family

The situation is very different in our setup, generally the couple does not remember any of the events and either the earlier pregnancies were unsupervised or they have lost all the papers.

So we have to mainly depend on the examination and investigations.

Q.1. What is the etiology of IUFD?

Ans: IUFD may occur during pregnancy or during labor. Generally, the cause of IUFD is different in

antepartum period from that of intrapartum period. Antepartum IUFD may occur in following situations:[1]

1. Genetic abnormalities
2. Infections-viruses, bacteria, protozoa or spirochetes
3. Placental abruption
4. Medical conditions-preeclampsia, diabetes mellitus, thyroid disorders, SLE, intrahepatic cholestasis of pregnancy and chronic liver disease.
5. Multifetal pregnancies
6. Antiphospholipid antibody syndrome (acquired thrombophilia)
7. Inherited thrombophilia

Q.2. What are the genetic abnormalities responsible for IUFD?

Ans: Chromosomal anomalies are responsible for around 6-12% of IUFD.[2] The most common among these are aneuploidies and the most common aneuploidies are trisomies (trisomy 21, 18 and 13). A genetic abnormality which is confined to placenta with normal fetal karyotype (known as confined placental mosaicism, CPM) is responsible for severe IUGR and IUFD.

Q.3. Which infections can cause IUFD?

Ans: 10-25% of IUFD occur because of the maternal infections.[3]

Cardiovascular sequelae of some infections like maternal influenza, dengue, chicken pox, and polio lead to IUFD.

However, infection with malaria leads to infection of placenta and placental insufficiency resulting in IUFD.

Parvovirus infects the fetus through membranes and results in fetal organ damage, nonimmune hydrops fetalis and IUFD. Exposure of a nonimmune mother results in maternal infection in 25% of cases. Out of these, 30% will pass the infection to fetus, only 10% will develop hydrops and 1% will have IUFD. The first infection results in subsequent protection against maternal and fetal infections.

Maternal syphilis is another important cause for IUFD.

On history, the patient says the IUFDs were at around eight month period of gestation with spontaneous onset of labor. All were singleton pregnancies with macerated stillbirth and the weight of the babies is not available and there were no congenital malformations in any of the fetuses. There is no history suggestive of any medical disorder in the mother.

Detailed examination is performed.

Thorough general physical examination and systemic examination is done. Important points to be kept in mind are:

- BMI is important. The malnourishment and obesity both have been associated with adverse pregnancy outcomes.
- Look for anemia, jaundice, cyanosis, clubbing
- Thyroid swelling
- Look for hepatosplenomegaly

Detailed obstetric examination is performed for fetal growth.

On examination, the patient is average built and height, with mild IUGR.

The most important causes for recurrent IUFD are diabetes, thyroid disorder, antiphospholipid antibody syndrome, SLE, thrombophilias and syphilis. Therefore, patient would be investigated for these conditions.

The investigations are:

Routine investigations-

1. ABO grouping and cross-matching
2. Hemogram peripheral smear, platelet count
3. Serum VDRL
4. HIV
5. HbsAg
6. Urine R/M and culture

Special investigations

1. Glucose tolerance test (GTT) - undiagnosed diabetes is an important cause of unexplained third trimester IUFD. The reason for fetal demise is hyperglycemia, ketoacidosis, congenital anomalies and infections.
2. Thyroid profile - hypothyroidism has been implicated to increase pregnancy complications including stillbirths. Even subclinical hypothyroidism has been found to increase the risk of abruption and preterm birth.
3. Antiphospholipid antibodies
4. Thrombophilia work up

The last two investigations are performed if GTT and thyroid profile are normal.

Q.4. What are the antiphospholipid antibodies?

Ans: These are anticardiolipin antibodies (ACA) and lupus anticoagulant (LA). These are immunoglobulins directed against proteins bound to negatively charged phospholipids.

Q.5. What is antiphospholipid antibody syndrome?

Ans: Clinically, it is defined as presence of venous or arterial thrombosis, intrauterine fetal death in second or third trimester, or thrombocytopenia, combined with laboratory evidence of presence of anticardiolipin antibodies or lupus anticoagulant in maternal serum.[1]

Q.6. How antiphospholipid antibody syndrome causes IUD?

Ans: Antiphospholipid antibodies cause placental thrombosis and IUFD by various mechanisms:

- Interference with prostacyclin and thromboxane balance
- Interference with activation of protein C
- Inhibition of activity of protein C directly or through its cofactor protein S
- Through antibodies directed against the substrates of activated protein C thus preventing them from inactivation.

Q.7. What is thrombophilia workup?

Ans: For detection of maternal inherited thrombophilia (1) following investigations are done:[1]

	Detection method
Factor V Leiden (FVL) mutation	PCR
Prothrombin 20210A mutation	PCR
Hyperhomocysteinemia	ELISA
Antithrombin deficiency	Functional assay with a cut off of <60%
Protein S deficiency	Measure total free antigen with a cut off of <45% during pregnancy
Protein C deficiency	Functional assay with a cutoff of <50%
Protein Z antigen	ELISA

Q.8. What is the role of inherited thrombophilia in causing IUFD?

Ans: Combined thrombophilic defects exert a greater influence on fetus as compared to isolated thrombophilia.[4] Association is most strong with FVL resulting from point mutation in factor V gene. The European Prospective Cohort on Thrombophilia Study showed two times increase in risk of IUFD in subjects with combined thrombophilic defects and antithrombin deficiency.

Q.9. Which subjects would you like to screen for thrombophilia?

Ans:

- History of unexplained IUFD in second or third trimester
- History of recurrent severe preeclampsia or HELLP

- H/O unexplained abruption
- Personal/family h/o thrombosis

On investigations, this patient has found protein S deficiency how will you proceed?

Studies have revealed that treatment with low molecular weight heparin and low dose aspirin reduces the recurrence risk of fetal loss.[1] Treatment is started early in pregnancy and continued throughout pregnancy.

Q.10. How would you monitor the patient?

Ans: In patients with previous IUFD increased fetal surveillance increases the chance of fetal survival. When to start monitoring would depend upon the maternal age and the gestation at previous IUFDs. Usually, it is started at 32 weeks but started earlier in patients with IUGR. Surveillance includes:

- Daily fetal kick count-started at 28 weeks
- USG scan for fetal growth- every 2 weeks
- NST- twice weekly
- Biophysical profile- twice weekly

Q.11. When would you terminate the pregnancy?

Ans: Pregnancy is terminated at 39 weeks or at 37-38 weeks after confirmation of fetal lung maturity.

CASE 2

Mrs B G2P1LO presented with 9 months amenorrhea with history of previous IUD.

History is taken to know about the cause of previous IUD.

This was an intrapartum death when patient was in spontaneous labor. She had labor for 40 hours, there was thick meconium stained liquor and baby was fresh stillborn.

In this case, the history suggested the pregnancy was post-dated with intrapartum birth asphyxia.

From the history, it is revealed that the labor was prolonged therefore it is important to know the cause for prolonged labor. We have to rule out cephalopelvic disproportion and uterine incoordinate activity.

Q.12. How are you going to manage the case?

Ans: The patient is monitored strictly by DFMC, NST and biophysical profile. If everything is normal patient can be induced after 39 completed weeks. She is not allowed to go postdate. Cephalopelvic disproportion should be ruled out. During labor, patient is considered as a high-risk patient and strict monitoring of FHR and progress of labor should be done.

Partogram is maintained in active labor.

CASE 3

Mrs C G3P2L1 presented with 9 months amenorrhea with history of previous IUD.

History is taken to know about the cause of previous IUD.

Previous pregnancy was an unbooked pregnancy and patient presented at term in spontaneous early labor. During labor, she had a gush of leaking and the cord prolapsed. She delivered after 2 hours an average-sized fresh still born baby.

From the history, it is revealed there was cord prolapse during labor which resulted in fresh stillbirth. The reason for prolapse of cord is usually contracted pelvis, hydramnios or cephalopelvic disproportion leading to non-engagement of fetal head, malpresentations and malpositions.

During labor, the uterine contraction-force is directed to the loose fetal membranes overlying cervix. It results in early rupture of membranes and cord prolapse.

Q.13. How are you going to manage the case?

Ans: Since patient is in labor, complete general physical, systemic and obstetric examination performed to rule out contracted pelvis and cephalopelvic disproportion. Obstetric examination is performed to know the size of the fetus, lie and engagement of fetal head. Pelvic examination is carried out for adequacy of pelvis, dilatation and effacement of cervix and station of fetal head. If cephalopelvic disproportion ruled out, patient is allowed for spontaneous labor, maintaining partogram. Patient kept in lateral position and under continuous CTG monitoring if available.

CASE 4

Mrs D G3P2LO presented with 2 months amenorrhea with history of previous IUD.

Detailed history is taken to know about the cause of previous IUDs.

The first pregnancy was an unbooked pregnancy, in the 9th month of pregnancy she had loss of fetal movements for 2 days and delivered stillborn baby at home. The baby was of good size and there were no congenital anomalies according to patient. Second pregnancy was again an unbooked pregnancy. At 9 month of pregnancy, she was diagnosed to have IUFD and delivered a macerated baby after 4 days.

Q.14. How are you going to manage the case?

Ans: This patient should be investigated with routine investigations and 100 g oral GTT and thyroid profile.

On GTT, the 1 and 2 hour plasma glucose values were 200 mg/dl and 160 mg/dl respectively.

The patient explained about effects of high blood sugar levels on herself and the fetus as well as the importance of blood sugar level control. She is advised diabetic diet with total calorie intake of 30 kcal/ kg of body weight and total calorie requirement is divided into 3 major and 3 minor meals covering the whole day.

Patient advised following investigations:[5]

- Glycosylated Hb–Done in the first trimester.
- Glucose profile-performed every week. 7 values including fasting, 1 hour post-breakfast, prelunch, 1 hour post-lunch, predinner, bed time and at 2 am.

  The target levels of patient monitored capillary blood glucose levels are:

  Fasting:-60-90 mg/dl

  Premeal:-60-105 mg/dl

  Postprandial 1 hour:-140 mgm%

  2 am-6 am:-60-120 mg/dl
- First trimester and second trimester ultrasound screening for congenital anomalies.
- Maternal serum alpha-fetoprotein at 16 weeks
- Fetal echo at 20-24 weeks
- Maternal fundus examination for retinopathy
- Fetal surveillance in addition to above investigations
  - Daily fetal movement count started at 28 weeks
  - Biweekly nonstress test and weekly biophysical test started at 28 weeks in patients on insulin or at 36 weeks in patients on diet control.
- At 36 weeks fetal weight estimated by ultrasound.

The 7-value glucose profile performed after 7 days and if blood glucose is not controlled, patient should be switched over to insulin therapy.

Patients of GDM on diet can carry pregnancy up to 40 weeks but in this case since she had an IUD at 9 months amenorrhea, the obstetrician would feel safer to deliver her once fetal maturity is certain.

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13 Preterm Labor

DEFINITION

Preterm labor is defined as presence of uterine contraction of sufficient frequency and intensity to cause progressive effacement and dilatation of cervix before 37 weeks of gestation. If uterine contractions are perceived in the absence of cervical changes, the condition is called threatened preterm labor.

The incidence of preterm birth ranges from 10-15% of all deliveries. Preterm birth leads to perinatal morbidity and mortality. Neonatal mortality rate varies from 5/1000 babies in USA to 40-150/1000 birth in India.[1]

CASE

Mrs X 32 years old G3P+0+1+0+1 with 32weeks pregnancy presented to the Gynecological casualty as unbooked patient with complaints of pain in lower abdomen for last 4 hours, pain is dull in nature, coming at half hourly interval, also associated with tightening of the abdomen; there are no relieving or aggravating factors.

Points to be noted in history

- History of perception of normal fetal movements.
- Any history of bleeding, leaking or foul smelling discharge per vaginum.
- Any history of fever.
- Any history suggestive of urinary or bowel complaints.
- Any history of trauma, blow over abdomen.
- Any history of coitus recently (Sometimes coitus can initiate uterine contractions).
- Confirmation of dates and maturity is important to rule out any wrong dates.
- Any history of dragging sensation or heaviness in lower abdomen or menstrual like cramps.
- Any history of labor pains prior to that or any drug intake for the same complaints.

Obstetric history

- In multipara history of previous recurrent abortions especially second trimester (spontaneous or induced) or previous history of preterm labor.
- Short intervals between two pregnancies(less than 12 months) are more prone to preterm labor.

Menstrual history: Any history of prolonged or short cycles for ascertaining maturity of the fetus.

Past medical history: History of hypertension, diabetes, renal disease, heart disease, asthma, thyroid disease or severe periodontal disease or any other chronic illness can predispose to preterm labor.

Past Surgical history: Any history of cervical conization or in multipara history of cervical encerclage is to be elicited.

Personal history: History of any alcohol or drug abuse or smoking is associated with higher

incidence of preterm labor. Any history of domestic violence especially injury due to physical abuse is associated with preterm birth.

Occupational history: Long hours of standing, physical fatigue during work and high stress jobs are strong predictors of labor.

Dietary history: Patient with poor nutritional status is more prone to preterm labor.

Socioeconomic history: Patient with low socioeconomic status is more prone to preterm labor.

Q.1. What are the important points to be noted on examination?

Ans:

- Built and nutrition (Thin built and poor nutrition are more prone to preterm labor).
- Height, weight and BMI –(BMI<19.8 is associated with more risk of preterm labor).
- Pulse, BP, Temperature (infections can lead to preterm labor).
- Pallor, pedal edema, icterus, thyromegaly and lymphadenopathy.
- Chest and CVS examination.

Per abdomen examination of the above patient Mrs X revealed following findings:

On Inspection: Abdomen is uniformly distended, umbilicus is inverted, striae gravidarum and linea nigra are present. No scar marks, no obvious pulsations and peristalsis. Hernial sites are free.

On Palpation: Fundal height is corresponding to 32 weeks pregnancy.

Symphysio fundal height is 32 cm.

By all grips fetus is in longitudinal lie and cephalic presentation.

Uterine contractions are present, coming at an interval of 20 min and each contraction lasting for 15 seconds, there is no uterine tenderness.

On Ascultation: Fetal heart rate is 144/min regular auscultated in left spino umbilical line.

On per speculum examination: No leaking or bleeding is observed, Cervix is patulous and central in position.

On Per vaginum examination: Cervix is 2 cm dilated, 80% effaced, soft, central, appears membranes present, head at -3 station, Pelvis gynecoid and adequate for vaginal delivery.

Diagnosis- Early Preterm labor

- Early preterm labor is when on digital exami-nation cervix is more than 1 cm but less than 3 cm dilated and more than 80% effaced in a patient with preterm labor pains.
- Advanced preterm labor is when cervix is 3 or more cm dilated in a patient with preterm labor pains.
- Threatened preterm labor is when digital examination reveals cervix < 1 cm dilated and < 80% effaced and cervical length on ultrasound is < 2.5 cm.
- False labor pains are when cervix is < 1 cm dilated and < 80% effaced on digital examination and cervical length on ultrasound is > 2.5 cm.

Q.2. What would be the management of this case?

Ans:

A. This patient should be admitted to labor ward:
   - Adequate rest should be advised.
   - Reassurance and counseling regarding risk of preterm delivery.
   - Prognosis of preterm baby to be explained in writing.
   - Pulse and temperature charting should be done.
   - Frequency and intensity of uterine contractions is to be monitored.

B. Investigations:
   - Hb, TLC, DLC
   - ABO Rh
   - Routine antenatal investigations –CGI, STS, HIV, HBsAg, urine for routine and microscopy
   - C Reactive Protein (CRP)—(>3-4 mg/dl indicate infection)
   - Urine for culture and sensitivity
   - High vaginal swab for microscopy and culture sensitivity

- Vaginal fluid for pH
- CTG tracing for fetal heart rate pattern
- Ultrasonography: For fetal growth, morphology, estimated fetal weight, amount of liquor, location and grade of placenta (any decreased liquor or prematurely calcified placenta may be suggestive of placental insufficiency as cause of preterm labor).

C. Management:

After detailed history and examination one should look for any indication of termination of pregnancy given in the Box 13.1.

Box 13.1: Iindications of termination of pregnancy in patient with early preterm labor

1. Features of choriamnionitis – occurs in 0.5-1.0% of all pregnancies. Patient would present with:
   - Tachycardia (p >100/min)
   - Fever (>100°F)
   - Fetal tachycardia (>160 bpm)
   - Uterine tenderness
   - Foul smelling discharge
   - TLC>15000 cell/mm^3
   - CRP >3-4 mg/dl
   - Increased IL-6 in amniotic fluid[3]
2. Adequate lung maturity by L:S ratio or POG >34 weeks
3. Nonreactive nonstress test or repeated severe variable decelerations
4. USG suggestive of congenital anomalies, severe IUGR or oligohydroamnios or severe placental insufficiency.
5. Associated complicating factors like-Abruption, uncontrolled DM

If there are any indications of termination of pregnancy, one should allow the labor to continue as preterm labor is protective mechanism for fetus threatened by problems like infection, placental insufficiency or abruption. Steroids to be started to accelerate pulmonary maturity.

If there are no indications of termination of pregnancy the patient should be managed conservatively till fetal lung maturity or 34 weeks POG on following:

1. **Steroids:** Steroid administration reduces the incidence and severity of respiratory distress syndrome and hence reduces neonatal morbidity and mortality.

   Dose: Inj. Betamethasone 12 mg 2 doses 24 hours apart or Inj. Dexamethasone 6 mg 4 doses 12 hours apart.

   Delivery should be delayed by tocolysis for minimum 12 hours for maximum effect of steroid, although optimal benefit begins 24 hours after therapy and lasts for seven days. Benefit of repeated courses of glucocorticoids is doubtful and not currently recommended.[6,7]
2. **Tocolytic agents:** Maintenance tocolysis is not recommended in routine practice. Various tocolytic agents are described.

   Before starting tocolytic agent one should rule out any contraindication to tocolytic therapy given in Box 13.2.

Box 13.2: Contraindications of tocolytic therapy

1. Advanced labor (cervix >4 cm dilated)
2. Features of chorioamnionitis.
3. Severe preeclampsia and eclampsia.
4. Abruptio/placenta praevia with hemodynamic instabilities.
5. Acute fetal distress
6. Fetal demise (singleton)/congenital malformations.
7. Fetal maturity (>34 weeks)
8. Hyperthyroidism
9. Severe anemia

Nifedepine: It is a calcium channel blocker and safe and effective tocolytic. It is considered the best first line tocolytic agent and is recommended by RCOG as the first line treatment in preference to β mimetics.

Dose is 20-30 mg orally stat followed by same dose after 30 min if contractions persists and maintain at 10-20 mg 6 hourly for 48-72 hours. Maximum dose is 160 mg in 24 hours.

Main side effect is maternal hypotension, tachycardia, headache, dizziness and facial flushing.

The patient is monitored with pulse rate prior to each dose of medications and new dose is postponed if the pulse rate is more than 100 beats/min.

Contraindications of nifedepine are maternal cardiac disease, maternal hypotension (<90/50 mm Hg). It should be used cautiously in renal compromise. Its concomitant use with Magnesium sulphate should be avoided.

Maternal tachycardia > 120 bpm, BP < 100/60 mm Hg, pulse oxymetry <95% or fever are reasons to discontinue the treatment.

Other tocolytics which can be prescribed are

Betamimetic agents:[2] available drugs are terbutaline, ritodrine and isoxsuprine.

i. **Terbutaline** can be given as 0.25 mg S/C every 20 min to 3 hours, dose is to be omitted if pulse rate is >120 beats/min.
   Side effects of terbutaline are cardiac arrhythmias, pulmonary edema, myocardial ischemia, hypotension, tachycardia, shortness of breath, hyperglycemia, hyperinsulinemia, antidiuresis, altered thyroid function, hyperkalemia, hypokalemia, tremor, nervousness and nausea or vomiting,.
   Fetal side effects are fetal tachycardia, hyperinsulinemia and fetal hyperglycemia.

ii. **Ritodrine**: 2 ampules (100 mg) in 500 ml of 5% Dextrose @5 drops/min (0.05 mg) and increasing by 5 drops/min every 15 min. up to 15 drops/min.
   Effective dose is 0.05-0.15 mg/min and maximum up to 0.30 mg/min.
   Side effect of ritodrine is maternal hallucinations.

iii. **Isoxsuprine**: 4 ampules (40 mg) in 500 ml of 5% Dextrose
   0.2-0.5 mg/min IV over 10 hours followed by 0.1-0.3 mg/min IV over 12 hours. Maintain at 10-20 mg IM 6-8 hrly.

Patient on oral β adrenergic therapy should be monitored with pulse rate and the next dose should be postponed till the pulse rate is less than 100 beats/min. When the pulse rate is more than 120 beats/min, 90% of the β adrenergic receptors are saturated hence an additional dose will not be beneficial for the patient, rather the possibility of serious side effects is increased (Boxes 13.3 and 13.4).

Box 13.3: Recommended guidelines for monitoring IV β agonists

Monitoring:
- Maternal Pulse and BP every 15 min
- Chest auscultation every 4 hours
- Strict intake and output chart for fluid balance
- Urea, electrolytes, and hematocrit every 24 hours
- Maternal blood glucose every 4 hr

Box 13.4: Contraindications to the use of IV Beta adrenergic agents

- Symptomatic heart disease especially outflow obstruction
- Symptomatic cardiac rhythm and conduction disturbances
- Sickle cell disease
- Hyperthyroidism
- Uncontrolled insulin dependent diabetes
- Patients on monoamine oxidase inhibitors for psychiatric treatment
- Relatively contraindicated in asthmatics

Magnesium sulphate: 4-6 gm IV over 20 min. followed by 2-3 g/hr as continuous infusion.

Magnesium sulphate being highly toxic is monitored with urine output charting (25-30 ml/hr), respiratory rate and deep tendon reflexes.

Nitroglycerine: Is the tocolysis of choice in case of an emergency, used as IV 100 µg bolus followed by IV infusion @1 µg/kg/min. It can also be used as transdermal patch 50 µg patch for 24 hours.

Side effects of nitroglycerine are headache and maternal and fetal hypotension.

Diazoxide: It is structurally related to thiazide diuretic and acts by inhibiting contractility of arterial and venous smooth muscles. Dose- 5 mg/kg slow IV over 15-30 min.

Side effects are tachycardia, hypotension and decreased uteroplacental blood flow.

NSAIDs: Indomethacin, ketorolac and sulindac are the NSAIDs which can be used as tocolytics.

Indomethacin is preferably used in preterm labor associated with polyhydramnios. Dose is 100mg per rectal followed by 50mg orally every 6-8 hrly.

Potential fetal adverse effects include premature closure of the ductus arteriosus, necrotizing enterocolitis, respiratory distress syndrome and bronchopulmonary dysplasia and potential increased risk of development of periventricular leukomalacia.

Ketorolac: Dose is 60 mg IM then 30 mg IM 6 hrly. It is contraindicated in active peptic ulcer disease.

Sulindac: Dose is 200 mg orally every 12 hrly. It is contraindicated in coagulation disorders or thrombocytopenias or any sensitivity to NSAIDs.

Side effects of NSAIDs are nausea, heartburn gastritis, proctitis with hemalochezia, impairment of renal function, increased postpartum hemorrhage, heartburn, headache, dizziness and depression.

In fetus they may cause constriction of ductus arteriousus, pulmonary hypertension, reversible decrease in renal function with oligohydramnios, intraventricular hemorrhage, hyperbilirubinemia, and necrotizing enterocolitis.

Oxytocin antagonist: Atosiban is an oxytocin antagonist. It is recommended by RCOG as a first line agent in the management of preterm labor though its cost may be a factor to preclude its use in developing countries.

Dose: 6.75 mg IV stat over one minute followed by an infusion of 18 mg/hr for 3 hours and then 6 mg/hr for up to 45 hours. Total duration of treatment should not exceed 48 hours and the total dose not be more than 330 mg of atosiban.

Side effects of atosiban can be chest pain, palpitations, tachycardia, hypotension, dyspnea, nausea, vomiting and headache (Evidence level Ia).

Trials of the drug were carried out in UK and the drug is licenced for usage in Europe and is currently not available in India.

3. **Antibiotics:** Antibiotics in case of preterm labor are recommended for –
   Prevention of group B streptococcus infection in fetus, Prophylaxis for genital tract infections mainly bacterial vaginosis.
   Antibiotics of choice in this case is Inj. Penicillin 5 million U IV followed by 2.5 mU every 4 hours after sensitivity testing till delivery. Due to highly allergic reaction to penicillin group of drugs, combination of Inj Clinda-mycin 900 mg IV 8 hrly and Erythromycin 500 mg every 6 hrly is preferred. Due to increased number of reports of resistance of GBS to both erythromycin and clindamycin, Inj. cefazolin is the best choice.[3,4] The dose is 2 gm IV followed by 1 gm IV 8 hourly.
4. **Treatment of associated infections –** 5-10% of patients in preterm labor may have infection outside uterus, mostly in the urinary tract and they should be treated by appropriate antibiotics.
5. **Intrapartum management –** If inspite of tocolytic therapy, labor progresses, then labor should be allowed. Aim of management is to prevent asphyxia and birth trauma. Patient should be delivered in place where adequate facility for premature neonate is present.

First stage

- Bed rest to prevent premature rupture of membrane.
- Delivery by LSCS not preferred as there is no difference in frequency of periventricular-intraventricular hemorrhage.

- Strong sedatives and oxytocics are avoided.
- Intensive clinical monitoring with CTG is ideal.
- Repeat digital examination is to be avoided to increase risk of infection.
- Epidural analgesia can be given

Second stage

- Delivery should be attended by Obstetrics and Pediatrics registrar.
- Episiotomy is recommended especially in primigravida to minimize head compression.
- Prophylactic forceps should not be used.
- Immediate cord clamping should be done to prevent hypervolemia to baby.
- Role of Inj. Vit K is controversial for prevention of IVH.

Q.3. How would you manage a patient in advanced preterm labor?

Ans: Patients in advanced preterm labor are to be assessed for any indication of termination of pregnancy as given in Box 13.1. In those conditions, labor should be allowed. If there are no contra-indications to conservative management patient can be put on tocolytics, steroid and antibiotics. If labor pains subside, patient can be put on expec-tant management.

Q.4. What are the risk factors for preterm labor and what are the methods to identify women at risk of preterm birth?

Ans: Risk factors of preterm labor include:

- Lower socioeconomic status
- Extremes of maternal age < 17 yrs and > 35 yrs.
- Stressful maternal conditions.
- Low pre-pregnancy weight.
- Low BMI.
- Poor nutritional status.
- Previous history of preterm birth, multiple induced 2nd trimester abortion (2 fold increase in risk).
- Cervical incompetence, cervical conization.
- Multiple pregnancies.
- Medical problems (pre-eclampsia, DM, asthma, thyroid disease, cardiac diseases).
- Chorioamnionitis.
- Extrauterine infections (5-10%).
- Drugs and alcohol in pregnancy.

Methods to identify women at risk of preterm birth are

1. **Questionnaire** evaluation of above mentioned risk factors
2. **Home uterine activity monitoring (HUAM):** It has been tried in women with risk markers for preterm labor. This system provides recording and transmission of uterine activity by a device called tocodynamometry and giving feedback to the health practitioner on daily basis. Though it has been described in European literature, the method is not yet available in India. A large trial on 2422 patients showed no benefit in predicting preterm labor. Hence this method cannot be recommended in routine clinical practice.[9]
3. **Cervicovaginal fibronectin levels (fFN):**[5] It is a basement membrane protein which is normally secreted by chorionic tissues and acts as glue between chorioamnion and deciduas. It is present in cervicovaginal secretions up to 16-22 weeks, then disappears and reappears after 37 weeks till labor. Presence of fFN in cervical secretions after 24 weeks of pregnancy may indicate disruption between decidua and chorioamnion. The test is performed by taking swab from ectocervix or posterior vaginal wall, ELISA done to detect fetal fibronectin. It has got a negative predictive value of 99.7% and a positive predictive value of 14.7%. This test has a value in excluding risk of preterm delivery within 2-3 weeks. Its presence between 24-37 weeks is an important marker of preterm labor. A negative fFN test rules out an imminent

preterm delivery whereas implication of a positive test is uncertain.

4. **Salivary estriol levels:** Premature activation of fetal hypothalamo-pituitary-adrenal axis may result in increase in production of estriol from placenta and hence increase in serum and salivary levels of estriol can predict preterm labor. Maternal estriol has diurnal variation and is suppressed by betamethasone given to affect surfactant production, therefore has got low positive predictive value. However, this test also has poor sensitivity and specificity and high false positive rate.
5. **Cervical length measurement by endovaginal USG:** Short cervical length < 25 mm is taken as a cut off for short cervix predicting preterm labor; It has positive predictive value of 14% and high negative predictive value of 97%. There is no evidence to support routine cervical assessment using ultrasound between 24-28 weeks for predicting preterm labor, however combination of ultrasound with fFN may help in predicting preterm delivery in high risk women.

Table 13.1: Combination of cervical length assessment and fFN in predicting recurrent risk of preterm delivery[9]

Cervical length	*Recurrent risk of preterm delivery*	
Cervical length	fFN positive	fFN negative
<25mm	65%	25%
26-35mm	45%	14%
>25mm	25%	7%

6. **Search for vaginal infections:** Bacterial vaginosis (BV) refers to alteration of normal bacterial flora of the vagina where lactobacilli are replaced by anaerobic infection. BV may be present in 10-25% of pregnant women and half of these women are asymptomatic. An association has been found between BV and preterm labor, it increases the risk by two fold. Attempts have been made to screen for bacteria in the vagina so that antibiotic treatment can be given to prevent infection and hence preterm labor. Most commonly involved organisms are group B streptococcus, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycoplasma hominis* and *Fusobacterium species.*

Q.5. What are the warning symptoms and signs of preterm labor?

Ans: In most of the patients who develop preterm labor, some of the patients may develop warning symptoms several days or weeks before the regular contractions, though these warning symptoms are nonspecific and should not be disregarded as a minor complaint or may be attributed to round ligament pain or gastrointestinal flu. Warning symptoms and signs can be:

1. Menstrual like cramps—off and on or constant.
2. Dull low backache—off and on or constant.
3. Pressure sensation as if baby is pushing down.
4. Abdominal cramping with/without diarrhea.
5. Increase or change in the vaginal discharge which may be watery, thick or bloody.
6. Leaking per vaginum.
7. Uterine contractions.
8. Short cervix.
9. Lower uterine segment thinned (developed).
10. Presenting part deep in the pelvis.

Q.6. What are the various tests for assessing fetal lung maturity?

Ans: The various tests are done on amniotic fluid collected on amniocentesis. These tests may be required to be done when maturity of the fetus is in doubt and termination of pregnancy is required to be done.

a. **L:S Ratio,** i.e. lecithin to sphingomyelin ratio in amniotic fluid. A ratio of 1.8 or more is an indicator of fetal lung maturity in 95% of fetuses for absence of HMD (hyaline membrane

disease). However, false positive results can be there in 5% of cases. L:S ratio is not informative if amniotic fluid is contaminated with blood or meconium.

b. **Phosphatidylglycerol (PG):** The 5% false positive result of L:S ratio can be decreased by simultaneously determining the presence of PG in the amniotic fluid. Presence of PG in the amniotic fluid is a marker of final biochemical maturation of the fetal lungs.
c. **Dipalmitoylphosphatidyl Choline(DPPC):** It is the main component of pulmonary surfactant and is not present in the blood or meconium or in vaginal secretions so when the amniotic fluid is contaminated with blood or meconium, quantitative measure of DPPC should be used instead of L/S ratio to assess fetal pulmonary maturity. DPPC > 500 µgm/dl is predictive of fetal lung maturity.
d. **Fluorescent polarization:** This test measures the micro viscosity of the amniotic fluid phospholipids in fluorescence polarization units, although the test is unreliable if the amniotic fluid is contaminated with blood or meconium.
e. **Amniotic fluid optical density** at 650 nm will accurately predict mature L/S ratio in 92% of the cases. Values between 0.1-0.2 should be evaluated with additional fetal lung maturity tests.
f. **Shake test:** It estimates qualitatively the stability of the bubbles that are formed after shaking a mixture of amniotic fluid with ethanol. The test is easy to perform and the accuracy is close to 100%, but a negative test is not a good predictor of pulmonary immaturity. A negative test is to be confirmed by further testing.
g. **Foam stability index (FSI):** The test is a semiquantative measurement of the surfactant present in the amniotic fluid. Amniotic fluid is mixed with ethanol in the necessary amounts to achieve alcohol concentration ranging from 44-50%. The chances of developing RDS is 0.35% if the bubbles are produced when the ethanol concentration is 47%.
h. **Tap test:** One ml of amniotic fluid is added to one drop of 6N HCl and 1.5 ml of diethyl ether. Bubbles are created after briskly tapping the test tube. In mature fetus the bubbles will rise to the surface and break down. If the fetus is immature the bubbles are stable or break down slowly. The test has an excellent positive predictive value up to 100% but a negative test is not a good predictor of fetal lung immaturity.

Q.7. What is the role of steroids in management of preterm labor?

Ans: Glucocorticoid administration is recommended for gestation age between 24-34 weeks. It was introduced in 1972 for enhancing fetal lung maturity and preventing respiratory distress syndrome and neonatal mortality.[6] It stimulates differentiation of epithelial cells into type II pneumocytes and synthesis and release of surfactant from type II pneumocytes into alveolar spaces. Besides lung maturity steroid causes decrease in water loss from skin, decrease in chances of necrotizing enterocolitis and intraventricular hemorrhage. Delivery should be delayed for minimum 12 hours for maximum effect of steroid, although optimal benefit begins 24 hours after therapy and lasts for seven days. Benefit of repeated courses of glucocorticoids is doubtful and not currently recommended.[6,7]

Q.8. What is the role of infection in onset of preterm labor?

Ans: There is strong evidence that infection plays a role in pathogenesis of preterm labor. Three lines of evidence that support the role of infection in onset of preterm labor are:[10]

- Abortion or labor is induced by administration of bacteria or bacterial products in animals.

- Systemic infections in the patient like pyelonephritis, pneumonia, malaria and typhoid fever are associated with the onset of preterm labor.
- Intrauterine infections are associated with onset of preterm labor and delivery.

Microorganisms may gain access to the amniotic cavity and the fetus via any of the following pathways.

- Ascending from the vagina and the cervix. (most common route).
- Transplacental
- Retrograde from the peritoneal cavity through the fallopian tubes.
- Iatrogenic introduction at the time of procedures like amniocentesis, chorionic villus sampling, percutaneous fetal blood sampling.

The definitive test for the diagnosis of an intrauterine infection is a positive microbiological culture for microorganisms that can be either intra-amniotic or extra-amniotic. Amniotic fluid sample can be obtained from the amniotic cavity but it is not easy to obtain material from decidua (extra-amniotic). Therefore practically, most studies in patients with preterm labor have focused on amniotic fluid culture obtained by transabdominal amniocentesis.

The term 'clinical chorioamnionitis' is described as a clinical syndrome associated with microbial invasion of the amniotic cavity. Studies have shown that only 12.5% of women with preterm labor and intact membrane with positive amniotic fluid culture have clinical chorioamniotic[10] as compared to 32.4% positive amniotic fluid cultures in women in preterm PROM.

The most common microorganisms isolated from amniotic cavity of women with preterm labor and intact membranes are: Ureaplasma urealyticum, fusobacterium species, Mycoplasma hominis. In 50% of the patients, more than one microorganisms are isolated from amniotic cavity.

Of all the preterm deliveries one third is associated with preterm labor with intact membranes, another third is associated with preterm premature rupture of the membranes and the remaining third results from delivery of the preterm baby due to maternal or fetal indications (preeclampsia, eclampsia, IUGR).

The prevalence of endometritis is also higher in women delivering preterm as compared to term. The prevalence of neonatal sepsis is 4.3 per 1000 livebirths as compared to 0.8 per 1000 livebirths in term fetus. The overall mortality rate of neonates with congenital neonatal sepsis ranges between 25-90%.

Q.9. What are the neonatal complications of a preterm baby?

Ans:

1. HMD: See below
2. Hypoxia-ischemia in the preterm is characterized by necrosis of periventricular white matter. Preterm infants are more severely affected by hypoxia and acidosis than the fetus at term.
3. Hypothermia Preterm infant is more prone to hypothermia.
4. Intraventricular hemorrhage (IVH): The most common site is subependymal germinal matrix. The severity of IVH is estimated by USG and CT scan of the fetal head and depends on the characteristics of the bleeding.
   Grade I-bleeding is confined to the germinal matrix.
   Grade II-bleeding is extending to the lateral ventricles.
   Grade III is IVH with ventricular enlargement.
   Grade IV is bleeding in the cerebral parenchyma.
   The incidence of IVH and grade I to grade III or IV is related to active phase of labor rather than the route of delivery. Mild-to-moderate degree of IVH is associated with good prognosis and recovery without neurological sequel. Severe bleeding is usually fatal and survivors frequently develop hydrocephaly.

5 Sepsis: The common types of infections in preterm infant are bronchopneumonia, meningitis and gastroenteritis.
6. Jaundice: Because of immature liver function, the bilirubin produced by hemolysis cannot be conjugated adequately leading to rise in unconjugated bilirubin which results in exaggerated physiological jaundice. The level however may rarely be raised to toxic level requiring treatment.
7. Retinopathy of prematurity

Q.10. What is hyaline membrane disease of newborn and describe its management?

Ans: Hyaline membrane disease is the most common cause of neonatal respiratory distress syndrome. It is more commonly seen in preterm babies, babies of diabetic mothers, infant's delivered by caesarean section.

It is due to the inadequate production of pulmonary surfactant by alveolar cells type II. The surfactant spreads in the lung tissue, preventing the alveolar collapse during expiration and allows the alveoli to open up during next inspiration. Surfactant deficiency increases the alveolar surface tension, thus the alveoli collapse during expiration and require considerable effort to open up during inspiration. There is poor lung compliance, reduction in ventilation-perfusion and progressive atelectasis. Pneumocyte nutrition is compromised by hypoxia and systemic hypotension leading to ischemic necrosis of alveolar cells. Protein filled fluid leaks into the alveolar ducts, and the cells lining the ducts slough off. Thus, the hyaline membrane forms which is composed of fibrin rich protein and cellular debris lining the alveoli and terminal bronchioles. The underlying epithelium becomes necrotic.

The clinical features may range from a mild distress to rapidly progressive fatal disease. The features appear abruptly few (4-6) hours after birth. Clinical features include hyperventilation, respiratory rate>60/min, nasal flaring, rib retraction, expiratory grunt, cyanosis.

X-ray shows a ground glass appearance due to severe atelectasis.

Meconium aspiration syndrome, pneumothorax, diaphragmatic hernias, congenital heart disease, are the other causes of respiratory distress syndrome in a newborn which is a differential diagnosis of HMD.

Treatment aims at:

1. Prevention of hypoxia and acidosis
2. Maintain fluid balance
3. Prevent atelectasis and pulmonary edema
4. Avoid lung Injury and infection

Management:

- Baby should be placed in a neonatal ICU and should be kept in an incubator with high humidity with ventilatory support. Continuous positive pressure ventilation prevents the collapse of the alveoli. High frequency oscillatory ventilation can also be used; it reduces barotrauma; in this a low constant pressure is maintained and small variations to promote alveolar patency. Air passages should be cleared periodically through endotracheal suctioning.
- Hypoxemia is indicative of need of oxygen. Warm, humidified oxygen therapy should be used with maintenance of PO_2 not more than 50 mm Hg. Higher concentration may cause lung injury and retinopathy of prematurity.
- Monitoring of PO_2, PCO_2, and pH to diagnose respiratory and metabolic acidosis. Any abnormality must be rectified.
- Correction of anemia, electrolyte imbalance, hypovolemia, if any.
- Surfactant therapy.

- Intragastric feeding is the preferred method. If there is risk of vomiting and aspiration, IV fluids are preferred.

Q.11. What is surfactant and how is replacement therapy given?

Ans: Surfactant is a complex mixture of phospholipids and proteins. The most important phospholipids are DPPC and PG. The most important proteins are surfactant associated proteins A, B and C. Both natural and artificial surfactant can be used for the treatment of neonatal HMD. Natural surfactant can be obtained from the human amniotic fluid and cow, calf and pork lungs. The artificial surfactants are made up of mixtures of DPPC and PG with or without emulsifiers. Surfactant can be used as soon as a preterm baby is delivered and before the development of symptoms and signs of HMD. It can also be used after the development of symptoms. It is administered via an endotracheal tube. It is given in single or multiple doses according to different protocols. The response to the surfactant is immediate, resulting in decrease of oxygen requirement and ventilation pressure.

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Mumtaz Khan

14 Antepartum Hemorrhage

Antepartum hemorrhage (APH) is defined as bleeding from or into the genital tract from 20/22 weeks of pregnancy (period of viability) till the birth of the baby. It complicates 2-5% of all pregnancies and is a leading cause of maternal and perinatal morbidity and mortality the world over.

The bleeding may be from the placental site or extraplacental in origin.

The main causes of placental site bleeding are:

a. from an abnormally situated low lying placenta (**placenta previa**)
b. or due to separation of a normally situated placenta (**abruptio placentae or accidental hemorrhage**).

Together these two conditions account for more than 50% of causes of APH.

Antepartum hemorrhage is a potentially serious complication of pregnancy where both mother and fetus are at risk. The patient's condition can deteriorate suddenly at any time.

The aim of management is to institute:

a. **General measures** to prevent deterioration
b. **Specific measures** are taken to reach a diagnosis and plan further management.

Management of such patients should be in a hospital with facilities for **blood transfusion**, **operative delivery, neonatal resuscitation and intensive care**.

Any patient with significant bleeding should be transferred by ambulance (after immediate resuscitation) to above recommended facility.

DISCUSSION

CASE 1

A 32-year-old G3 P2+0+0+2 with 32 weeks pregnancy reported to gynae casualty with history of bleeding per vaginum for 2 hours. On examination, a cesarean scar is present and the uterus is relaxed. How will you manage this patient?

Q.1. What are the important causes of APH and their incidence?

Ans: It is important to keep the various causes of APH in mind while evaluating a patient so that a probable diagnosis is reached soon after history and examination.

Causes	Incidence
1. Placenta previa	31.0%
2. Abruptio placentae	22.0%
3. Unclassified	47.0%
Marginal	60.0%
Show	20.0%
Cervicitis	8.0%
Trauma	5.0%
Vulvovaginal varicosity	2.0%
Genital tumor	0.5%
Genital infection	0.5%
Hematuria	0.5%
Vasa previa	0.5%
Others	0.5%

Q.2. What are the important points to be elicited in the history?

Ans:

Bleeding per vaginum

- Ascertain the **amount** of bleeding (soaked how many garments, spoonful, glassful, presence of clots, etc.) to decide the need for transfusion.
- **Painless** or is associated with **pain abdomen**
- What **initiated** the bleeding—history of **intercourse, trauma, fall, etc**.
- **Recurrent bleeding,** whether the patient has had **similar episodes** earlier in this pregnancy.
- **Color** and **character** of the bleeding. Is it bright red or dark altered blood?
- Whether the bleeding has stopped on its own or is still continuing?
- **Unprovoked, painless, causeless, recurrent bleeding** is characteristic of **placenta previa.** Sometimes it can be initiated by an act of **coitus.** Bleeding is **inevitable** in placenta previa and the color of blood is **bright red.**

The first episode of bleeding in placenta previa usually occurs:

- **Before 30 weeks in** 1/3rd of cases
- **Between** 30 to 35 weeks in 1/3rd of cases
- **After** 36 or more weeks in 1/3rd of patients (Crenshaw et al 1973).

The initial episode is **small** and **stops** completely on its own. It is a **warning hemorrhage** which should not be ignored.

The second major cause of bleeding is **abruptio placentae**, where the bleeding is from the separation of a normally situated placenta which depends on the site and amount of placental separation. It is usually associated with uterine contractions. The bleeding may be **concealed** or **revealed** and by the time it trickles down it is **dark and altered blood.**

In **ruptured uterus,** the bleeding is **fresh** and **red** in color**.**

Pain abdomen

- Is pain abdomen associated with bleeding? If so it is
- Is the pain **intermittent** and **colicky**, or is it **constant, continuous** and of **great intensity?**
- Has the pain **subsided** since then?
- Is the pain associated with **rupture of membranes?** If the liquor is blood stained it is suggestive of revealed abruption placenta
- Intermittent colicky pain could be the onset of **labor**, and the presence of blood mixed with mucos could be **show** (at times the bleeding may be more than normal and will require careful evaluation).

In concealed **abruptio placentae** the pain may be continuous and severe as the **retroplacental** collection of blood stretches the uterus to produce pain.

Pain is **less** common in **posterior placed placentae**.

10% of women with **placenta previa** can have coexisting abruption and can present with pain abdomen. Also onset of labor pains following bleeding in placenta previa can cause confusion in diagnosis.

Pain which was severe and subsides dramatically could be diagnostic of **rupture uterus.**

Gestational age and parity

Ascertain the gestational age by **last menstrual period (LMP**), or if the patient has an **early (first trimester) ultrasound.**

Management will depend on the diagnosis, condition of the patient and gestational age and parity. **Increased parity is a risk factor for both placenta previa and placental abruption.**

Placental localization

If there is an early 18-20 week ultrasound

- Try to localize the placenta, and rule out **placenta previa.**
- Rule out **multiple pregnancy** (which is a risk factor for both placenta previa and abruption)
- And congenital **malformation** in the fetus, which will affect the management of the case. (There is a high association of congenital malformations with placenta previa).

Fetal movements-

- Is the patient perceiving fetal movements and how frequently?
- Is there a history of loss of fetal movements?

In case of concealed and severe revealed hemorrhage in abruption, the fetus may already be dead.

In placenta previa despite heavy bleeding the fetus is usually alive, except in severe shock.

In ruptured uterus, the fetus may be dead or severely distressed.

Symptoms of pre-eclampsia/impending eclampsia–

- Are there any past **BP records** in this pregnancy and whether they were **high** readings?
- Is she having **headache, blurring of vision, pain right hypochondrium, edema of legs, puffiness of face or sudden gain in weight, tightening of finger rings, etc?**
- History of any episode of convulsion?

15-30% of women with abruption have symptoms of pre-eclampsia.

History of previous abortions (spontaneous or induced)

- The greater the number of surgical abortions, greater the risk of **placenta previa** and **morbid adherence of the placenta.**
- A previous surgical abortion increases the risk by a factor of 1.8.

History of previous cesarean section

- The risk of placenta previa increases with the number of cesarean sections performed on the patient.
  After 1 CS risk is 0.65%
  After 2 CS risk is 1.5%
  After 3 CS risk is 2.2%
  After 4 CS risk is 10%
- Chances of **placenta accreta** and the need for **cesarean hysterectomy** are also greater in patients with **placenta previa with prior cesarean section** than in patients of placenta previa with an unscarred uterus.
- Previous cesarean section is also a risk factor for ruptured uterus.

History of APH in earlier pregnancy and its cause-

- Risk of recurrence of both placenta previa and placental abruption is there.
- The recurrence risk for placenta previa is increased 12 times.
- The risk of a placenta previa is also increased if the previous pregnancy was complicated by abruption.
- For placental abruption risk of recurrence is 6-16.7% after one episode and 25% after second episode.

History of an overdistended uterus (multiple pregnancy, hydramnios) with **sudden rupture of membranes**

- Sudden decompression of an over-distended uterus, can lead to placental abruption.
- History of **preterm premature rupture of membranes** is also a causal factor for placental abruption.

History of any manipulation performed on the uterus prior to onset of bleeding

- **External cephalic version** which may lead to placental abruption.
- It may also cause rupture uterus, more common in scarred uterus

Past history

- History of hypertension, diabetes mellitus, heart disease, tuberculosis.
- History of any **bleeding diathesis** or **thrombophilia** (Any history of venous thrombosis)
- The common thrombophilias are: factor V Leiden mutation, the prothrombin gene (G20210A) mutation, the antiphospholipid syndrome, antithrombin III (ATIII) deficiency, methylene tetrahydrofolate reductase polymorphisms, hyperhomocysteinemia, protein C deficiency and protein S deficiency.

- Any history suggestive of **fibroid uterus** (menorrhagia, dysmenorrhea, previous history of abortions) is a risk factor for abruption.

Family history

Hypertension, diabetes mellitus and any bleeding diathesis or thrombophilias running in the family.

Personal history

- **Smoking and drug abuse (cocaine)** are important factors in the etiology of both placenta previa and abruptio placentae
- In placental abruption there is a 90% increase in risk with smoking, also there is a positive correlation between the risk and the **amount** smoked.

Menstrual history

Document the date of last menstrual period and calculate the expected date of delivery to ascertain the gestation period**.** Regularity of cycles is important to determine gestation age.

Obstetric history

- History of **first or second trimester abortions**, spontaneous or induced, whether followed by **D and E** or not?
- Find out about the mode of previous deliveries (whether **vaginal or cesarean section**). Placenta previa with previous LSCS can be complicated by morbidly adherent placenta.
- Indication for previous LSCS.
- Enquire about any **antepartum**, **intrapartum** and **postpartum complications.**
- History of APH in prior pregnancies.

In this case, she is G3P2002, first a normal vaginal delivery at term 5 years ago, second a cesarean section for transverse lie at 36 weeks in labor, 3 years ago. Both children are alive and healthy.

There is history of spotting 2 weeks ago and now she has soaked her under garment and 2-3 pads. There is no history of pain abdomen.

From her history she is probably a case of **placenta previa.**

Examination:

Proceed for examination as follows:-

General physical examination-

- Assess the **general condition** of the patient whether it is **good or poor**?
- Whether patient is **conscious, oriented** to time and place or is confused or in **shock**.
- Assess quickly the amount of **blood loss**.
- Look for **pallor, jaundice, cyanosis** and **peripheral edema**.
- Check the **pulse, blood pressure, respiratory rate** and **temperature** of the patient.

Pallor, tachycardia and hypotension are directly proportional to the blood loss.

Shock out of proportion to the visible blood loss is a feature of **abruptio placentae,** especially the concealed variety.

Edema and hypertension could also be associated with abruption, and hypertension could mask **true hypovolemia**.

- Assess the patient for the need for blood transfusion
- Start I/V infusion with a wide bore cannula (14-16 G)
- Draw blood samples for blood grouping and cross matching and for other investigations as will be discussed later.

Systemic examination

The cardiovascular system and the chest are evaluated for any evidence of associated heart or respiratory disease.

Abdominal examination is performed to check

1. **Height of uterus**
   - In placenta previa, the **height of uterus corresponds** to the period of gestation
   - In abruption the fundal height is more than period of gestation because of retroplacental accumulation of blood.
2. **Uterus contour and consistency and presence of tenderness**

- The contour of the uterus is maintained in both placenta previa and abruption,
- In ruptured uterus, the contour may be distorted, fetal parts may be felt easily, abdomen will be tense and tender with evidence of free fluid.
- In placenta previa, the uterus is relaxed and fetal parts are easily palpable and presenting part can be felt easily.
- In a case of abruptio placentae, the uterus is **tense, tender and rigid** (depending on the severity of abruption) and the fetal parts are felt with difficulty.

3. **Presentation**
   - **Malpresentations** like **breech, transverse, oblique lie or a free floating head** are common in placenta previa and are attributed to the presence of the placenta in the lower segment which prevents stabilization of the head.
   - In abruption the lie is usually vertical and the head is often engaged.
4. **Fetal heart sounds**
   - Are usually present in case of placenta previa unless the patient is in shock.
   - In case of abruption, the fetal heart sounds are absent in concealed type or severe revealed type, but are present in less severe degrees.
   - In ruptured uterus, the fetal heart sounds may be absent or there may be fetal distress.
5. **Multiple pregnancy**
   - The number of fetuses and their lie and presentation to be noted.
   - Multiple pregnancy is a risk factor for both placenta previa and abruption.
6. **Uterine contractions**
   - The presence of uterine contractions is to be noted as further management will depend on it.
   - This may indicate onset of labor.

Vaginal examination

- **As mentioned earlier vaginal examination is contraindicated at this stage unless placenta previa is ruled out.**
- **Every case of bleeding P/V in late pregnancy is presumed to be placenta previa unless proved otherwise.** (Even when the vaginal examination is done very gently and cautiously, 1 out of every 16 examinations produces a major hemorrhage and 1 out of every 25 examinations results in hypovolemic shock).[1]
- **Such digital cervical examination is never permissible unless the woman is in an operating room with all the preparations for immediate cesarean delivery- even the gentlest digital examination can cause torrential hemorrhage.** Furthermore, this type of examination should not be performed unless delivery is planned.
- An examination of the vulva can be done to ascertain whether bleeding is still continuing or has stopped and also to note the amount of bleeding.
- A gentle **speculum examination** may be performed after 5-7 days to rule out other local causes such as cervicitis, trauma, cervical polyps or cervical malignancy. Speculum examination is not associated with increased risk of hemorrhage. The presence of any of these still does not rule out placenta previa.
- In severe bleeding, speculum examination need not be done.

This patient is conscious, oriented, vitals are maintained, and pallor is mild. The uterus is relaxed, 32 weeks in size, cephalic free floating, fetal movements are present and fetal heart sounds heard. No active bleeding seen at present.

Q.3. What is your provisional diagnosis?

Ans: In this case under discussion she is most likely a case of **placenta previa** as:

1. The bleeding was painless, fresh, red in color
2. There is history of previous cesarean section
3. The uterus is relaxed, not tense or tender
4. Height of uterus corresponds to period of gestation
5. Head free floating
6. No scar tenderness
7. Fetal movements perceived and fetal heart sounds heard.

Q.4. What are the differential diagnoses?

Ans:

- Placenta previa
- Abruptio placentae
- Marginal bleed
- Ruptured uterus
- Bloody show
- Cervicitis
- Trauma
- Vulvovaginal varicosities
- Genital tumors
- Genital infections
- Hematuria
- Vasa previa

Q.5. What investigations are to be done in a case of APH?

Ans: The following investigations are recommended:-

- Investigations are done after initial resuscitation and stabilization of patient.
- Blood sample is taken for **blood grouping and cross-matching** and arranging blood as per the need. (In case of severe bleeding, 4 units of blood must be cross matched and made readily available).
- Complete **hemogram** with **hematocrit** and **platelet counts** is to be sent.
- **BT, CT** and **CRT** is done in all cases of APH.
- **Coagulation profile** is to be done keeping in mind abruptio placentae and associated disseminated intravascular coagulation. **PT, PTT, Serum Fibrinogen, Fibrinogen degradation products (FDP) and D-Dimer** to be done depending on facilities available. (For emergency management of patient these are not essentially required if BT, CT and CRT are normal).
- **Blood urea, serum creatinine, serum electrolytes** and **blood sugar** are done as base line investigations and also for anesthesia purposes if surgery is to be performed.
- **Urinalysis** must be done for presence of **proteins** and **sugar.**
- An **Apt test** can be performed on vaginal blood if **Vasa previa** is suspected and the blood is suspected to be fetal in origin.

Ultrasonography:

- **Ultrasonography** is essential for localizing the placenta.
- The ultrasound could be a **transabdominal** or an **endovaginal** ultrasound.
- The accuracy of transabdominal USG is excellent with false positive and false negative rates of 7 and 8% respectively.
- The accuracy is further improved with endovaginal method (positive predictive value of 93.3% and negative predictive value of 97.6%)—Farine et al, 1988.[2]
- Endovaginal technique is not only safe but also superior to transabdominal method, as the internal cervical os was visualized in all cases with endovaginal USG, but only in 70% cases by transabdominal method.
- **Transperineal USG** also allowed visualization of the internal os in all the cases studied and has a positive predictive value of 90% and negative predictive value of 100%—Hertzberg and associates (1992).
- **False-positive results** on transabdominal scans are usually due to **bladder distension**. Hence in apparently positive cases the scan should be repeated after emptying the bladder.
- Another cause of wrong reporting is the finding of abundant placental tissue implanted in the

fundus of the uterus, and presuming it to be in upper segment, but failing to appreciate a large placenta extending all the way down to the internal os.

If the placenta is found located in the lower segment of the uterus the diagnosis of placenta previa is clinched.

Q.6. What are the different types of placenta previa?

Ans: With use of endovaginal ultrasound one can identify the type of placenta previa.

Depending on the distance of the lower edge of the placenta from the internal cervical os:-

a. **Low lying**—When the placental border is more than 2.0 cm from the internal os.
b. **Partial previa**—When the placenta does not cover the internal os but its lower border is within 2.0 cm of the internal os.
c. **Total previa**—When the placenta completely covers the os and extends over both lips.

The latter two are major degrees of placenta previa and it has been seen that the cesarean rate is 90% when placenta is within 2.0 cm of the os and 37% when it is over 2.0 cm (Bhide et al, 2003).[3]

Q.7. What else to look for in USG after placental localization?

Ans:

- Look for **retroplacental clots** (also important in cases of placenta previa because of its association with abruption).
- The diagnosis of placental abruption is mainly clinical but rarely one can see signs of placental separation such as **membrane elevation.**
- It is important to note that negative findings on USG do not exclude placental abruption. It can diagnose 15-25% of this condition.
- Always keep in mind the **morbid adherence** of the placenta in cases of placenta previa, especially those associated with previous cesarean section (18% versus 4.5%).This abnormally firm attachment of the placenta may be due to poor decidualization of the lower segment of the uterus and may present as **placenta accreta** or in more advanced forms as **placenta increta** or **percreta**.
- Other findings to be noted on USG are **gestational age** of the fetus/**birth weight, fetal heart, presentation, amount of liquor, multiple pregnancy** and to rule out **congenital malformations.**

Q.8. Is there any role of color Doppler in diagnosis?

Ans: Transvaginal sonography and color Doppler imaging improve the diagnostic accuracy in the prediction of placenta accreta in patients with persistent placenta previa. A pattern of turbulent blood flow extending from the placenta into the surrounding tissues should alert the physician to the possibility of placenta accreta.

Twickler and colleagues (2000) reported that two factors were highly predictive of myometrial invasion: (1) A distance less than 1 mm between the uterine serosal- bladder interface and the retroplacental vessels, and (2) Identifications of large intraplacental lakes. These had a sensitivity of 100 percent and positive predictive value of 78 percent.

Q.9. Is there any role of MRI in diagnosis?

Ans: Magnetic resonance imaging (MRI) has been used successfully in identifying morbidly adherent placentation, but its high cost and nonavailability in most centers has limited its use. In times to come it may prove useful.

From above history, examination, investigations and USG (if available) a diagnosis as to the cause of APH is reached and in this case it is a case of placenta previa as the USG reveals anterior placenta 1.6 cm from cervical os and there is no evidence of morbid adherence on color Doppler.

Q.10. What is the management of placenta previa with reference to this case in particular?

Ans: Management can be in the form of **expectant** or **active management** depending on

- The severity of blood loss and whether it has stopped or is continuing
- The condition of the mother and fetus
- Gestational age
- The onset of labor.

The **aim** of management of pregnancies complicated by placenta previa is

- To allow them to progress to as close to term as possible and then terminate them by cesarean section.
- Only in case of minor degrees of previa (Type I and Type II anterior) vaginal delivery can be allowed (provided there is no obstetrical contraindication).

As in this patient the gestational age is 32 weeks and bleeding has stopped since admission, it is advisable to continue with conservative/ expectant management to allow for fetal lung maturity, provided the mothers' condition remains stable. Steroids to be given and a cesarean section should be performed around 36-37 weeks.

Q.11. What is expectant management?

Ans:

- It is conservative management
- The aim is to delay delivery as much as possible to allow for fetal lung maturity and at the same time not jeopardizing the condition of the mother**.**
- Only hemodynamically stable patients remote from term should be managed conservatively**.**
- The objective is to reduce perinatal mortality and morbidity due to prematurity.

Q.12. When should the expectant management be interfered with?

Ans: This expectant line of management must be abandoned when

a. Pregnancy reaches 36-37 weeks.
b. There is severe hemorrhage at any time endangering the life of the mother.
c. The fetus is dead or is malformed.
d. At onset of labor or rupture of membranes.
e. When frank accidental hemorrhage is suspected as cause of APH.

Q.13. What protocol is to be followed in expectant management?

Ans: Following protocol is followed for expectant management:[4]

1. **Admit** the patient in labor room, give **sedation** and keep her **nil orally**.
2. Start an **IV drip** and draw blood for grouping and cross-matching and send all relevant investigations as discussed earlier.
3. **Monitor the vitals** of the patient- pulse, BP, every 15 minutes till there is active bleeding and then ½ hourly. Record output one hourly and maintain an I/O chart.
4. Assess the blood loss and **transfuse** if bleeding is moderately severe or patient is already anemic. Aim is to maintain a Hb level of 10 gm/dl or hematocrit of 30% for fetal oxygenation.
5. Maintain an **abdominal girth** and **fundal height** chart ½ hourly to rule out abruption and concealed hemorrhage.
6. **Monitor fetal heart** sound by auscultation or electronic fetal monitoring.
7. **Steroids** must be given for lung maturity. Betamethasone 12 mg IM 24 hourly for 2 doses.
8. In selected cases, **tocolysis** should be given to prolong the gestation, once bleeding has stopped.
   - Nifedipine 10 to 20 mg orally is the drug of choice and should continue till patient delivers.
   - Terbutaline and Ritodrine cause maternal tachycardia and make the assessment of the patients pulse rate unreliable.

- Indocin is also not preferred as it prolongs the bleeding time.

However, the evidence suggesting that administration of tocolytic agents results in better pregnancy outcomes is not conclusive.

9. Rhesus negative women require a **Kliehauer test** every time there is fresh bleeding and appropriate **anti-D immunoglobulin prophylaxis**.
10. Once the bleeding has stopped patient can be shifted to the ward after 24 hours.
    - She should continue with bedrest
    - Give iron supplementation.
    - Stool softener is advisable to prevent straining at stools
    - Intercourse, vaginal douching and suppositories are contra indicated
    - Limited bathroom facilities are permitted once bleeding has stopped for 6-7 days
11. A per speculum examination is done, 5-7 days after bleeding has stopped, to exclude any local pathology.
12. USG if not done earlier can be done now.

Q.14. Can anything more be done to delay delivery in a case of placenta previa?

Ans: Elective cervical cerclage is one intervention that may be considered.

- Its benefits are still doubtful as two studies are in favor with respect to prolongation of pregnancy, increase in birth weight and reduction in number of bleeding episodes, while the third study does not show any such benefit**.**
- Further studies need to be done to prove its benefits.

Q.15. What is the mode of delivery in placenta previa?

Ans: Termination of pregnancy is done by

- **Cesarean section in major degree of placenta previa.**
- In **minor degree** of placenta previa **artificial rupture of membranes** is followed by **oxytocin drip**. This helps in effectively controlling hemorrhage from further placental separation.
- At any time if bleeding is excessive cesarean section should be done.

In this particular case, the mode of delivery should be by cesarean section as it is a case of previous cesarean section with major degree of placenta previa.

Q.16. Supposing the USG facility is not available, how would you manage the patient?

Ans: If and when ultrasound findings are inconclusive for placenta previa, or if USG facility not available, the patient can be taken for examination in operation theater (also known as **double set-up examination)** as this provides the most accurate assessment of the relationship between the lower edge of the placenta and the cervical os.

Q.17. What is double set-up examination?

Ans: Double set-up examination is p/v examination in operation theater to assess the relationship of the lower edge of the placenta with the cervical os.

- It is done only when delivery is to be undertaken.
- A second obstetrician is scrubbed and ready for performing cesarean if required, along with a nurse who is also scrubbed and the surgery and anesthesia trolleys kept ready.
- Anesthetist and pediatrician must be present.
- Cross matched blood should be available.
- The examination can be performed with or without anesthesia with everything ready to quickly induce the patient if cesarean is to be performed.
- The patient is put in lithotomy position and cleaned (only the vulva, not the vagina) and draped, bladder is emptied.
- A per speculum examination is done to look for any local cause of bleeding.

- Two fingers are then introduced carefully into the vagina and directed towards the fornices. Each fornix is then palpated to feel the presence of placenta between the presenting part and the vaginal fornix. There is a feeling of bogginess if placenta is present.
- If the fornices are empty then the index finger is gently introduced in the os and the surrounding is felt for the placental edge.
- If no placental edge is felt within 3 cm of the os, or if it is felt only anteriorly but does not reach the os and no bleeding is provoked the membranes should be ruptured in preparation for vaginal delivery.
- An organized blood clot can at times be mistaken for the placenta, but the former is friable unlike the placenta which is firm and nonfriable.
- If the os is closed or there is bright red persistent bleeding after membrane rupture, or there is brisk vaginal bleeding during the procedure, it should be abandoned and cesarean performed immediately.

Q.18. What are the contraindications for the above procedure?

Ans:

1. Profuse hemorrhage where immediate delivery is to be undertaken.
2. Clear cut sonographic evidence of major degree of placenta previa.
3. Malpresentation, malposition or other conditions where vaginal delivery cannot be undertaken.
4. Fetal distress

Q.19. Do patients with placenta previa need to be in hospital all the time?

Ans:

- Continued hospitalization is the best management option for patients of placenta previa.
- A few patients can be managed on an outpatient basis if the following criteria are fulfilled:-
  1. No bleeding for 72 hours while being observed as inpatient.
  2. Stable, serial hematocrit of 35% or more.
  3. Reactive nonstress test at time of discharge.
  4. Compliance with bed rest at home.
  5. Availability of transport 24×7 between home and hospital.
  6. Communication facility to be available.
  7. Patient and family members must be counseled and made aware of potential complications.
  8. Follow-up every week in ANC till delivery or readmission.

Q.20. Supposing this patient was bleeding profusely and signs of shock were present, what would be the management then?

Ans: After initial resuscitation with crystalloids and blood transfusion, patient to be taken up for emergency cesarean section after ruling out/correction of DIC and arranging adequate blood and blood products. This would be in maternal interest.

Q.21. What is active management of a case of antepartum hemorrhage?

Ans: Active management is

- The decision to terminate the pregnancy immediately after resuscitating the mother and stabilizing her condition.
- Coagulation profile should be corrected before any operative intervention.

Active management is to be considered in following circumstances:

1. When the fetus is mature.
2. The fetus is dead or has an anomaly not compatible with life, such as anencephaly.
3. There is risk to the life of the mother because of excessive and/or continuing blood loss.
4. Patient is in labor.

5. When accidental hemorrhage is suspected clinically and ultrasound confirms the placenta is located in the upper segment. In such cases:
   - P/V examination is done in labor room after admitting the patient
   - Depending on the cervical status an artificial rupture of membranes is done, followed by oxytocin drip.
   - If the fetus is salvageable patient may be taken for cesarean section in the interest of the fetus.
   - Only mild cases of abruption can be left on conservative management under careful monitoring.

Q.22. What protocol is followed for active management?

Ans: Following protocol is to be followed for active management:-

1. Resuscitate the patient by giving I/V fluids, blood transfusion
2. Correct coagulation profile by giving fresh frozen plasma or other blood components depending on the laboratory reports.
3. Arrange operation theater and shift patient to OT.
4. Counsel the relatives about the high risk condition of the mother and fetus.
5. Take informed consent for the need for cesarean section and maybe hysterectomy.
6. Keep adequate blood and blood components ready for surgery.
7. Cesarean section is to be performed directly in cases of
   - Major degree of placenta previa confirmed on ultrasound
   - If there is profuse bleeding
   - There are other obstetric conditions in which vaginal delivery is contraindicated, e.g. malpresentation and previous cesarean section etc.
8. If no facility for USG is available or if the USG report is inconclusive a p/v examination is done in OT under double set up arrangement in cases of mild to moderate APH
   In minor degree-type I and type IIa, the membranes can be ruptured and oxytocin drip is started and patient may be kept for vaginal delivery. In type IIb, III and IV placenta previa, immediate cesarean section is performed.
9. When no placenta is felt on digital examination (as in cases of abruptio placentae) then also the membranes are ruptured and oxytocin drip is started and patient allowed to deliver vaginally. If the cervix is not favorable and the fetus is salvageable a cesarean section may be performed in fetal interest.
10. If the patient continues to bleed following artificial rupture of membranes, decision for cesarean section is to be taken in maternal interest.

Q.23. Is the method of performing cesarean section any different in case of placenta previa?

Ans: Technique of cesarean section in cases of placenta previa.

- All major degree of placenta previa require cesarean delivery either emergency or elective.
- It is better to plan an elective cesarean as there is increased perinatal morbidity and mortality irrespective of gestational age following an emergency section
- A senior obstetrician should perform the section as there are great chances of complications in the hands of inexperienced obstetricians.
- The uterus is usually opened by a transverse incision in the lower segment. In case of any difficulty this incision may be extended to an inverted T, J or U shape.
- At times the lower segment may be nonexistent or it may be very vascular or when the placenta

is anterior, going through the placenta may cause fetal bleeding. In such circumstances some people have advocated a vertical incision. Such an incision is rarely justified because of its long-term consequences.

- After the transverse incision in the uterus one may either go through the placenta to deliver the baby or go by the side of the placenta and rupture the membranes to extract the fetus.
- Early cord clamping should be done.
- **If there is suspicion or prenatal diagnosis of a morbidly adherent anteriorly sited placenta previa then an upper segment cesarean section is preferable with the placenta left intact and may even be left *in situ*.**

Q.24. How to control the bleeding from the lower segment following cesarean?

Ans: Intraoperative hemorrhage is quite common as the lower segment is less muscular and contraction and retraction do not occlude the placental bed sinuses adequately. This bleeding can be controlled by:-

- Applying mattress sutures intermittently on the placental bed with 0 chromic sutures.
- Cho and colleagues (1991) have described the placement of square interrupted 0 chromic sutures around the lower segment above and below the transverse incision to control the hemorrhage.
- **Uterine artery ligation** and unilateral or bilateral **internal iliac artery ligation** can be considered.
- When these conservative approaches fail total hysterectomy is performed in maternal interest.
- **Hysterectomy** is particularly indicated in cases where there is morbid adherence of the placenta (accrete, increta or percreta). This situation is commonly seen in cases of previous uterine scar including cesarean with the placenta anterior and encroaching on to the scar and is becoming common because of the increased incidence of cesarean births.
- **Arterial embolization** in selected cases is another method of controlling intraoperative and postpartum hemorrhage. If antenatal ultrasound suggests morbid adherence of the placenta one should discuss preoperative arterial balloon embolization of the uterine/internal iliac arteries with the interventional radiologist as a method of controlling hemorrhage. The catheters are placed before starting the cesarean and soon after the baby is delivered, the arteries are embolized.

Q.25. What type of anesthesia is preferable for LSCS in a case of placenta previa?

Ans: Earlier the dictum was that for a cesarean for placenta previa only general anesthesia should be given, and regional anesthesia was considered a contraindication because of the ensuing hemorrhage and associated hypotension.

- Epidural anesthesia by lowering blood pressure may critically reduce uterine and placental perfusion endangering the life of the fetus.
- Now there is sufficient data to establish the safety of regional anesthesia in the hands of experienced anesthetists and also the amount of blood loss is less, compared to general anesthesia.
- When the patient condition is stable and there is no active bleeding, epidural or spinal anesthesia is no longer contraindicated in experienced hands.

Q.26. What are the maternal risks associated with placenta previa?

Ans:

- Hypovolemic shock due to hemorrhage (antepartum and intrapartum/intraoperative).
- Postpartum hemorrhage due to inadequate occlusion of sinuses in the lower segment following delivery.

- Anesthetic and surgical risks especially during emergency cesarean section.
- Puerperal sepsis due to ascending infection.
- Air embolism is a rare possibility when the sinuses get torn.
- Disseminated intravascular coagulation may occur with massive hemorrhge, although it is less common with placenta previa.
- **Placenta accreta** leading to increased maternal mortality and morbidity because of increased chances of postcesarean hysterectomy and intraoperative bleeding.
- Recurrence risk of placenta previa in future pregnancies.

Q.27. What are the risks to the fetus?

Ans:

- Increased perinatal morbidity and mortality due to preterm birth.
- Intrauterine growth restriction (more common with repeated episodes of bleeding).
- Congenital malformations usually of the CNS, CVS, respiratory and GI systems.
- Fetal anemia following accidental vasa previa rupture.
- Sudden intrauterine death when there is severe maternal hypovolemic shock.
- Risks associated with malpresentations, cord prolapse, etc.

Q.28. How to assess the severity of blood loss in cases of antepartum hemorrhage?.

Ans:

- It is difficult to gauge the severity of bleeding and the amount of blood loss as blood pressure and pulse may remain normal despite significant blood loss in a pregnant patient because of hypervolemia.
- The hemoglobin and hematocrit may be normal for some time in a bleeding patient not receiving fluids.
- One also has to take into account the clinical condition of the patient before bleeding started. An anemic patient may not withstand a loss of one unit of blood and will have hypovolemia whereas a normal patient may not manifest any changes in vitals following a similar loss.
- For purposes of uniformity, severity of bleeding may be classified into four groups:[5]-
  1. In the **first group,** the bleeding is said to be **mild** with blood loss <750 ml (only 15% of the intravascular volume).There is no change in the vitals, urinary output or CNS.
  2. In **group II** or those with **moderate bleeding**, blood loss is between 750 to 1500 ml. These patients have base line tachycardia (change of 10 to 20 beats per minute) and a fall in BP (drop of 10 mm or more in diastolic BP), urine output is between 20 -30 ml per hour and patient may be anxious and agitated.
  3. In **group III and IV**, those with **severe bleeding** the blood loss is1500 ml to more than 2500 ml and 30% to more than 40% blood volume is depleted. Patient is in shock with decreased or unrecordable BP, oliguria or anuria and patient may be confused or lethargic. The fetus may be severely distressed or dead.

Q.29. How to manage patients with severe bleeding?

Ans:

- Assessment of blood loss is important for initial management of the patient.
- This particular classification can be useful in guiding volume replacement.
- Patients with severe bleeding require **life support measures** and immediate **operative intervention** to save the mother.
- Besides **intensive monitoring, intravenous fluid replacement** and **transfusion therapy** is required.

- **Crystalloids** such as Ringer lactate is given fast, till blood is made available for transfusion. **One liter of crystalloid solution expands the intravascular volume by approximately 250 ml.**
- The patients' response to I/V fluids is a rough guide to assess severity of bleeding. If with less than 3 liters of fluid the blood pressure becomes normal and pulse rate decreases then the blood volume loss is probably less than 50%.
- **Packed red cells and specific blood components** should be used for combating shock and replacement of blood and clotting factors where required.
- In extreme emergency situations if type specific blood is not readily available patient should be transfused O negative or even O positive blood.
- With massive transfusions (more than 10 units in 24 hours) the clotting factors get depleted and an assessment should be done for the same, especially platelet counts.
- **Platelet transfusion** should be given when counts are less than 50,000/mm^3. It is preferable to give platelets from a single donor to reduce antigenic exposure.
- **One unit of single donor platelets increase the count by 50,000** approximately, while pooled platelets from multiple donors will accomplish the same with 5-6 units and antigenic exposure will be much more.
- If there are alterations in PT or PTT then fresh frozen plasma should be given. **For every 4 units of packed cells I unit of fresh frozen plasma should be transfused.**
- In patients in critical condition it may not be possible to monitor the intravascular status with pulse and BP monitoring alone, hence there is need for a **central venous pressure line** to monitor fluid replacement. If coagulopathy is suspected a more **peripheral CVP** line is preferred.
- **Urine output** measurement is an important aspect in management of patients with severe bleeding and shock. A Foleys' catheter must be inserted and the output should be aimed to be maintained at 30 ml/hour to protect the kidneys from damage from acute tubular or cortical necrosis leading to anuria or oliguria.
- Following expansion of intravascular compartment by adequate fluid and blood replacement, Frusemide 20-40 mg may be given I/V to reestablish urinary output.
- Remember that blood loss is grossly underestimated.

Q.30. Is postpartum hemorrhage common in a case of APH and why?

Ans: Yes, in all cases of APH one should anticipate PPH. In placenta previa, PPH is caused because of:

a. Failure of the lower segment to retract properly.
b. Large surface area of the placenta with atonic uterus.
c. Morbidly adherent placenta.

In abruptio placentae PPH is due to:

a. Atonic uterus.
b. Coagulation failure.
c. Couvelaire uterus.

Q.31. How to prevent or control PPH in a case of APH?

Ans:

- Active management of the third stage is important for controlling PPH.
- Intravenous methergine, oxytocin infusion (10-40 units), intramuscular PG F2α 250 µg and misoprostol 800 µg per rectum may be used to control PPH.
- Replace blood adequately and correct coagulopathy.
- If these measures fail internal iliac ligation/ arterial embolization to be attempted.
- Hysterectomy is the last resort.
- In a case of placenta previa at cesarean section hemostatic sutures to be applied on the placental bed.

- Systematic devascularization of the uterus to be done.
- B-Lynch suture can be tried.
- Internal iliac ligation and hysterectomy as a last resort.
- Hysterectomy for placenta previa should be a **total hysterectomy**.

CASE 2

A 30-year-old primigravida with 36 weeks pregnancy presented to gynae casualty with bleeding P/V and pain abdomen for 1 hour. On examination her BP is 144/90 mm of Hg, pulse 120/minute, severe pallor+, uterus is tense and tender, FHS is absent. Urine albumin is ++. What is your diagnosis and how will you manage this case?

As already discussed in the previous case scenario immediate aim is

- To resuscitate the patient,
- Ascertain the amount of bleeding
- Take a quick history followed by examination in order to reach a provisional diagnosis as to the cause of bleeding.
- Further management will depend on the maternal and fetal condition. In this case the fetus is already dead.

Q.32. What are the differential diagnosis?

Ans:

- Placenta previa
- Abruptio placentae
- Unclassified bleeding (marginal sinus rupture)
- Vasa previa
- Ruptured uterus
- Labor pains
- Bloody show
- Other local cervical and vaginal pathology.

In concealed type of accidental hemorrhage following conditions to be kept in mind as differential diagnosis:[6]

- Nonobstetric acute abdominal conditions such as acute appendicitis.
- Hematoma of the rectus abdominis muscle.
- Acute hydramnios.
- Retroperitoneal hematoma.

Q.33. What is the provisional diagnosis and why?

Ans:

- In this patient, the bleeding is associated with pain abdomen.
- Features of pre-eclampsia are present
- Uterus is tense and tender
- The fetus is dead.

These findings are in favor of **abruptio placentae** rather than placenta previa (see history and examination for differential diagnosis). The abruption is also of severe variety (more of concealed) as the fetus is already dead. Patient must have been hypertensive as the BP after the episode is 130/90 mm of Hg.

Q.34. Why it could not be a case of ruptured uterus?

Ans: It could not be a case of ruptured uterus because:

- Patient is a primigravida
- There is no history of previous scarring of uterus
- No history of any abortion or MTP
- Patient has not been in labor for long
- Pain abdomen is still present (not subsided as it should dramatically stop after ruptured uterus)
- The uterine contour is maintained
- In ruptured uterus, the fetal parts are felt superficially and the uterus contour is not maintained and it may be felt as a mass in the abdomen-which is not the case in this patient.

Q.35. What investigations are required for diagnosis and management of this case?

Ans:

- The diagnosis of placental abruption is based on history and clinical findings.
- All investigations as listed in the previous case are to be done.

- The DIC profile is important in this case to confirm and manage DIC.
- An ultrasound examination is important to rule out placenta previa and to see any features of abruption (as detailed earlier).

Q.36. What are the values of various components in the DIC profile?

Ans:

- Fibrinogen—150-600 mg/dl.
- Prothrombin time (PT)—11-16 seconds.
- Partial thromboplastin time (APTT)—22-37 seconds.
- Platelet count—120,000-350,000/mm.^{3}
- D-dimer—<0.5 mg/L.
- Fibrin degradation products FDP—less than 10 µg/dl.

Q. 37. What is the role of ultrasonography in diagnosis of placental abruption?

Ans:

- As stated earlier placenta previa should be excluded by USG in all cases of antepartum hemorrhage.
- The sensitivity of USG for presence of an abruption is poor (24%), although it is often performed in cases where immediate delivery is not indicated.
- When the retroplacental clot is large USG identifies it as hyperechogenic or isoechogenic compared to the placenta, and may be misinterpreted as a thick placenta.
- A resolving clot becomes sonolucent within 2 weeks.
- In concealed hemorrhage, the placenta appears thick and globular, almost 6 cm in diameter.
- Ultrasound is also useful in assessing fetal presentation, fetal weight and well-being.

Q.38. What is placental abruption and how does it manifest?

Ans: Abruptio placentae is the premature separation of a normally situated placenta before the birth of the baby, resulting in bleeding into the decidua basalis.

- Its incidence is 1% approximately.
- On histological examination of the placenta it is noted that many cases go undetected. Histological examination incidence is 4.5%.
- The incidence of abruption increases with gestational age and more than 90% fetuses weigh 1500 gm and above at birth.
- Abruptio placentae presents as **vaginal bleeding**, present in 78% of the cases—**revealed type** or the **concealed type** where there is no overt bleeding (around one third of all cases).
- **Uterine tenderness** and **back pain** in 66% of patients.
- **Uterine hypertonicity** and **contractions** in 17% of the patients. Woody consistency of uterus.
- Size of the uterus more than period of gestation.
- Shock may be out of proportion to the apparent blood loss.
- **Fetal death** may occur in 25-35% of cases before admission.
- It is rare to find all of these features together, but at least one is present. Sometimes none may be present.
- The concealed type where there is no vaginal bleeding is the more severe form of the disease (25-35%). It is usually associated with **DIC (disseminated intravascular coagulopathy)** and the abruption is severe enough to cause fetal demise.

Q.39. What are the risk factors for developing abruption placentae?

a. Cigarette smoking has an increase in risk upto 90%, with a direct correlation with the amount smoked.
b. Pre-existing hypertension and hypertensive disorders of pregnancy. Together with smoking the risk increases further.

c. Abdominal trauma sustained in a fall, road traffic accident or physical abuse.
d. Sudden decompression of an overdistended uterus such as membrane rupture in polyhydramnios, multiple pregnancy.
e. External cephalic version.
f. Preterm premature rupture of membranes, specially in cases where bleeding precedes rupture of membranes.
g. Acquired and inherited thrombophilias-factor V Leiden mutation, the prothrombin gene mutation, antiphospholipid syndrome, antithrombin III (ATIII) deficiency, methylene tetrahydrofolate reductase polymorphisms, hyperhomocysteinemia, protein C deficiency and protein S deficiency.
h. Increased maternal age, parity, diabetes mellitus.
i. Unexplained elevation in maternal serum alphaproteins (after excluding neural tube defects, multiple pregnancy and intrauterine hemorrhage).
j. Cocaine abuse.
k. Uterine leiomyomata especially if they are located behind the placental implantation.
l. Uterine malformations.

Q.40. What is the grading of placental abruption?

Ans: Clinical classification of Abruptio placentae:

- **Grade 0**: The patient is asymptomatic and it is incidentally diagnosed on seeing retroplacental clots after delivery of placenta.
- **Grade I**: Hemorrhage with pain and irritable uterus but no fetal or maternal compromise.
- **Grade II**: No maternal compromise but fetal distress is evident.
- **Grade III**: There is uterine tetany, maternal compromise and fetal demise. DIC and renal shut down are important complications. Average retroplacental blood loss is said to be more than 2500 ml.

In all symptomatic grades, the hemorrhage may be concealed or revealed.

Q.41. What is the management in this case?

Ans: As discussed earlier the immediate management is:

- **General management**
  1. Resuscitate the patient by expanding the intravascular volume with crystalloids
  2. Replace blood by transfusing packed red cells
  3. Stabilize the vitals and maintain adequate urinary output.
  4. It is then followed by **specific management** pertaining to the diagnosis.
- Management of abruptio placentae is guided by
- The grade at presentation
- Gestational age
- Presence of complications**.**

The objective of management of severe abruption causing fetal demise as in this case is to decrease maternal morbidity and mortality and this can be achieved by delivery of the fetus.

When the fetus is dead

- The placental separation is more than 50%
- Coagulopathy is present in 30% of the cases
- Renal failure in about 10%.

A careful assessment of the maternal condition should be undertaken and blood clotting factors to be replaced.

- As the blood loss in cases of abruption severe enough to kill the fetus is estimated to be around 2500 ml. All patients must be transfused 2 units of PRC (packed red cells) irrespective of their initial vital parameters and hemoglobin/ hematocrit, to prevent further impairment in organ perfusion.
- If the patient was hypertensive then the initial BP may be normal, the pulse may also rise when the vascular compartment expands.
- In concealed hemorrhage, the blood loss is grossly underestimated and by the time the vitals

deteriorate there is profound hypovolemia and it is difficult to reverse the shock.
- While waiting for PRC, the intravascular volume should be expanded with Lactated Ringer solution at a rapid rate.
- The aim should be to maintain a hematocrit of 30% and an output of 30 ml/hour.
- A CVP line should be inserted to monitor fluid replacement.

Q.42. What is the pathophysiology of DIC in abruption placentae?

Ans: DIC in cases of abruption develops due to massive release of thromboplastin into the circulation which in turn leads to:
- Intravascular formation of fibrin
- Consumption of coagulation factors
- Subsequent activation of the fibrinolytic system.

Q.43. How to diagnose and manage coagulopathy?

Ans:
- For evaluation of coagulopathy a DIC profile is done.
- There is a drop in fibrinogen level to 100 mg/dl or less.
- PT and PTT are prolonged
- Platelets are reduced
- D-dimer values are raised.
- Abnormal values do not warrant therapy unless excessive bleeding is seen to be present.
- Vaginal delivery can be effected in the presence of depleted coagulation factors, but to avoid excessive bleeding at time of delivery and subsequently, it is prudent to correct the coagulopathy.
- Correction of coagulopathy is by transfusing **platelets, fresh frozen plasma** and **cryoprecipitate**.
- No surgical intervention should be undertaken before correcting the coagulopathy as severe bleeding may ensue.
- The coagulopathy resolves early in the postpartum period but the high levels of FDP (fibrinogen degradation products) interfere with myometrial contractility and cause postpartum hemorrhage. Hence, all steps outlined earlier for prevention and control of PPH must be followed.

Q. 44. In what dose is cryoprecipitate given and when?

Ans: Patients having a fibrinogen level of less than 100 mg/dl should be administered cryoprecipitate in a dose of 10-20 units immediately before and during cesarean section.

Q.45. Is there any role of heparin in management of coagulopathy?

Ans:
- Heparin should not be used for management of DIC in a case of abruption as it increases the blood loss and there is need for further transfusion.
- As DIC in abruption is due to a premature separation of the placenta, treatment is to deliver the fetus and placenta at the earliest.

Q.46. What should be the mode of delivery when fetus is dead as in this case?

Ans: When fetus is dead
- Vaginal delivery should be aimed for, unless
- There is a malpresentation warranting a cesarean section,
- Or the hemorrhage is brisk endangering the mothers' life.
- The presentation should be confirmed by ultrasound as it is difficult to find out clinically with a rigid uterus.
- External version should not be attempted in cases of abruption with a rigid uterus.
- Amniotomy should be performed early
- Oxytocin infusion to be started.

- Parity and maternal age are no contraindication for oxytocin infusion, unless labor has already started.
- With a dead fetus and an unripe cervix either misoprostol 50 µg every 4 hourly 5 doses intravaginally or high doses of oxytocin will be required.
- Uterine contractions may not be appreciated clinically because of the rigid uterus and already raised baseline intrauterine pressure.
- Cervical dilatation is the best index for progress of labor.
- **With a dead fetus there is no time limit for obtaining a vaginal delivery**, unlike in earlier times when it was 6-8 hours. It can now be safely extended to 24 hours.
- Maternal outcome depends on the adequate expansion of intravascular compartment with fluid and replacement of blood, rather than on the interval to delivery.

Q.47. If the fetus was alive in this case would the management change?

Ans: Yes, the management would be more complex as

- Both mother and fetus are at risk of death.
- Two groups are identified, one where the **uterus is rigid** and another where the uterus is **soft**.

When the fetus is alive and the uterus is rigid

1. It is presumed that the abruption is large but probably less than 50%.
2. Allowing such patients to go into labor means that chances of fetal distress will be as high as 90%.
3. Hence these patients should be prepared for emergency cesarean section except when the fetus is previable or the maternal condition is serious and will deteriorate with surgery.
4. The rest of the management (replacement of blood, expansion of intravascular volume with fluids and work up for DIC) should continue simultaneously.

With the fetus alive and the uterus soft

1. The grading is of a less severe degree and it is presumed that abruption is no more than 25%.
2. The chances of coagulopathy are also very low.
3. Such patients should have induction of labor and a vaginal delivery.
4. Cesarean section may be done if there is fetal distress at any time.

Q.48. Is there any role of conservative/expectant management in abruption placentae?

Ans: Expectant management has a role

- In cases of mild placental abruption with pregnancy less than 34 weeks,with stable maternal and fetal condition and normal laboratory values. This management should be on an inpatient basis.
- The aim is to prolong pregnancy to allow for fetal lung maturity.
- These patients have mild bleeding and pain and are hemodynamically stable.
- There should be regular assessment of maternal condition (maternal hematologic parameters and coagulation profile).
- The fetus should be monitored closely in this period with nonstress test and biophysical profile.
- Betamethasone to be administered.
- Tocolysis in select cases.
- Anti-D where needed.
- Pregnancy should be terminated when there is recurrent bleeding, or any feature of fetal compromise such as fetal growth restriction, oligamnios, abnormal CTG or BPS.
- With no maternal or fetal compromise still induction of labor at term is advocated.

Q.49. What tests are performed to assess fetal lung maturity?

Ans: The **Lecithin to Sphingomyelin L/S ratio** is the test used for assessing fetal lung maturity.

- If the ratio is greater than 2, the patient should be delivered.

- There are 2 other rapid tests—fetal lung maturity (FLM) and Phosphatidyl glycerol and in majority of patients under 36 weeks they show fetal lung immaturity.
- Delivery should not be delayed because of these once L/S ratio is more than 2 as the chances of developing RDS would be less than 5% and it would be of a mild variety.

Q.50. Is tocolysis advocated in abruptio placentae?

Ans:

- Mild cases of abruption complicated by labor may be given a trial of tocolytics to prolong the pregnancy in order to achieve fetal lung maturity.
- Many people say that tocolytics are contraindicated as they worsen abruption.
- Scientific evidence supports tocolytic therapy in an environment where close maternal and fetal monitoring is feasible and facilities for emergency cesarean section exist.[1]

Q.51. What are the risks to the mother with placental abruption?

Ans:

a. Chances of **maternal mortality** around 1% and **higher morbidity**. The maternal mortality is on account of **severe hemorrhage** and also due to **disseminated intravascular coagulation** which again causes further bleeding and renal failure.
b. Hypovolemic shock, especially in concealed hemorrhage where blood loss is underestimated.
c. Disseminated intravascular coagulation. Coagulopathy present in 10% cases of abruption. Fulminant DIC ensues within 1-2 hours of complete abruption and is present in 40% of cases with fetal demise.
d. Acute renal failure attributed to hypovolemia as well as to DIC.
e. Postpartum hemorrhage of the atonic type, may be due to coagulopathy or development of Couvelaire uterus.
f. Amniotic fluid embolization.
g. Puerperal sepsis.
h. Fetomaternal hemorrhages can be large in abruption and risk of alloimmunization is increased. There is need to give larger doses of anti-D. All patients to undergo a Kleihauer Betke test to quantify the fetomaternal hemorrhage and adjustment of anti-D dosage.
i. Pulmonary edema, cesarean section and postpartum anemia are other major maternal morbidities.
j. Risk of recurrence in future pregnancies.

Q.52. What is Couvelaire uterus and what are its implications?

Ans: Couvelaire uterus is:

- The condition in which severe bleeding occurs into the myometrium subsequent to placental abruption.
- This impairs the ability of the myometrium to contract and is one of the reasons for postpartum hemorrhage in a case of abruption.
- Diagnosis of Couvelaire uterus is confirmed at cesarean section/laparotomy where the uterus shows bluish discoloration (because of blood seeping under the serosa) and the uterus is large and flaccid.
- Effusion of blood can also be seen under the tubal serosa, in the connective tissue of the broad ligaments, in the substance of the ovaries and also free in the peritoneal cavity.
- **It is not an indication to perform cesarean section or hysterectomy per se.**
- Uterotonics are used to make the uterus contract and control postpartum hemorrhage.
- The bleeding is not severe enough to warrant a hysterectomy.

Q.53. What is the recurrence rate of placental abruption and what is the prognosis for future pregnancies?

Ans:

- The recurrence rate is 6-17% after one episode and increases to 25% after second episode.
- Severe abruption causing fetal demise has the same outcome in next pregnancy in approximately 7% of cases.14% of future pregnancies end in abortions and almost 30% do not produce a living child.
- Incidence of recurrence may be reduced by correction of causative factors such as poor nutrition, smoking, low folate intake and poor weight gain.
- Induction of labor before term has no proven benefit for preventing recurrence.

Q.54. What are the fetal risks associated with placental abruption?

Ans:

a. High incidence of **perinatal mortality** and **morbidity** which is directly proportionate to the gestational age, 50% of these are still births. Incidence varies from 4.4% to 68% depending on the newborn care available. Besides **prematurity**, other causes contributing to fetal mortality are **fetal growth restriction, congenital malformations** and associated **maternal hypertension**.
b. Fetal growth restriction in approximately 80%.
c. Congenital malformations (4.4%) and are mostly involving the central nervous system.
d. Fetal anemia as a result of fetal bleeding and deranged hematology.
e. Respiratory distress syndrome.
f. Hyperbilirubinemia.
g. Fetal hypoxia.
h. Hypovolemic shock of the newborn, although rare, it can be associated with any kind of APH.
i. A fetal and neonatal coagulopathy associated with abruption, but it is very uncommon.
j. Of the surviving infants there are adverse sequelae in the form of neurological deficit within 1 year of life and cerebral palsy, etc.

Q.55. If placenta previa and abruptio placentae are ruled out, what could be the cause of APH?

Ans: In about 47% cases the cause of bleeding is not known or it may become evident later on.The causes identified are:

a. Marginal sinus rupture 60%.
b. Show 20%.
c. Cervicitis 18%.
d. Trauma 5%.
e. Vulvovaricosities 2%.
f. Genital tumors, hematuria, genital infection and vasa previa 0.5% each.

These are grouped under **"unclassified bleeding"** and **marginal sinus rupture** is the most important cause. Minor cases of placenta previa and abruption also get included in this group.

Q.56. What is marginal sinus rupture and why is it important?

Ans:

- This is a diagnosis of exclusion and can be confirmed or ruled out after delivery.
- The speculum examination is negative.
- There is peripheral placental separation which manifests as a clot at the junction of the membranes and the placental border on examination of the placenta after delivery.
- It can rarely be diagnosed by ultrasonography.
- Its importance is because of its association with **preterm labor** and **premature rupture of membranes**
- Patients with chronic bleeding may also develop **chorioamnionitis**.

Q.57. What is the management?

Ans:

- As the bleeding is usually not severe and it stops spontaneously, the management is **expectant**.

- Maternal and fetal monitoring is carried on at regular intervals
- Pregnancy is allowed to progress to term.
- Some people advocate induction of labor at 38 weeks citing placental dysfunction as a cause, and risk to the fetus.
- Opinion is in favor of intervention when fetus is in distress.
- Tocolytics can also be used safely to prevent preterm labor.

Q.58. What is vasa previa?

Ans:

- Vasa previa is a rare condition (1 in 2000-3000 deliveries) wherein the fetoplacental blood vessels rather than the placenta are overlying the internal cervical os, traversing the membranes and lying ahead of the presenting part.
- In this position they are likely to get lacerated at the time of membrane rupture and may cause severe fetal bleeding.
- During labor they may get compressed by the presenting part and cause fetal hypoxia.
- It is associated with a very high fetal mortality (75-100%).
- As the bleeding is mainly fetal in origin the risk to the mother is not much increased.

Q.59. How to diagnose Vasa previa?

Ans:

- Diagnosis of vasa previa is usually made when there is bleeding following amniotomy or after spontaneous rupture of membrane.
- There is fetal bradycardia accompanying,or tochographic evidence of fetal compromise is present.
- A bedside test is done to find out if the bleeding is of fetal origin by testing the fetal hemoglobins' ability to withstand alkali denaturation. It can sometimes be diagnosed on antenatal or intranatal p/v examination when vessels are felt, or before doing an amniotomy.

Q.60. Are there any conditions where vasa previa should be suspected antenatally?

Ans:

- Vasa previa is associated with placentas that are low-lying, and have succenturiate or multilobed composition.
- It is also seen with velamentous insertion of cord which in turn is found more commonly with artificial reproductive techniques such as in-vitro fertilization (due to disturbed orientation of the blastocyst on implantation). It is also more common in multiple pregnancies.
- Antenatal diagnosis is possible in these conditions by color Doppler visualization of these vessels by endocavitary ultrasound.
- Sometimes the diagnosis is made antenatally during a p/v examination before or during labor, or at the time of amniotomy when these vessels are felt.

Q.61. How is Apt test performed?

Ans:

- This is a simple test to differentiate fetal from maternal blood.
- 5 ml of tap water is taken in two test tubes and six drops of 10% KOH is added to each. To one test tube add 3 drops of vaginal blood and to the other add 3 drops of maternal blood.
- After 2 minutes the maternal blood in test tube will turn green yellowish brown.
- If there are fetal red cells in the other test tube containing vaginal blood the KOH will remain pink (Loendersloot,1979).

Q.62. How to manage vasa previa?

Ans: As the fetal mortality and morbidity is very high**, emergency cesarean** section must be done once diagnosis is confirmed by presence of fetal red cells in the vaginal blood.

Q.63. What are the recent advances in the diagnosis and management of APH?

Ans: Human recombinant factor VIIa

- Is a new, potent drug for control of obstetric hemorrhage specially severe bleeding associated with abnormalities of hemostasis.
- This medication complexes with tissue factor and promotes the activation of factors IX and X and synthesis of thrombin.
- It is given as a bolus injection of 60-100 μg/kg. and the effect is seen after 10 minutes.

Cervical cerclage

- In cases of placenta previa with prematurity in order to prolong pregnancy.
- A recent Cochrane systematic review looked at the information available (Neilson 2003) and found that cervical cerclage may reduce the risk of delivery before 34 weeks (RR 0.45, CI 0. 23-0.87) and that of the birth of a baby less than 2 kg. (RR 0.34, CI 0.14-0.83) or having a low 5 minute Apgar score (RR 0.19, CI 0.04-1.00).
- Conclusion is to encourage further work on this subject.

Role of MRI to study the placenta.

- Compared to ultrasound imaging it allows for better visualization of soft tissues, clearer definition of cervix and reduced margin of error from overfilling of bladder.
- MRI has made possible the antenatal diagnoss of placenta **accreta, increta and percreta** allowing one to plan the management timely and reducing the risks.

Safety of regional anesthesia for cesarean section in cases of APH:

- Cesarean section in a case of placenta previa has commonly been performed under general anesthesia rather than regional anesthesia because of fear of hemorrhage and hypotension.
- Recent data suggest that the hemorrhage may increase under general anesthesia and that regional anesthetic techniques-both epidural and spinal anesthesia are quite safe for both elective and emergency cesareans in cases of placenta previa.

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Shikha Sharma

15 HIV Positive Pregnancy

The human immunodeficiency virus (HIV) is a small RNA retrovirus that causes the clinical disease termed as the acquired immunodeficiency syndrome (AIDS) was first described in 1981.[1,2] Roughly one-third of infected patients develop clinical AIDS within the first five years after inoculation and 75 percent by the end of ten years.[3]

The virus may be transmitted through:

- Unprotected anal or vaginal intercourse especially in the presence of genital ulceration,
- Sharing of contaminated needles,
- Unscreened blood products,
- Vertical transmission either antepartum, intrapartum or postpartum (breast milk).

Early HIV infection is characterised by a high viral load. The main target of HIV is to the CD4 lymphocyte population and which are gradually lost during the latent phase. Loss of CD4 lymphocytes reduces both cell-mediated immunity and humoral immunity, leading to the development of infections and allowing more rapid replication of HIV.

CASE 1

Mrs A, a primigravida, at 20 weeks gestation has come to ANC Clinic for the first time. Will you counsel the women to take HIV test? If yes, how is HIV Testing done?

HIV testing is the first step towards PPTCT (Prevention of parent to child transmission) aimed at reducing the vertical transmission of HIV infection.

All women should be counseled to undertake HIV testing prepregnancy or early pregnancy or whenever they come in contact with the health care system. Therefore, the concerned women would be counseled to undertake HIV Test. Before undertaking the test, pretest counseling is performed which includes:

- Information regarding HIV and modes of acquiring infection
- Effect of HIV on pregnancy
- Parent to child transmission and its prevention
- Safe sex practices.

As antibodies to HIV are far easier to detect than the virus itself, it is the basis for the most widely used screening test of HIV infection. To confirm an initial positive a repeated Enzyme Linked Immunoassays (ELISA)/Rapid tests or electrophoresis test for a multiple of specific viral proteins, usually the Western blot[4] [specific antibody to viral core protein (p24) and envelop glycoprotein (gp41)] is done. This protocol has a specificity of 99.4% and a false positive rate of less than 0.001%, when used with the modern ELISA/ Rapid tests and Western blot methods.[5] In the PPTCT centre (or asymptomatic individuals) 3 HIV kits based on three different principles and/or different antigens are used. The Strategy/Algorithm followed is:[6]

1. If first test kit shows positive result (A_{1+}), proceed to the second and third kit.
2. If second and third kit also shows positive result (A_{1+} $A_{2+}A_{3+}$), test is labelled as positive.
3. If both second and third kit show negative result ($A_{1+}A_{2-}A_{3-}$), test result is reported as negative. (Here the reasoning being that 1st screening test is as sensitive as possible while 2nd and 3rd test should have highest specificity).
4. If either of the second or the third kit shows negative result, test is labelled as indeterminate.
5. "Indeterminate" (discordant) test result should be repeated on second blood sample after 4-6 weeks or Western blot test performed. Western blot assay also gives indeterminate results in some cases.

Following the availability of results post-test counseling is performed.

Q.1. How is counseling different if the test is negative or positive?

Ans: *If Test is HIV negative:*

- Client is advised regarding safe sex practices and if she falls in high risk category she is explained about window period and the requirement of repeat test after three months.

If HIV test is positive:

- Results are disclosed on one to one basis maintaining utmost confidentiality.
- Partner testing and disclosure is important.
- Course of infection and transmission to the fetus and infant and the effect of pregnancy on infection so as to make an informed choice regarding continuation of pregnancy or MTP.
- Information is provided regarding measures to decrease mother to child transmission.
- Importance of delivering in a multidisciplinary setting is emphasized with involvement of other relevant health professionals.

Q.2. Mrs A, was tested positive for HIV during routine screening. How will you proceed?

Ans: The pregnant woman with HIV infection should be provided with appropriate counseling about her disease, its implications for herself and her baby, and the importance of medical care in the post-test counseling.

After taking detailed history, performing clinical examination and investigations, we assess the stage of disease and identify risk factors, to see whether patient requires immediate antenatal (anti-retroviral therapy or treatment for accompanying infections) treatment or not.

Q.3. What is important to be elicited in history and clinical examination?

Ans: History and clinical examination should be able to clinically stage the disease and be able to aid in diagnosing the specific opportunistic infection if present.

Therefore the following points should be kept in mind while taking history:

a. Detail and duration of presenting complaints if any
   - Prolonged history (>1 month)
     - fever (intermittent or continuous)
     - cough
     - diarrhea
     - weight loss(>10% body weight)
   - Associated symptoms - acquiring infections early.

b. Obstetric history
   - Parity is important- if multiparous women present in first trimester, MTP can be offered
   - Record of earlier HIV testing (previous pregnancy)
   - HIV status of previous issue

c. Past history
   - Any prolonged illness
   - Blood transfusion

d. Family/Sexual/Personal History
   - Husband's HIV status if known
   - Sexual contact –self/partner
   - Drug abuse/alcohol intake/smoking

e. Vaccination History
   - BCG
   - Hepatitis A vaccine
   - Hepatitis B vaccine

Clinical Examination

Should include a detailed general physical examination followed by systemic and local examination as we follow with other patients but with emphasis on the following.

General Physical Examination

- General build and nutritional status (including weight and height).
- Generalized lymphadenopathy
- Fundus examination (CMV retinitis)
- Skin examination for lesions or abnormal patches (opportunistic infections)
- Mouth - inspection for candidiasis

Systemic Examination – should include detailed

- Neurological examination
  - Visual fields and signs of neuropathy
  - Focal neurologic deficit
- Respiratory examination
  - Opportunistic infections
- Abdomen
  - Hepatosplenomegaly, masses

Local examination should include

Per speculum and Per vaginum examination – to rule out

- Other STD's
- Look for bacterial vaginosis, candidiasis
- Cervical cancer

Q.4. What are the various stages of disease in HIV infection?

Ans: The clinical features of HIV infection have been classified into four broad categories.[7]

Initial infection

Except for a generally mild illness (fever, sore throat and rash) which about 70 per cent of people experience a few weeks after initial infection with the virus, most HIV-infected people have no symptoms for the first five years or so.

HIV antibodies usually take between 2 to 12 weeks to appear in the blood-stream. The period before antibodies are produced is the "window period" during which, although the person is particularly infectious because of the high concentration of virus in the blood, he or she will test negative on the standard antibody blood test.

Asymptomatic carrier state

Infected people have antibodies (i.e. test positive on routine screen for HIV) but no overt signs of disease except persistent generalized lymphadenopathy.

AIDS-related complex (ARC)

A person with ARC has illnesses caused by damage to the immune system, but without the opportunistic infections (Fig. 15.1) and cancers associated with AIDS, but they exhibit one or more of the following clinical signs; unexplained diarrhea lasting longer than a month, fatigue, malaise, loss of more than 10 per cent body weight, fever, night sweats, or other milder opportunistic infections such as oral thrush, generalized lymphadenopathy or enlarged spleen.

Patients from high-risk groups who have two or more of these manifestations (typically including generalized lymphadenopathy), and who have a decreased number of T helper lymphocytes are considered to have AIDS-related complex.

AIDS

AIDS is the end-stage of HIV infection. A number of opportunist infections commonly occur at this stage (Fig. 15.1).

Q.5. How do the various opportunistic infections present in HIV-infected individuals? Is there a relationship between these infections and CD4 count of these individuals?

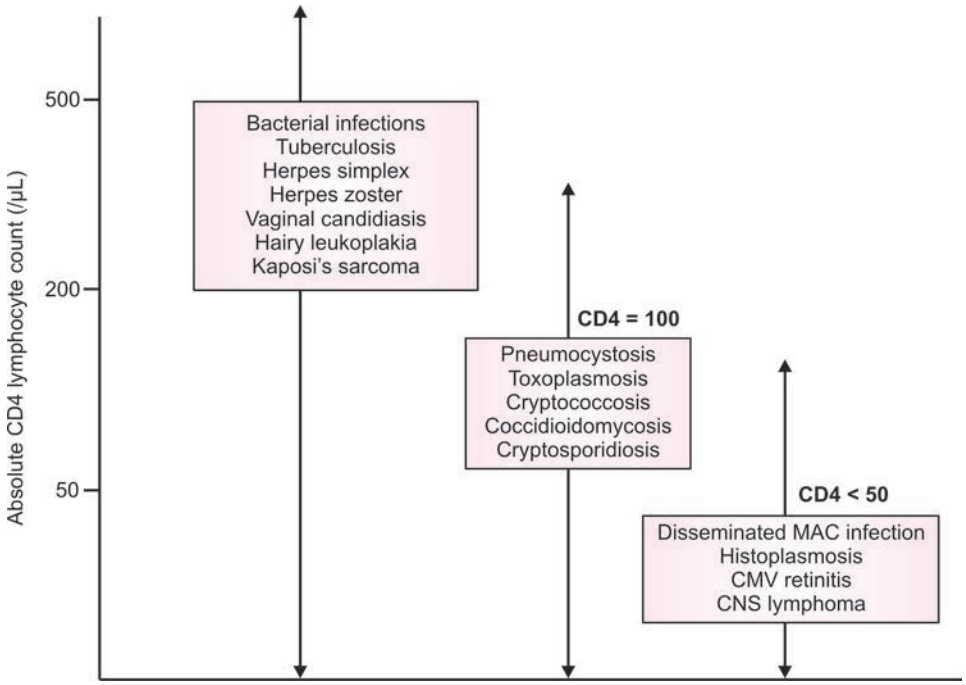

Fig. 15.1: Relationship of CD4 count to development of opportunistic infection (*Source:* See Reference 9)

Ans: To diagnose various opportunistic infections we should know about their clinical features (sign and symptoms).

Tuberculosis

When the immune system breaks down, as in HIV infection, tuberculosis becomes active and the person becomes contagious to others. HIV–positive individuals are 30-50 times more likely to develop active tuberculosis than HIV negative people.[8]

Persistent Generalized Lymphadenopathy

Lymph nodes are larger than one centimeter in diameter, in two or more sites other than the groin area for a period of at least three months.

Kaposi's Sarcoma

A tumor featuring reddish brown or purplish plaques or nodules on the skin and mucous membranes. It is characterized by lesions in the mouth or gut; or lesions are generalized (in two or more places) or rapidly progressive or invasive.

Oropharyngeal Candidiasis

Caused by a common yeast fungus, oral thrush presents with soreness and redness, with white plaques on the tongue, and in the mouth and throat; and sometimes a white fibrous layer covering the tonsils and back of the mouth. Infection of the esophagus presents with pain behind the breastbone.

Cytomegalovirus Retinitis

Inflammation of the eye (retina) which may lead to blindness.

***Pneumocystis Carinii* Pneumonia**

Symptoms can include a dry, non-productive cough; inability to take a full breath and occasional pain on breathing; and weight loss and fever.

Toxoplasma Encephalitis

Protozoal infection in the central nervous system, presenting with focal neurological signs such as mild hemiplegia or stroke, resulting from damage to part of the brain, seizures or altered mental status.

Hairy Leukoplakia
White patches on the sides of the tongue, in vertical folds resembling corrugations.

Cryptoccocal Meningitis
A fungal infection in the central nervous system which usually presents with fever, headache, vomiting and neck stiffness.

Herpes Zoster or Shingles
Viral inflammation of the central nervous system, presenting with localized pain and burning sensations, followed by vesicle eruption (skin blistering) and ulceration.

Severe Prurigo or Pruritic Dermatitis
Chronic skin inflammation in the form of a very itchy rash of small flat spot developing into blisters.

Severe or Recurrent Skin Infections
Warts; dermatophytosis or ring-worm; and folliculitis (inflammation of hair follicles).

The Figure 15.1 shows a relationship between various opportunistic infections and CD4 count of a HIV-infected individual.

Q.6. What investigations would you like to do for this patient?

Ans: Routine

- Blood group and Rh factor
- Complete blood count (CBC)
- Urine examination
- Glucose challenge test (GCT)
- VDRL/TPHA (syphilis screening) for both partners
- Ultrasound – To confirm gestational age, screen for anomalies, placental localization at about 18 weeks.

HIV Related

- Hepatitis A, B, and C serologies and LFTs
- Pap smear in all HIV positive women
- Test for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in order to identify high-risk behavior and the need for STD therapy
- Toxoplasma gondii IgM and IgG
- Chest X-ray with abdominal shield if clinically indicated due to suspicion of PCP or tuberculosis

HIV Specific (Table 15.1)

Table 15.1: Laboratory finding with HIV infection

Test	*Significance*
HIV-enzyme-linked immunosorbent assay (ELISA)	Screening test for HIV infection.
Western blot	Confirmatory test for HIV. Specificity when combined with ELISA >99.99%. Indeterminate results with early HIV infection, HIV-2 infection, autoimmune disease, pregnancy and recent tetanus toxoid administration.
CBC	Anemia, neutropenia, and thrombocytopenia common with advanced HIV infection.
Absolute CD_4 lymphocyte count	Most widely used predictor of HIV progression. Risk of progression to an AIDS opportunistic infection or malignancy is high with $CD_4 < 200$ cell/ml.
CD_4 lymphocyte percentage	Percentage may be more reliable than the CD_4 count. Risk of progression to an AIDS opportunistic infection or malignancy is high with percentage < 20%
HIV viral load tests	These tests measure the amount of actively replicating HIV virus. Correlates with disease progression and response to antiretroviral drugs.(available only in specialized center)
p24 antigen	Indicates active HIV replication. Tends to be positive prior to seroconversion and with advanced disease.

(*Source:* See References 9 and 10)

Q.7. How would you manage Mrs A and when would you add prophylaxis for any opportunistic infections in such a patient?

Ans: HIV positive pregnant women should be jointly followed by an HIV specialist, an obstetrician with expertise in managing HIV pregnancy, and a pediatrician.

- Nutritional assessment, correct diet and weight monitoring and counseling for the same.
- Regular ANC check-up
- Treat any associated RTI and STI (Respiratory tract and sexually transmitted infections)
- Treat bacterial vaginosis, candidiasis
- Care of opportunistic infections, if any, and if absent
  - *Pneumocystis carinii* prophylaxis is required if CD4 < 200. Co-trimoxazole (Trimethoprim/sulphamethoxazole) DS (160/800 mg) 1 tablet a day is the drug of choice.
  - Toxoplasmosis if Antitoxoplasma IgG is positive and CD4 < 100. Trimethoprim/sulphamethoxazole DS 1 tablet is given once a day.
  - Mycobacterium Avium intracellulare Complex (MAC) prophylaxis is added when CD4 < 50 in the form of Azithromycin 1200 mg/week. However, routine prophylaxis for MAC is presently not recommended in India.[11]
  - *Pneumococcus*, Hepatitis A and B, Influenza Vaccination should be performed if available and not provided in prepregnancy period.
  - Postexposure Prophylaxis should be given for Hepatitis A, Hepatitis B and Varicella Zoster exposure in the form of immunoglobulins in all patients before the CD4 count falls to < 200/cumm,[11] after consultation with an expert in HIV and viral hepatitis infection and screening for complete viral serology.
  - Measles vaccine is contra-indicated during pregnancy.
- Counseling regarding breastfeed or replacement feed should be done during antenatal period so that decision regarding the same is made prior to delivery.

Q.8. What are the criteria for starting antiretroviral (ARV) therapy in a HIV positive patient who has been diagnosed for the first time during routine screening in pregnancy?

Ans: *All HIV positive women should be referred to the ART center for registration into care and screened for medical eligibility for ART once they have been diagnosed in the PPTCT program.*

In the case of pregnant HIV – positive women, the CD4 count should be assessed as per the national guidelines. These women should be jointly managed by the ART center for the HIV/ART aspects and the antenatal team for obstetric concerns.

The criteria for initiating ART in pregnant women are the same as for other adults (Table 15.2).

- WHO clinical stage 3 or 4 disease
- WHO clinical stage 1 or 2 disease and CD4 < 200 cell/mm^3
- WHO stage 3 disease and CD4 < 350 cell/mm^3

Table 15.2 : When to start ART in pregnant women

WHO stage	*CD4 testing not available (or results pending)*	*CD4 testing available*
1	Do not treat	
2	Do not treat	
3	Treat	Treat if CD4 < 350 cells/mm^3
4	Treat	Treat irrespective of CD4

Note: Consider initiation of ART in asymptomatic HIV-infected pregnant women with CD4 < 250 cells/mm^3 and initiate before CD4 count drops below 200 cells/mm^3 (*Source:* See Reference 12)

The initiation of ART helps prevent transmission of HIV to the newborn and also benefits the mother's own health. Once initiated, it should be continued postpartum.

The total lymphocyte count (TLC) is no longer used in the national ART program as global evidence has shown that TLC is a poor parameter for deciding on the initiation of ART, especially in asymptomatic persons, and monitoring the response to ART.

1. Women who need antiretro-viral therapy for their own health should continue with treatment during pregnancy and afterwards.
2. HIV positive pregnant women who do not have indication for antiretro-viral therapy should have ART prophylaxis to prevent mother to child transmission

Q.9. Should ART be started in the presence of active Opportunistic Infections (OIs)? If not, then, when should it be started?

Ans: Do not start ART in the presence of an active OI. In general, OIs should be treated or stabilized before commencing ART. Mycobacterium Avium Complex (MAC) and progressive multifocal leukoencephalopathy (PML) are exceptions, in which commencing ART may be preferred treatment, especially when specific MAC therapy is not available.

- Some conditions which may regress following the commencement of ART include candidiasis, cryptosporidiosis and microsporidiosis and skin conditions such as seborrheic dermatitis, HIV-related exfoliative dermatitis.
- The OIs and HIV-related illnesses need treatment or stabilization before commencing ART (Table 15.3).

Q.10. What are the group of drugs available and their doses under ARV therapy?

Ans: Different groups of drugs available for ARV therapy along with their side effects and ways to monitor them are listed in Table 15.4.

Table 15.3: Managing OIs before starting ART

Clinical picture	*Action*
Any undiagnosed active infection with fever	Diagnose and treat first; start ART when stable
TB	Treat TB first; start ART as recommended by HIV specialist
PCP	Treat PCP first; start ART when PCP treatment is completed
Invasive fungal diseases: esophageal candidiasis,	Treat esophageal candidiasis first; start ART as soon as the patient can swallow comfortably
cryptococcal meningitis, penicillosis, Histoplasmosis	Treat cryptococcal meningitis, penicilliosis, histoplasmosis first; start ART when patient is stabilized or OI treatment is completed
Bacterial pneumonia	Treat pneumonia first; start ART when treatment is completed
Malaria	Treat malaria first; start ART when treatment is completed
Drug reaction	Do not start ART during an acute reaction
Acute diarrhea which may reduce absorption of ART	Diagnose and treat first; start ART when diarrhea is stabilized or controlled
Non-severe anemia (Hb< 8 g/liter)	Start ART if no other causes for anemia are found (HIV is often the cause of anemia); avoid AZT
Cytomegalovirus infection	Treat if drugs available; if not, start ART
Toxoplasmosis	Treat; start ART after 6 weeks of treatment and when patient is stabilized

(*Source:* See Reference 12)

Q.11. If the patient, Mrs A, has CD4 count < 200 cells/mm^3, how would you start ARV therapy?

Ans: Two different types of combination regimes have demonstrated maximum virologic and immunlogic efficacy:

A. Non-nucleoside Reverse Transcriptase Inhibitor – based (1 NNRTI + 2 NRTIs): Preferred NNRTI is Nevirapine and preferred NRTI are

Table 15.4: Anti-retroviral therapy

Drug	*Dose*	*Common side effects*	*Monitoring*
Nucleoside analogs (NRTIs)			
Zidovudine (AZT)	500-600 mg orally daily in two or three divided doses	Anemia, neutropenia, nausea, malaise, headache, insomnia, myopathy	Complete blood count and differential (every 3 months once stable)
Didanosine (ddI)	300 mg orally once daily (for pill formulation)	Peripheral neuropathy, pancreatitis, dry mouth, hepatitis	CBC and differential, aminotransferases K^+, amylase, triglycerides, bimonthly neurologic questionnaire for neuropathy
Zalcitabine (ddC)	0.375-0.75 mg orally three times a day	Peripheral neuropathy, aphthous ulcers, hepatitis	Monthly neurologic questionnaire for neuropathy, aminotransferases
Stavudine (d4T)	30 mg orally twice daily	Peripheral neuropathy, hepatitis , pancreatitis	Monthly neurologic questionnaire for neuropathy, aminotransferases, amylase
Lamivudine (3TC)	150 mg orally twice daily	Rash, Peripheral neuropathy	No additional monitoring
Abacavir (ABC)	300 mg orally twice daily	Rash, fever-if occur, rechallenge may be fatal	No specific monitoring
Nucleotide analog (NRTIs)			
Tenofovir (TDF)	300 mg orally once daily	Gastrointestinal distress	Renal function
Protease inhibitors			
Saquinavir (SQV)	600 mg orally three times daily	Gastrointestinal distress, headache	No additional monitoring
Ritonavir (RTV)	600 mg orally twice daily or 400 mg orally twice daily in combination with other protease inhibitors	Gastrointestinal distress, peripheral paresthesias	Bimonthly aminotransferases, uric acid, triglycerides
Indinavir (IDV)	800 mg orally three times daily	Kidney stones	Bimonthly aminotransferases, bilirubin level
Nelfinavir (NLF)	750 mg orally Three times daily	Diarrhea	No additional monitoring
Amprenavir	1200 mg orally twice daily	Gastrointestinal, rash	Cholesterol, triglycerides
Lopinavir/ritonavir (LPV-r)	400 mg/100 mg orally twice daily	Diarrhea	Cholesterol, triglycerides, every other month aminotransferases
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)			
Nevirapine (NVP)	200 mg orally daily for 2 weeks, then 200 mg orally twice daily	Rash	No additional monitoring
Delavirdine	400 mg orally three times daily	Rash	No additional monitoring
Efavirenz (EFV)	600 mg orally daily	Neurologic disturbances	No additional monitoring

(*Source:* See Reference 10)

Table 15.5: Recommended first-line antiretroviral regimens

Recommendation	*Regimen*	*Comments*
Preferred first-line regimen	AZT+3TC+NVP	AZT may cause anemia, which requires Hb monitoring, but is preferred over d4T toxicity (lipoatrophy, lactic acidosis, peripheral neuropathy) Patients who develop severe anaemia while on an AZT-based regimen should not be re-challenged with AZT. In such cases, the patient should receive either d4T or TDF in place of AZT. For women with CD4> 250 cells/mm^3, monitor for hepatotoxicity closely if started on the NVP-based regimen
Alternative first-line regimens	AZT+3TC+EFV	EFV is substituted for NVP in cases of intolerance to the latter or if patients are receiving rifampicin-containing anti-TB treatment. EFV should not be used in patients with grade 4 or higher elevations of ALT or first trimester of pregnancy
	D4T+ 3TC + (NVP or EFV)	If the patients have anemia, a d4T-based regimen should be prescribed
Other Options	TDF + 3TC + (NVP+EFV) or AZT + 3TC +TDF	TDF substituted for AZT or d4T when there is toxicity or contraindications For individuals unable to tolerate NVP+EFV

Zidovudine (AZT), Lamivudine (3TC) or Stavudine (d4T).

Recommended choices of first-line regimens by NACO (Table 15.5)

Principles for selecting the first-line regimen:

1. Choose 3TC (Lamivudine) in all regimens
2. Choose one NRTI to combine with 3TC (AZT or d4T)
3. Choose one NNRTI (NVP or EFV)

B. Protease inhibitor based (1PI with or without ritonavir boosting + 2NRTI): PI based regimens are costlier and associated with hyperglycemia, new onset diabetes mellitus and require a close monitoring in pregnancy and are second line drugs in ARV therapy.

Q.12. What is the latest recommendation on stavudine (d4T) dosing?

Ans: Previously, the preferred d4T dosing was weight-based. Dosing for patients > 60 kg was recommended at 40 mg twice daily; dosing for patients < 60 kg was recommended at 30 mg twice daily.

Based on review of available evidence, WHO recommends that 30 mg formulation of stavudine, dosed twice daily, should be used irrespective of the patient's body weight in adults and adolescents.

This recommendation is now the preferred dose when d4T is used as part of an ARV therapeutic regimen.

Q.13. What is fixed-dose combinations (FDCs)?

Ans: Currently, the National programme (under NACO guidelines) provides the following combinations for first-line regimens.[12]

Stavudine (30 mg) + Lamivudine (150 mg).
Zidovudine (300 mg) + Lamivudine (150 mg)
Stavudine (30 mg) + Lamivudine (150 mg) + Nevirapine (200 mg)
Zidovudine (300 mg) + Lamivudine (150 mg) + Nevirapine (200 mg)
Efavirenz (600 mg)
Nevirapine (200 mg)

Fixed-dose combinations (FDCs) are preferred because they are easy to use, have distribution advantages (procurement and stock management), improve adherence to treatment and thus reduce the chances of development of drug resistance. The current national experience shows that bid (twice a day) regimens of FDCs are well-

tolerated and complied with. At present, second-line drug regimens are not available under the national program.

Q.14. How will you start as NVP-based regimen? Or What is lead-in period for NVP dosing?

Ans: The lead-in period for NVP dosing at 200 mg once daily for the first two weeks produces adequate NVP levels. Due to enzyme auto-induction, NVP levels decline over two weeks and an increase in the dosage to 200 bid is required to maintain adequate levels. Starting with the full NVP dosage without a lead-in period results in a very high serum concentration of the drug and increases the risk of hepatotoxicity and rash. If NVP is restarted after more than 14 days of treatment interruption (due to whatever reason, e.g. elevated liver enzymes), the lead-in dosing is again necessary (Table 15.6).

Pls are not recommended in first-line regimen because their use in an initial treatment regimen essentially rules out second-line regimen options.

Table 15.6: Starting an NVP-based regimen

Starting nevirapine-based regimen		
	Morning	*Evening*
Lead-in NVP dose for the first 2 weeks	FDC (AZT or d4T + 3TC) one pill + NVP one pill	FDC (AZT or d4T + 3TC) one pill No NVP
Escalate to full NVP dose after 2 weeks	FDC (AZT or d4T + NVP) one pill	FDC (AZT or d4T + TC + NVP) one pill

(*Source:* Reference 12)

Q.15. What are the indications and contra-indications of Efavirenz (EFV)?

Ans: Efavirenz (EFV) should be given to the following groups of persons:

- In patients receiving concurrent rifampicin-containing anti-TB regimen (ATT) for the duration of the anti-TB treatment.
- In cases with clinical or laboratory evidence of hepatic dysfunction, e.g. due to hepatitis B/C co-infection or other causes.
- In patients with significant NVP side-effects/ toxicity and in whom NVP re-challenge cannot be done.

Patients on an NVP regimen who have been switched over to EFV because of rifampicin-containing anti-TB treatment should be shifted back to NVP after completion of the TB treatment (unless other contraindications to NVP exist).

- The change from EFV to NVP should be made two weeks after completing the anti-TB treatment.
- In this particular scenario, the lead-in dose/ period is not necessary while shifting from EFV to NVP (i.e. should start immediately on bid NVP dosage).
- Patient should be monitored closely for NVP toxicity (hepatotoxicity), particularly if the CD4 count is >250 cells/mm^3, especially in women.

EFV is contraindicated in pregnancy HIV-infected women during the first trimester of pregnancy because of concerns of teratogenicity

Q.16. Is there any relationship between NVP and CD4 count?

Ans: NVP in women with CD4 count of 200-350 cells/mm^3: There are data to show that women with a CD4 count of > 250 cells/mm^3 face a higher risk of severe hepatotoxicity when they are started on an NVP based regimen. This happens most often in the first 6-12 weeks of therapy. It is recommended that such women should undergo the following.

- Close observation over the first 12 weeks of therapy (every 2 weeks).
- Baseline and regular monitoring of liver enzymes (at baseline and at 2, 4, 8 and 12 weeks, followed by symptom-directed evaluation).
- Patient education to encourage them to return if there are problems such as rash, abdominal pain, jaundice and fever.

If the liver enzymes increase to grade 3 or higher (ALT and/or AST > 5.1 times the upper normal limit) without an alternative explanation, NVP should be permanently discontinued. If symptoms suggesting hepatic toxicity, including rash, develop in pregnant women, NVP should be discontinued immediately.

For those with anemia during pregnancy, the problem should be managed by conservative methods, such as giving ferrous folate, other oral preparations and blood transfusion (if required).

Q.17. How will you monitor response to ART?

Ans: Response to ART is monitored by:

1. CD4 T-cell estimation
2. Viral load assays
   a. RT-PCR (reverse transcriptase polymerase chain reaction)
   b. b-DNA assay
   c. Nucleic acid based amplification (NASDA)

Monitoring is done

- 2-3 weeks—after initiating ART
- Every 3-4 months—during ART

CASE 2

A primigravida, 8 weeks of gestation already on ART reports to ANC Clinic and has no problem otherwise. What is the recommended treatment?

Women who have been receiving antiretroviral treatment for their HIV-1 infection should continue same treatment during pregnancy, intrapartum and postpartum period except for Efavirenz (EFV). Although exposure to EFV during pregnancy is not an indication for abortion for women who become pregnant while receiving an EFV-containing regimen and are in the first trimester of pregnancy, NVP should be substituted for EFV. Close monitoring of those women who have CD4 cell counts more than 250 cells/mm^3 is required while starting NVP as hepatotoxicity along with skin rash has been observed in these women. Women who are receiving EFV and are in the second or third trimester of pregnancy can continue the current regimen. Alternatively, a triple Nucloside Reverse Transcriptase Inhibitor (NRTI) or Protease Inhibitor (PI) based regimen could be used.

Q.18. How is a pregnant woman, who has already been diagnosed HIV +ve (whether in present pregnancy or earlier) and has CD4 count 475 cells/mm^3, managed?

Ans: The maternal ARV prophylaxis for prevention of HIV transmission in HIV-infected pregnant women who do not need treatment for their own health, two equally efficacious options recommended[13] are:-

1. Option A consists of

- Antepartum daily AZT
- sd-NVP (Single dose NVP) at onset of labor
- AZT + 3TC during labor and delivery
- AZT + 3TC for 7 days postpartum

sd-NVP and AZT + 3TC intra and postpartum can be omitted if mother receives more than 4 weeks of AZT during pregnancy.

In breastfeeding infants, maternal ARV prophylaxis should be coupled with daily administration of NVP to the infant for birth until one week after all exposure to breast milk has ended.

In non-breastfeeding infants, maternal ARV prophylaxis should be coupled with daily administration of AZT or NVP from birth until 6 weeks of age.

2. Option B consists of:

For all HIV-infected pregnant women who are not eligible for ART, ARV prophylaxis option B consists of triple ARV drugs provided to pregnant women starting from as early as 14 weeks of gestation until one week after all exposure to breast milk has ended (Table 15.7). The recommended regimens include:

- AZT + 3TC + LPV/r
- AZT + 3TC + ABC

Table 15.7: ARV-prophylaxis options recommended for HIV-infected pregnant women who do not need treatment for their own health

Option A: Maternal AZT	*Option B: Maternal triple ARV prophylaxis*
Mother	*Mother*
• Antepartum AZT (from as early as 14 weeks gestation) • sd-NVP at onset of labor* • AZT + 3TC during labor and delivery* • AZT + 3TC for 7 days postpartum*	Triple ARV from 14 weeks until one week after all exposure to breast milk has ended • AZT + 3TC + LPV/r • AZT + 3TC + ABC • AZT + 3TC + EFV • TDF + XTC + EFV
*sd-NVP and AZT+3TC can be omitted if mother receives > 4 weeks of AZT antepartum	
Infant	*Infant*
Breastfeeding infant Daily NVP from birth until one week after all exposure to breast milk has ended	Breastfeeding infant Daily NVP from birth to 6 weeks
Non-breastfeeding infant AZT or NVP for 6 weeks	Non-breastfeeding infant AZT or NVP for 6 weeks

- AZT + 3TC + EFV
- TDF + XTC + EFV

In breastfeeding infants, the maternal triple ARV prophylaxis should be coupled with the daily administration NVP to the infant from birth until 6 weeks of age.

In non-breastfeeding infants, the maternal triple ARV prophylaxis should be coupled with the daily administration of AZT or NVP to the infant from birth until 6 weeks of age.

Q.19. What are the doses of the drugs used in option A?

Ans:

1. Nevirapine – single dose tab. Nevirapine 200 mg to the pregnant women in labor 4-6 hrs before expected time of delivery and Syrup Nevirapine 2 mg/kg body weight to the baby within 72 hours of birth reduces the HIV transmission rate. It is cheap and can be given orally and therefore ideal for low resource settings. However, as it is a highly lipophilic drug and stays in circulation in low concentration for almost one week, this regimen is associated with development of resistance to Nevirapine (NVP) therefore compromising the treatment option of the women and the child in future. If the patient has to undergo elective cesarean section Tablet Nevirapine should be given four to six hours prior to starting the surgery.
2. Antenatal Tab. Zidovudine (AZT) 300 mg BD after 28 weeks. Dosage of Lamivudine (3TC) is 150 mg BD. Both are given intrapartum and 7 days postpartum.

Q.20. Should a HIV-positive patient be offered LSCS or normal vaginal delivery?

Ans: Mode of delivery should be decided upon after taking into various factors which determine the viral transmission, the disease stage and the availability of resources.

Patient having viral load of less than 50 copies/ml at 36 weeks can be offered vaginal delivery if no obstetric contraindication.

Developed countries are recommending Highly Active Anti-Retroviral Therapy (HAART) which reduces the HIV RNA load to undetectable levels and thus reducing the HIV transmission.

- If cesarean section is done before onset of labor or rupture of membranes, it reduces perinatal HIV-1 transmission by 50-87% even if no chemoprophylaxis is given by reducing the time the fetus is in contact with virus containing maternal blood and cervicovaginal secretions. However, it is associated with increased maternal morbidity, especially with advanced disease.
- Note should be made of any concurrent untreated genital infections as viral load is higher in vaginal secretions as compared to plasma in women with bacterial vaginosis or genital infections.
- If Bishop's score is poor or prolonged and difficult labor or Instrumental delivery is anticipated, the women should be counseled accordingly regarding the chances of HIV transmission during vaginal delivery.

Therefore, HIV infected women should be counseled regarding the increased risks and potential benefits associated with cesarean delivery based on their HIV-1 RNA levels, CD4 count, current antiretro-viral therapy and presence of any obstetric indication for cesarean section. Decision regarding mode of delivery should be taken accordingly.

Q.21. How would you manage labor in a HIV positive women?

Ans: Intrapartum management is aimed at minimizing the exposure of the baby to infected cervicovaginal secretions. If the mode of delivery decided upon is cesarean section, standard precautions should be taken before starting the cesarean section. Antiretro-viral prophylaxis should be given as discussed above.

Following precautions should be taken in case of vaginal delivery.

1st Stage of Labor

- Nutrition
- Psychosocial support to boost up morale
- ARV prophylaxis
- Partogram
- Augment labor to expedite
- Avoid multiple per vaginal examinations
- Avoid early ARM. Preserve membrane as long as possible
- Avoid fetal invasive procedure
  - (Like Fetal Blood Sampling. Fetal scalp electrode, etc.).
- Prophylactic antibiotics to be given

2nd Stage of Labor

- Avoid episiotomy
- If given, stitch without delay
- Avoid instrumental and traumatic delivery

3rd Stage of Labor

- Active management of third stage of labor
- Given oxytocin immediately after birth
- Safe disposal of placenta, blood and body fluids
- Avoid operative procedure on baby before bath
- Minimize risk of postpartum hemorrhage
- Repair genital tract lacerations
- Carefully remove all products of conception
- Do not milk umbilical cord at the time of tying the umbilical cord.
- Management of neonate – 2 mg/kg single dose NVP within 72 hrs or Zidovudine (AZT) 2 mg/kg 6 hrly for 6 weeks postpartum in patients who were on ARV during antenatal period.
- DNA PCR is done to diagnose infection in the neonate at 6-8 weeks. A positive PCR result during window period must be confirmed by demonstration of seroconversion for which ELISA is done at 18 months.

Q.22. What are the recommendations for breast-feeding for a HIV-positive patient?

Ans: Decision regarding the type of feed, i.e. breast-feed for replacement feed, should be made during antenatal period itself depending upon whether replacement feed is *Acceptable, Feasible, Affordable, Sustainable and Safe* (AFASS). As mixed feed is associated with increased rate of HIV

transmission as compared to breastfeed alone, it is suggested the weaning must be complete and abrupt after six months of breastfeed or earlier if replacement feed is AFASS. Dopamine agonist Tab. Cabergoline 0.5 mg is indicated for milk suppression along with tight breast support if decision is taken for replacement feed.

Q.23. What advice regarding contraception is given to such a woman?

Ans: Both permanent as well as temporary methods of contraception may be offered to the couple depending on whether they have completed their family. If they have not completed their family combined oral contraceptive pills along with the use of Barrier contraception provides good contraceptive coverage along with protection from STD's. DMPA should be avoided as it adversely affects the HIV related immune system. Intra-uterine Contraceptive Devices are also not contraindicated unless the female suffers from advanced disease or in the presence of high risk behavior in which case there is increased risk of PID. The couple is counseled regarding safe sex practices and maintaining relations with single partner.

Q.24. What is the interaction between ART and hormonal contraception? What is recommended?

Ans: NVP, Ritonavir (RTV), Nelfinavir (NLF), Lopinavir/ritonavir (LPV/r) and Saquinavir/ritonavir (SQV/r) result in reduced ethinyl estradiol levels. Estrogens are slightly increased by Atazanavir (ATV), Indinavir (IDV) and Efavirenz (EFV). Thus, women on ART should not use hormonal contraception or should use it with caution and appropriate dose adjustment. They should consult a gynecologist for expert opinion.

Intrauterine contraceptive devices may be used with caution in HIV-infected women with close monitoring because of the risk of intrauterine infection.

The consistent use of condoms is recommended for all HIV-infected women who are on ART. This is for the prevention of secondary transmission of HIV from/to the partner, as well as the prevention of unplanned pregnancy.[14]

Q.25. What pre-pregnancy counseling is given to a HIV positive woman?

Ans: HIV-infected women should have preconceptional counseling to optimize their status before pregnancy.

- They should be educated and counseled about risk factors for perinatal HIV transmission, strategies to reduce those risks, and potential effects of HIV or treatment on pregnancy course and outcomes.
- They should be counseled on safe sexual practices that prevent HIV transmission to sexual partners and protect women from acquiring sexually transmitted diseases and the potential to acquire more virulent or resistant HIV strains.
- HIV positive women should be evaluated for appropriate prophylaxis for opportunistic infections and administration of medical immunizations (e.g. influenza, pneumococcal, or hepatitis B vaccines) as indicated.
- Before taking the decision for pregnancy, the woman's nutritional status, her clinical stage of disease and CD4 cell count be obtained and if need be, change in ARV drugs to be done.

Q.26. What is a discordant couple? Who is more likely to be infected during sexual contact in case of a discordant couple? What is the advice given?

Ans: A discordant couple is a couple where only one partner is HIV positive. Women are more likely to be infected through sexual contact than men in such a case.

For HIV discordant couples where the woman is HIV positive, the couple may be advised about artificial insemination at the time of ovulation.

Where a woman who is HIV negative has a HIV-positive partner, the risk of transmission to the woman, estimated as approximately 1:500 per sexual act, can be reduced by limiting sexual intercourse to around the time of ovulation. 'Sperm washing', whereby spermatozoa are separated from surrounding HIV-infected seminal plasma by a sperm swim-up technique can also be tried.

Q.27. What are the salient points of WHO's latest Nov 2009 guidelines which were revised from previous (2006) guidelines?

Ans: They are as follows[13]

- Initiation of ART for her own health is recommended for all HIV infected pregnant women with CD4 cell count ≤ 350 cells/mm^3, irrespective of WHO clinical staging; and for all HIV infected pregnant women in WHO clinical stage 3 or 4 irrespective of CD4 cells count (earlier it was < 200 cells/mm^3).
- For infants of mothers with HIV who are taking therapeutic ART for their own health, the duration of prophylactic ART has been increased irrespective of whether the infant is breastfeeding or not. For breastfeeding infants, it is recommended that daily NVP is instituted from birth until 6 weeks of age. For non-breastfeeding infants: daily AZT or NVP from birth until 6 weeks of age is recommended.
- It is recommended that antepartum ARV prophylaxis should be started in all women from as early as 14 weeks gestation (second trimester) or as soon as possible when women present late in pregnancy, in labor or at deliver (earlier it was 28 weeks).
- For all HIV-infected pregnant women who are not in need of ART for their own health, ARV prophylaxis option A or B as outlined in Table 15.7. In the women who receive Prophylactic Triple, a continued regimen of triple therapy is recommended through the end of the breastfeeding period. In breastfeeding infants, maternal ARV prophylaxis should be coupled with daily administration of NVP to the infant from birth until one week after all exposure to breast milk has ended. In non-breastfeeding infants daily administration of AZT or NVP is recommended from birth until 6 weeks of age. Stopping breastfeeding abruptly is not advisable anymore. Rather, it is recommended that it should be done over a period of one month as rapid and abrupt cessation breastfeeding was reported to be associated with adverse consequences for the infant such as growth failure and increased prevalence of diarrhea.
- Mothers known to be HIV-infected (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter, and continue breastfeeding for the first 12 months of life. Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast milk can be provided.
- Mothers known to be HIV-infected may consider expressing and heat-treating breast milk as an **interim feeding strategy:**[15]
  - In special circumstances such as when the infant is born with low birth weight or is otherwise ill in the neonatal period and unable to breastfeed; or
  - When the mother is unwell and temporarily unable to breastfeed or has a temporary breast health problem such as mastitis: or
  - To assist mothers to stop breastfeeding: or
  - If antiretroviral drugs are temporarily not available
- If infants and young children are known to be HIV infected, the mothers are strongly encouraged to exclusively breastfeed for the first 6 months of life and continue breastfeeding as per the recommendations for the general population, i.e. up to 2 years or beyond.[15] (Mortality of HIV - infected infants was higher among those who stopped breastfeeding early).

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Rachna Sharma, Susmita Behera

16 Septic Abortion: A Clinical Review

INTRODUCTION

Septic abortion was once the leading cause of maternal death around the world and the condition remains still same in developing countries. In India 12% of maternal mortality is because of septic abortion. Mortality rate after voluntary termination of pregnancy is 0.6/100000. It is unfortunate that even after 40 years of legalization of abortion only 10% are registered.[1]

DISCUSSION

A 32 years old P6L5 A1 presented to gynecology emergency with chief complain of bleeding per vaginum on and off for 15 days, fever and pain abdomen with vomiting for 3 days following an evacuation at private clinic.

Detailed History of Present Illness

1. Bleeding Per vaginum (BPV)—duration/ amount/onset acute or chronic. How it started (whether continuous with last cycle/following amenorrhea/intermenstrual). This patient had amenorrhea of 2 months for which she took medicines after which she had bleeding per vaginum. In patients of septic abortion there is history of amenorrhea followed by interference followed by bleeding per vaginum.
2. Pain abdomen—duration, type (dull aching generalized, distension pain, suprapubic pain, spasmodic cramping pain) association with diarrhea, constipation, burning micturation.
3. Fever—duration, pattern (continuous low grade, spiking with chills rigor, progressively rising.
4. Other eliciting questions should be asked regarding drug intake, foreign body insertion. This patient had gone to a local doctor where she had evacuation done for excess bleeding and all her problems started since then.

Usually illegal terminations are by unauthorized persons, in below standard set-ups with lack of proper antisepsis, so actual history is concealed and efforts should be made to elicit the facts.

Menstrual History

- Whether she had previous normal cycles
- Her cycle pattern if prolonged
- Date of last menstrual period and whether it was overdue
- Amount of flow in her last cycle, whether normal or spotting only.

Obstetrics History

- Parity of patient and desire to have children in future.
- Number of previous spontaneous abortions/ MTPs (method, person, place, eventful or not)

Past Medical/Surgical History

History of previous hospital stay, surgical interventions, blood transfusions.

Personal History

- Contraception used (type of contraception used, regular or irregular use and any failure of contraception)
- History of sexual abuse, promiscuity, STDs

Socioeconomic Status

Poor socioeconomic status unable to avail medical services on time.

Illiteracy—lack of awareness of contraceptive options.

Q.1. What are other clinical presentations?

Ans: Presentation depends upon type of complication patient develops.[2]

1. Patient usually presents with pain, bleeding and low grade fever caused by retained products of conception (RPOC) known as *postabortion triad*.
2. Hemorrhage—excessive bleeding during or after abortion signify uterine atony, cervical laceration, uterine perforation, cervical pregnancy, a more advanced gestational age than anticipated or coagulopathy.
3. Postabortion syndrome—patient presents with lower abdominal pain, absent or decreased vaginal bleeding and at times hemodynamically compromised patients may have hematometra or retained product of conception (RPOC).
4. Patient presenting with abdominal pain, distension, fever, blood in stool, nausea and vomiting, failure to pass flatus are suggestive of bowel injury.
5. Patient presenting with suprapubic pain, hematuria, retention of urine, distension, features of peritonitis. Patient may have bladder injury.
6. Symptoms of sepsis—fever with chills, pain abdomen, foul smelling vaginal discharge and persistent vaginal bleeding.
7. Failed abortion (continued intrauterine or ectopic pregnancy)—failure to terminate pregnancy is relatively common with very early abortion < 6 weeks GA. Such patient presents with symptoms of continuing pregnancy such as hyperemesis, increased abdominal girth and breast engorgement. In addition an unrecognized ectopic pregnancy in postabortion period can present as acute abdomen.

Q.2. What is septic abortion?

Ans: The term septic abortion refers to spontaneous miscarriage or therapeutic/artificial abortion complicated by pelvic infection.[2]

Q.3. What are the causes of sepsis in abortion?

Ans: The uterus of pregnant women is normally protected by plug of mucus in cervix, and membrane surrounding the fetus.[3]

A septic abortion may be caused by any one or more of the following factors:

1. The membranes surrounding the fetus have ruptured, sometimes without being detected.
2. The woman has sexually transmitted disease, such as Chlamydia.
3. An intrauterine device (IUD) was left inside the uterus after a miscarriage or abortion.
4. Attempts were made to end the pregnancy, often illegally, by inserting tools, chemicals, or soaps into the uterus.

The infection can spread through fetal tissue to endometrium and further to myometrium and parametrium. Parametritis can progress to peritonitis. Such patient may develop bacteremia and sepsis at any stage and progress to multiorgan failure.

Q.4. What are the examination findings in a case of septic abortion?[2,3]

Ans: General examination: Patient may have

- Toxic look
- Pallor according to amount of blood loss, hemolysis.

- Icterus due to hemolysis.
- Peripheral edema due to hypoproteinemia, acute renal failure
- Ecchymosis due to coagulopathy, septicemia.
- Dry coated tongue dehydration, ketosis.
- Altered sensorium due to electrolyte imbalance.

Vital Signs

- Temperature—high to low grade fever.
- Increase in trend may be the sign of progressive uncontrolled infection.
- Hypothermia could be the ominous sign of endotoxic shock.
- Pulse and BP—tachycardia and hypotension may be sign of hemodynamic septic shock.
- Respiratory rate—increase respiration rate because of acidosis, and accessory muscles of respiration working due to pain and guarding of abdomen.

Abdominal Examination

- Suprapubic tenderness is common in the post-abortion period. Severe tenderness is unusual and may be a sign of hematometra, bladder perforation or bowel injury
- Tenderness in other areas of abdomen (e.g. rebound tenderness, guarding) strongly indicates instrumental injury complications (e.g. perforation, bowel injury, bladder injury)
- A tender mass in suprapubic area suggests hematometra.
- Diminished or absent bowel sounds are sign of developing peritonitis.

Vaginal Examination

- Assess the quantity and rate of hemorrhage.
- Look for possible vaginal and cervical laceration.
- Identify the source of bleeding (e.g. uterine, cervical, vulva and vagina).
- Cervical motion tenderness on bimanual examination may be suggestive of pelvic infection or ectopic pregnancy.
- A large tender uterus may be a sign of hematometra.
- Adnexal tenderness or a mass may suggest pelvic inflammatory disease (PID), ectopic pregnancy, ovarian cyst, or broad ligament hematoma.

Rectal Examination

- A rectal examination must be performed if bowel injury is suspected.
- The presence of rectal tenderness and blood (or guaiac positive stool) makes the diagnosis of bowel injury almost certain.

Case examination revealed a moderately ill patient
Temperature—102ºF
Pulse—108/min
Respiratory rate—28/min
BP—110/80 mm Hg

Per abdomen

- Mild distention, tenderness in lower abdomen, guarding and rigidity present
- Bowel sound present
- No free fluid

Local examination—mild offensive discharge present
Per vaginum—Uterus was multiparous size, tender and no adnexal mass —Cervical motion tenderness present, internal os admitting tip of finger. Patient was admitted and diagnosed the case of septic abortion.

Causative pathogens[2]

They are mixed and derived from normal vaginal flora, exogenous and sexually transmitted bacteria.

- *Escherichia coli* and other aerobic, enteric, gram-negative rods.
- Group B (beta hemolytic) streptococci.
- Staphylococcal organisms.
- *Bacteroides* species.
- *Neisseria gonorrhea*.
- *Chlamydia trachomatis*.
- *Clostridium perfringens*.
- *Mycoplasma hominis*.
- *Haemophilus influenza*.

Q.5. How to make the diagnosis of septic abortion?

Ans: A septic abortion is diagnosed when a woman has temperature of at least 100.4°F for 24 hours or more, offensive and purulent vaginal discharge and other evidence of pelvic infection such as lower abdominal pain and tenderness.[4]

Q.6. What are the clinical grading of septic abortion?

Ans: The grading of septic abortion is[1]

1. *Grade I*: Infection localized to uterus and its contents.
2. *Grade II*: Infection spreads beyond the uterus to parametrium, tubes and ovary or pelvic peritoneum.
3. *Grade III:* Generalized peritonitis and/or endotoxic shock, jaundice, or acute renal failure.

Q.7. How to manage a septic abortion?

Ans: Investigations[2,3]

Routine:

- Complete blood count
- Blood grouping and Rh typing.
- Kidney function test
- Liver function test
- Serum electrolytes
- Blood culture and sensitivity
- Coagulation profile
- Random blood sugar
- Serology for STD, HIV, Hbs Ag, syphilis
- High vaginal swab, Culture and sensitivity
- Urine routine/microscopic, culture and sensitivity
- X-ray abdomen supine and erect to look for free gas under diaphragm and multiple air fluid level
- Ultrasound abdomen and pelvis for retained POCs, adnexal mass, free fluid in abdomen and pelvis.

Special Investigations

- Urine and serum Beta-hCG if features suggestive of ectopic and choriocarcinoma.
- X-ray chest for pulmonary tuberculosis.
- CECT abdomen and pelvis (optional).
- Histopathology and culture of retained POCs evacuated.

Treatment and monitoring[2,3]

Prehospital care

- Monitor vital signs, stabilize with intravenous fluid.
- O_2 inhalation. Input/output charting then transfer to tertiary center.

Management at Tertiary Care Center.

Consultation with Gynecologists, Surgeons and Urologists.

Anesthetist for ICU cares if required.

Definite management:

- Tetanus toxoid/tetanus immunoglobulin
- Antigas gangrene serum in established cases of *Clostridium perfrigens* on blood cultures.
- Adequate blood, fresh frozen plasma and platelet to correct shock and deranged coagulation profile if deranged.
- Proper antibiotic therapy (broad spectrum antibiotics) covering both gram-positive, gram-negative and anaerobic organisms.
- Screen all patients for Rh factor and administer anti-D if patient is Rh incompatible and ICT negative.

Antibiotics

- *Cefoxitin*: For gram-positive cocci and gram-negative bacilli.
  Doses: 2 gm IV 6 hourly and doxycyclin 100 mg IV q 12 hour at least 48 hours after improvement followed by tab doxycycline 100 mg BD for 10-14 days.
- *Gentamycin*: For gram-negative coverage.
  Doses: Serious infection with normal KFT: 3 mg/kg/day q8h.

- Life-threatening infection: 5 mg/kg/day 6 - 8 hourly with Monitoring of kidney function test
- Maintenance: 1 - 2. 5 mg/kg/day q8h.
- Ticarcillin and clavunate potassium (Timentin)
- Presumptive therapy prior to identification of organism.
  Doses: < 60 kg : 200 - 300 mg/kg/day IV q 4- 6 hour >60 kg: 3.1 g IV q 4-6 hour or 200-300 mg/kg/day divided doses q 4-6 hourly not to exceed 18-24 gm/day
- Ampicillin and sulbactam sodium:
  Doses: 1.5 (1 g ampicillin + 0.5 g sulbactam) to 3 g (2 g ampicillin + 1 g sulbactam) IV/IM q6-8h; not to exceed 4 g/d sulbactam
- Imipenem and cilastatin sodium
  Dose: 250-500 mg IV divided q6h; not to exceed 3-4 g/d, based on severity of infection
  Alternatively, administer 500-750 mg IM or intra-abdominally q12h
- Piperacillin and tazobactam sodium
  Dose: 12 g piperacillin + 1.5 g tazobactam IV in equally divided doses of 3 g q6h for 7- 10 d
- Clindamycin
  Useful as treatment against aerobic streptococci and most staphylococci. Serious infections due to aerobic and anaerobic organisms: 600-1200 mg/d IV divided q6-8h
- Cefotaxime
  Moderate-to-severe infections: 1-2 g IV/IM q6-8h
  Life-threatening infections: 1-2 g IV/IM q4h
- Vancomycin HCl
  500 mg/d to 2 g/d IV tid/qid for 7-10 d
- Ceftriaxone
  1-2 g IV qid or divided bid depending on type and severity of the infection, to exceed 4 gram/day.

Surgical Management[6]

Indication of surgical intervention:
- Retained products of conception.
- Visceral injuries.
- Presence of foreign body.
- Unresponsive peritonitis or pelvic abscess.
- Septic shock or oliguria not responding to conservative treatment.

Surgical Options

Type of surgery needed depends on extent and type of pathology and they are:
- Evacuation and curettage.
- Posterior colpotomy
- Laparotomy—to drain pelvic abscess, to repair uterine perforation, gut injury with or without performing colostomy
- Hysterectomy

Evacuation and Curettage

- Give antibiotic coverage before 24 hours of the procedure
- If there is heavy bleeding, one may not wait for completion of 24 hours of antibiotics
- Inj. Prostodin 1 hr before the procedure
- Procedure has to be carried out by senior surgeon-gentle but complete evacuation has to be done
- *Avoid perforation:* It is likely as tissues are very friable
- Send the obtained tissue for histopathology and culture
- *Complications:* Perforation, bleeding

Posterior Colpotomy

Indication: Pelvic abscess drainage- diagnosed by constant throbbing pelvic pain, tenesmus, high rise of temperature, digital rectal examination showing bulging on anterior rectal wall and conformed on pelvic USG.

Pre-requisite for colpotomy drainage are that abscess must be
- In midline
- Adherent to cul-de-sac peritoneum
- Cystic or fluctuant

Complications
- False passage
- Intraperitoneal rupture of abscess
- Bleeding

Method of Posterior Colpotomy

- Anesthesia, lithotomy position, catheterization
- Examination under anesthesia to confirm area of maximum fluctuation
- Posterior lip of cervix grasped and pulled upwards and forwards.
- Colpopuncture with wide bore needle on near midline keeping direction of needle in axis of pelvis
- Pus withdrawn and sent for culture
- A transverse incision of 2 cm at the level of colpopuncture
- Blunt Kelly's forceps introduced in pouch of Douglas and opened to allow pus to drain.
- Septations in abscess cavity are broken with gloved index finger
- Drain kept and sutured with vaginal vault
- Drain should be removed after 48 hours to prevent pressure necrosis of anterial rectal wall
- Avoid extension of incision to laterally to prevent injury to ureter or uterine artery.

Laparotomy

Indications

- Injury to uterus, or gut
- Presence of foreign body in abdomen
- Unresponsive peritonitis or pelvic abscess

Method

- Transverse Maylard incision is ideal
- Pelvic adhesion released and bowel packed off
- pus drained out and sent for culture
- Foreign body removed
- Uterus, adenexa and intestines are explored for injury or bleeding
- Uterine perforation repaired in single layer
- Intestinal perforation repaired in 2 layers
- Peritoneal lavage with warm saline
- Drain kept
- Abdomen closed in layers

Laparotomy in case of Tubo-ovarian Abscess

- Midline vertical or paramedian incision
- Pus drained and sent for culture
- Omentum and small bowel separated from tubo-ovarian mass by gentle blunt dissection with fingers
- Separate ovary and tubes from uterus, sigmoid colon, and broad ligament
- Apply clamps
  - Clamp-1 Infundibulopelvic ligament
  - Clamp-2 Broad ligament below ovary
  - Clamp-3 Fallopian tube and ovarian tube and ovary removed, wash given, drain kept
- Abdomen closed in layers

Hysterectomy

Indication

- Irreparable injury to uterus and bilateral tubo-ovarian abscess
- Spreading gas gangrene infection in uterus.

Method

- Maylard or midline incision
- Pus drained out
- Separate T-O masses from bowel, back of uterus, POD and broad ligament by upward and lateral maneuvering
- First round ligament identified and ligated
- Anterior fold of peritoneum opened
- Infundibulopelvic ligament ligated
- Due precaution for ureter
- Subtotal hysterectomy may have to be done
- Vaginal vault kept open for drainage
- Abdomen closed in layers.

Q.8. What are the possible complications in Septic abortion?

Ans: ***Immediate***:[2,3]

1. Complications of anesthesia during surgical MTP.

General anesthesia: Atony leading to severe hemorrhage.

Local anesthesia: Paracervical block causing accidental intravascular injection of anesthetic agents leading seizure, cardiopulmonary arrest, and death.

2. *Neurogenic shock:* Vasovagal syncope produced by stimulation of the cervical canal during dilatation
3. *Hemorrhage:* Due to uterine atony, cervical laceration, uterine perforation, undiagnosed cervical pregnancy, more advanced gestational age than anticipated, coagulopathy.
4. *Perforation and peritonitis:* Uterine, bladder and bowel perforation. Perforation with suction cannula is more dangerous than a solid metallic dilator.
5. Disseminated intravascular coagulation-especially in mid trimester abortions and rate is even higher for saline instillation techniques due to electrolyte imbalance flaring of previous tubercular infection.

Sequelae

Septicemia and its associated multi organ involvement—Acute renal failure, hepatic failure, paralytic ileus, DIC and death.

Remote

1. Infection and surgical intervention can cause scar tissue leading to chronic pelvic pain (chronic PID)
2. Intestinal obstruction
3. Secondary infertility
4. Depression

Diagnosis and Management in this Case

In the case stated patient was admitted and all investigations sent. Patient was monitored for vitals, abdominal girth, input output, bleeding PV. Patient was kept nil orally with maintenance fluids and started on IV antibiotics (Tazobactam, piperacillin)

- Lab findings showed Hb 10.5 gm%, TLC 19000, Deranged LFT, urine—port-wine in color loaded with pus cells, strongly +ve for albumin. Urine bilirubin, not present. Coagulation profile was within normal limit.
- Cervical smear showed gram-negative rods suggestive of *E.coli*.
- Ultrasonography showed minimal fluid collection in uterine cavity with retained products
- X-Ray showed dilated loops intestine suggestive of paralytic ileus, no evidence of free gas or foreign body
- After correcting electrolyte imbalance, under antibiotic cover, evacuation was done. Patient improved after 48 hours, staying afebrile for 24 hours with relief of symptoms. She was discharged on 7th day with advice for sterilization after 6 weeks.

Deterrence and Prevention[2,3]

1. Educate patient about contraceptive methods and deter them from using abortion as means of birth control.
2. Safe and legal abortion
3. Easy access to prenatal care .and women to be tested and treated for common STDs in first trimester.
4. If a women thinks she might be miscarrying or has miscarried should call for health care provider right away.
5. Prompt diagnosis and timely antibiotics and prompt evacuation of retained POCs.

Medicolegal Pitfalls[2,3]

- Underestimating amount and rate of bleeding.
- Failure to diagnose uterine perforation and gut injuries.
- Failure to diagnose ectopic pregnancy.
- Failure to administer broad-spectrum antibiotic therapy and to treat shock.
- Failure to obtain adequate history about recent termination of pregnancy.
- Failure to immediate evacuation of uterus of its contents.
- Failure of timely laparotomy.

Special Case Reports

1. A 37-year-old G4 P3 presented with fever and right hip pain on POD11 from a second trimester abortion. She was initially found to have septic arthritis involving right Sacroiliac joint and Group B Streptococcal bacteremia with right-sided Endocarditis. She further developed septic pulmonary emboli and successfully treated with anticoagulation therapy and parenteral antibiotics.[7]
2. A woman developed necrotizing fascitis, myonecrosis and TSS, after elective MTP. She had confirmed Group A *Streptococcus* on blood culture and underwent surgical debridement. She survived after aggressive surgical treatment below knee amputation and antibiotics therapy.[8]
3. An unusual case of uterocutaneous fistula that developed in a multiparous woman was reported after surgical evacuation of an incomplete 1st trimester septic abortion. Fistulous tract was detected on CT scan and to verify methylene blue was injected transcervically and dye flow was seen through external opening of fistula. At laparotomy fistulous tract was excised with enclosing omentum.[9]
4. A multigravida at 18 weeks became septic after laminaria tent placement and rupture of membrane. She developed ovarian vein and IVC thrombosis and was treated successfully with retrievable IVC filter, anticoagulation and antibiotics. The filter was removed after 9th day.[10]

   So ovarian vein and IVC thrombosis are rare but life-threatening complication of severe obstetrics infection and IVC filters has been used to reduce the risk of pulmonary embolism in patients who has risk of recurrent thrombotic or embolic events or underlying risk factors.
5. A women at 10 weeks gestation developed abdominal pain, fever, leukositosis, peritoneal signs, closed cervix and a viable pregnancy. Progression from acute salpingitis to septic abortion was documented.[11]
6. A rare case of intra-abdominal hemorrhage following in expert injection into abdominal wall of calcium-heparin concentrate in a case of septic abortion was reported.[12]

Under research trial

Procalcitonin (PCT) as a monocytic marker for early diagnosis for septic abortion.[13]

PCT was recently promoted as a sensitive and specific marker of systemic infection. Daily PCT values in a patient of septic abortion were compared with established markers of systemic inflammation. Cultivated monocytes were analyzed by means of IIF .additionally PCT release into culture medium was examined. PCT was found superior to other inflammatory markers with regards to early and progression diagnosis.

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Deepti Goswami

17 Amenorrhea

Primary amenorrhea is diagnosed when there is absence of menses by age 14 years with the absence of development of secondary sexual characteristics or when there is absence of menses by age 16 years with normal development of secondary sexual characteristics.

Secondary amenorrhea is diagnosed when there is cessation of menstruation for at least 6 months or for at least 3 of the previous 3 cycle intervals in a woman who was previously menstruating.

CASE 1

A 17-year old girl presents with primary amenorrhea.

Q.1. What are the likely causes of amenorrhea?

Ans: Primary amenorrhea is usually the result of a genetic or anatomic abnormality. In about 60% of cases the underlying cause is abnormalities in the development of the ovaries, genital tract, or external genitalia. However, all causes of secondary amenorrhea can also present as primary amenorrhea.

The usual causes are:

- Chromosomal abnormalities (most common being Turner syndrome) — 45%
- Physiologic delay of puberty — 20%
- Müllerian agenesis (Mayer Rokitansky Kuster Hauser syndrome) — 15%
- Transverse vaginal septum or imperforate hymen — 5%
- Absent hypothalamic production of GnRH — 5%
- Anorexia nervosa — 2%
- Hypopituitarism — 2%

Q.2. What should be the approach to diagnosis in this case?

Ans: The evaluation of amenorrhea begins by establishing the presence or absence of the vagina. The other important point is to note the presence or absence of secondary sexual characteristics. The history and physical findings help in selecting tests to investigate primary amenorrhea.[1-3]

Q.3. What is important to elicit in history?

Ans:

- Childhood growth and development.
- If she has short stature compared to family members.
- Ascertaining the age at menarche of the patient's mother and sisters because the age at menarche in family members can occur within a year of the age in others.

- History of cyclical abdominal pain which may be progressively worsening. Patient may complain of difficulty in emptying the bladder or acute retention of urine. These features are classical of mullerian tract obstruction in the form of imperforate hymen or transverse vaginal septum.
- History of dyspareunia in a sexually active woman would suggest shortness of vaginal length.
- Information regarding, exercise, diet, recent weight change, home and school situations, and psychosocial issues.
- Symptoms of headache, hearing loss, visual changes, fatigue, polyuria or polydipsia, galactorrhea, virilizing changes.
- Sense of smell-anosmia is present in Kallman syndrome.
- Any history of poor nutrition and chronic illness (anorexia nervosa, malabsorption, regional ileitis, renal disease), trauma, surgery, irradiation chemotherapy and other medications.
- History of surgery for inguinal hernia in childhood should raise the suspicion for androgen insensitivity syndrome.
- A sexual history should be obtained in a confidential manner.
- Illegal drug use (especially marijuana).

Q.4. What are the important points in her examination?

Ans:

a. Vital signs, height and weight:
   - Short stature is a feature of Turner syndrome.
   - Tall stature may be seen in androgen insensitivity syndrome and hypogonadotropic hypogonadism.
   - Cachexia, bradycardia, hypotension, hypothermia, yellow skin (carotenemia), body mass index (BMI) of less than 18 are suggestive of anorexia nervosa.

b. General and neurological findings:
   - Fundi, visual field, sense of smell
   - Stigmata of Turner syndrome—short stature, a webbed neck, low hairline, low-set ears, a broad chest ("shield" chest) with widely spaced nipples, epicanthal folds, micrognathia, and an increased carrying angle of the arms.
   - Palpation of inguinal areas for masses-which may be testis in case of androgen insensitivity syndrome.

c. Breast findings and Tanner staging:
   - Turner syndrome - Undeveloped breasts, shield chest, and widely spaced nipples.
   - Delayed puberty is associated with underdeveloped breasts and sparse pubic hair.
   - Mullerian agenesis, obstruction in mullerian tract and complete androgen insensitivity syndrome are associated with normal breast development.
   - Hyperprolactinemia may cause galactorrhea.

d. Pubic hair and external genitalia findings and Tanner staging:
   - Turner syndrome—normal growth of pubic hair.
   - Delayed puberty is associated with sparse pubic hair.
   - Mullerian agenesis, obstruction in mullerian tract –normal pubic hair.
   - Complete androgen insensitivity syndrome —Absent or sparse axillary and pubic hair.

e. Signs of androgen excess: Acanthosis nigricans, hirsutism, acne, striae, clitromegaly. These may be seen in:
   - Androgen secreting tumors of the ovary.
   - Congenital adrenal hyperplasia.
   - Partial androgen insensitivity syndrome.
   - Cushing's syndrome.
   - Acanthosis nigricans and polycystic ovarian disease usually present with secondary amenorrhea.

f. Pelvic examination:
Check for the presence of patent vagina, cervix and uterus by per vaginum or per rectal examination. This will help detect imperforate hymen, vaginal septum, or congenital absence of the vagina. Rarely one may detect an ovarian mass on examination.
If normal vagina or uterus are not obviously present a pelvic ultrasonography (USG) helps confirm the presence or absence of uterus, and cervix. Ovaries can also be visualized on USG.
- Imperforate hymen – Bluish bulge seen at introitus. This may be associated with lower abdominal swelling—The distended bladder or a large cystic swelling anterior to rectum (hematocolpos).
- Mullerian agenesis – Absent or shortened (if patient is sexually active) vagina with a rudimentary or absent uterus.
- Androgen insensitivity syndrome – Shortened vagina without uterus. Gonads, which are the testes, may be palpable in the inguinal region in hernial sac.
- Uterine findings—If the uterus is enlarged, hematometra is an important cause of uterine enlargement in patient presenting with primary amenorrhea. Pregnancy must be excluded in girls with history of sexual contact.

Q.5. How will you investigate a case of primary amenorrhea who lacks a normal vagina but has well developed breasts?

Ans:

- In the patient who appears to lack a normal vagina, the first step is to distinguish true vaginal absence from an imperforate hymen or complete transverse vaginal septum; ultrasonography and at times magnetic resonance imaging (MRI) may provide useful information.
- In patients with mullerian agenesis it is important to screen for (a) anomalies of the kidneys (ranging from ectopic kidney to congenital absence) by USG and/or intravenous pyelography (IVP) and (b) skeletal abnormalities by X-ray of dorsolumbar spine.
- If no uterus is found and patient lacks pubic hair there is suspicion of androgen insensitivity syndrome. Women with complete androgen insensitivity syndrome have no functional androgen receptors and therefore do not have normal androgen-induced development of pubic and axillary hair. Further evaluation should include a karyotype (which would be 46 XY) and measurement of serum testosterone (which would be in normal male range).

Q.6. How will you investigate a case of primary amenorrhea with normal reproductive tract?

Ans:

- If the presence of a normal genital tract is confirmed, the next step is to investigate the patient's estrogen status. If the breasts have developed, then she has been exposed to estrogen, at least in the past. If no breast development has occurred, then the patient has never been exposed to estrogen, the explanation is likely to be failure of ovarian development or failure of gonadotropin production by the pituitary.
- An endocrine evaluation should be performed. Serum follicular stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), and prolactin should be checked. Low or absent gonadal estrogen production (hypogonadism) is due to (a) abnormal ovaries or to (b) abnormal hormonal stimulation of otherwise normal ovaries.
- Elevated FSH and LH levels in patients with primary amenorrhea are caused by gonadal dysgenesis or premature ovarian failure. Turner syndrome (45, XO karyotype) is the most

common form of female gonadal dysgenesis. A patient with primary amenorrhea, sexual infantilism (no normal breast development or secondary sexual characteristics), an elevated FSH value, and a 46, XY karyotype is typically diagnosed with Swyer syndrome. With absent or nonfunctioning ovaries, pituitary FSH production continues to rise (hypergonadotropic hypogonadism). A normal karyotype is treated as premature ovarian failure.

- Low FSH and LH levels (hypogonadotropic hypogonadism) may be a result of delay in progression of normal maturation or an inability to secrete adequate amounts of gonadotropins. The most common cause is constitutional delay of growth and puberty. A detailed family history may help detect this etiology, because it is often familial. The condition may be clinically indistinguishable from that associated with hypothalamic or pituitary failure but following features help in making the differential diagnosis.
  a. Kallmann syndrome, which can cause hypogonadotropic hypogonadism is associated with anosmia.
  b. MRI of the brain may detect abnormalities like tumor or empty sella syndrome where pituitary is significantly affected causing decreased gonadotropin secretion.
  c. Bone age radiograph: It helps distinguish the cases of constitutional delay of puberty from those with permanent hypogonadotropic hypogonadism.
- If signs or symptoms of hyperandrogenism are present, serum testosterone, dehydroepiandrosterone sulphate (DHEAS) and 17-hydroxyprogesterone should be measured to assess for an androgen-secreting tumor of the ovary or adrenal gland and for adrenal hyperplasia.
- Presence of galactorrhea or obvious thyroid enlargement should be investigated with serum prolactin and TSH levels.

Q.7. How should a case of constitutional delay of puberty be diagnosed and managed?

Ans: This condition is characterized by lack of physical development caused by delayed activation of the gonadotropin releasing hormone (GnRH) pulse generator. The patient will be short for her chronologic age and normal for her bone age. She will have underdeveloped breasts and sparse pubic hair. Normally plasma levels of sex hormones and gonadotropin correlate with bone age, not with chronological age. If gonadotropin levels are prepubertal in a patient who is otherwise healthy and has a bone age of >11 years it is unlikely to be constitutional delay and is due to gonadotropin deficiency.[4]

Cases with constitutional delay of puberty may have short stature but history reveals consistent growth rate and a family history of delayed puberty. There is no abnormality on assessment of smell, optic disks, and visual fields.

These patients achieve pubertal development on their own when bone age has advanced to 13 years. Watchful waiting is therefore appropriate. A rise in LH level is the sign of pubertal onset and eventually there is a normal pubertal development and establishment of normal menstrual cycles. A girl who has bone age >11 years for several years and continues to show low gonadotropic levels is likely to have permanent hypogonadism due to pituitary or hypothalamic cause.

Q.8. How will you manage a case of hypogonadotropic hypogonadism?

Ans:

- Low serum gonadotropins result from disturbances in pituitary or hypothalamus. Hypogonadism and delayed puberty in presence of low serum gonadotropins warrant brain evaluation by MRI to look for anatomic defects like tumor and empty sells syndrome.

- The anatomic defect will not reverse spontaneously (e.g., Kallmann syndrome; hypopituitarism; central nervous system tumors, trauma, infection, or irradiation). By contrast constitutional delay, anorexia, hypothyroidism are reversible causes which may respond to medical or surgical intervention or, in some cases, may resolve spontaneously.
- Management involves removal of any organic lesion which may be detected on MRI. In cases where pituitary is affected levels of other pituitary hormones should also be checked.
- Cases with absent sexual development require pubertal induction with low incremental doses of estrogen.[5] This is followed by cyclical estrogen-progesterone therapy or combined oral contraceptive pills to correct hypoestrogenism and provide regular withdrawal bleed.
- When fertility is required ovulation induction may be achieved by administration of exogenous gonadotropins or, more physiologically, by pulsatile gonadotropin releasing hormone treatment.

Q.9. How will you manage a case of Turner syndrome?

Ans:

- Turner syndrome (45XO karyotype) occurs due to ovarian dysgenesis and functionally presents with ovarian failure. The major health problems in Turner syndrome are: growth failure, cardiovascular disease, gonadal failure, and learning disabilities.[6,7]
- From gynecologic perspective hormonal replacement therapy should begin timely to facilitate pubertal induction and should be continued until the age of 50 years. For pubertal induction the dosing and timing of estrogen therapy should be aimed at mimicking normal pubertal development. Current recommendations advocate use of microdose estradiol to initiate puberty.
- Estrogen therapy should be coordinated with the use of growth hormone therapy. This should be individualized for each patient so as to optimize both growth and pubertal development.
- These patients have a high rate of cardiovascular and renal anomalies and are predisposed to Hashimoto's thyroiditis. The cardiovascular anomalies can be detected by echocardiography. Cardiac imaging should be repeated at 5- to 10-yr intervals and hypertension should be aggressively treated.
- Fertility is possible through donated oocytes. Their pregnancy is a high risk one due to associated cardiovascular problems and require close monitoring

Q.10. How will you manage a case of premature ovarian failure?

Ans:

- Premature ovarian failure is diagnosed on the basis of amenorrhea and raised serum FSH levels (>40 IU/L).[8,9] It may present with primary or secondary amenorrhea. Most of the cases are idiopathic. Karyotypic abnormalities in form of 45XO (Turner syndrome), 47XXX and structural abnormalities of X chromosomes need to be excluded.[10] Autoimmune disorders particularly of thyroid may coexist.[11]
- Management of POF involves explanation of the condition to the patient and counseling. The two major medical issues are—hormone replacement therapy and infertility. Young women with POF experience pathologically low serum estradiol levels which put them at risk of osteoporosis. Pubertal induction with low doses of estrogen may be needed in those who have not developed secondary sexual characters. Estrogen and progesterone replacement is required until the age of normal menopause. Ovarian biopsy is not required as it does not alter the management.

- These women may have associated pathology like thyroid dysfunction which needs evaluation and management. Long term follow-up is essential to monitor hormone replacement therapy and for health surveillance.
- Adoption and oocyte donation are among the available options for infertility treatment.
- Embryo cryopreservation, ovarian tissue or oocyte cryopreservation and *in vitro* maturation of oocytes hold promise in cases where ovarian failure is foreseeable as in women undergoing cancer treatments.

Q.11. Which patients with primary amenorrhea require surgical intervention?

Ans:

- Surgery is required in patients with either congenital anatomic lesions or Y chromosome material.
- Anatomic obstruction in mullerian tract may require drainage of hematocolpos, excision of vaginal septum and vaginoplasty.
  a. An imperforate membrane obstructing the lower vagina requires a simple incision to relieve the retained blood. All aseptic precautions should be taken and no instrument should be inserted inside the genital tract to avoid contamination of the blood collection.
  b. Vaginal absence requires the construction of an artificial vagina by one of a variety of methods. The most common technique being the Mc Indoe's vaginoplasty. Newer techniques including the laparoscopic ones are also described.
- In patients with Y chromosome, gonadectomy should be performed to prevent the development of gonadal neoplasia (usually gonadoblastoma).
  – In Swyer syndrome gonads are neither ovaries nor testes but, rather, an undifferentiated streak. They are at a significant risk of developing gonadal cancer; hence the gonads must be removed.[12]
  – Gonadectomy should be delayed until after puberty in patients with complete androgen insensitivity syndrome to ensure proper breast development which occurs due to peripheral aromatization of testosterone (secreted by the testis) to estrogen.
- Androgen secreting tumor of ovary or adrenal will require surgical removal.
- Rarely one may encounter patients with partial androgen insensitivity syndrome, congenital adrenal hyperplasia or rare enzymatic disorders who present with virlilization at puberty and clitromegaly which requires surgical correction.

CASE 2

A 30-year old lady presents with secondary amenorrhea of 6 months duration.

Q.12. What are the likely causes of amenorrhea?

Ans: First and foremost pregnancy should be excluded.

The causes of secondary amenorrhea are:

- Ovarian disease — 40%
- Hypothalamic dysfunction — 35%
- Pituitary disease — 19%
- Uterine disease — 5%
- Other — 1%

Q.13. What is important to elicit in history?

- Duration of amenorrhea, menstrual history
- Pregnancy to be ruled out
- Contraceptive history—Recent initiation or discontinuation of oral contraceptive pills or depot medroxyprogesterone acetate. Amenorrhea occurring after discontinuation of oral contraceptives ("post-pill" amenorrhea) is not caused by pill use but is attributable to other causes.
- Symptoms suggestive of hyperandrogenism-acne, hirsutism, voice deepening.

- Exercise levels, weight loss or gain, eating habits, and recent stressful events or illness.
- Symptoms of other hypothalamic-pituitary disease, including headaches, visual field defects, fatigue, or polyuria and polydipsia.
- Symptoms of estrogen deficiency, including hot flashes, vaginal dryness, poor sleep, or decreased libido.
- Inquiry about galactorrhea and hirutism (and other signs of hyperandrogenism).
- A thorough drug history should be taken, as several drugs can cause menstrual irregularity or amenorrhea, such as danazol/androgenic drugs, high-dose progestins, metoclopramide, the antipsychotic phenothiazines or previous treatment with cytotoxic agents.
- History of obstetrical catastrophe, severe bleeding (which may lead to Sheehan's syndrome).
- History of endometrial curettage (particularly multiple or after infection that might have caused scarring of the endometrial lining), endometritis (possible Asherman's syndrome).
- History of tuberculosis particularly with genital tract involvement.
- Past history of surgery, chronic diseases.

Q.14. What are the important points in her examination?

- Height and weight, body mass index (BMI)
  - BMI > 30 kg/m^2 seen in 50% of women with polycystic ovarian syndrome (PCOS).
  - BMI < 18.5 kg/m^2 may have functional hypothalamic amenorrhea.
- Signs of systemic illness/cachexia
- Neurological examination for visual field defects
- Skin exam, evaluating for
  - Stigmata of PCOS: Hirsutism, acne, acanthosis nigricans.
  - Stigmata of thyroid disorders: thyromegaly, thin/dry skin, skin thickening.
- Stigmata of Cushing's disease: striae, easy bruising.
- Breast- galactorrhea.
- Abdomen- masses, tenderness.
- Evaluate genital tissue for signs of estrogen deficiency.

Q.15. How will you investigate a case of secondary amenorrhea?

Ans:

- The most common cause of secondary amenorrhea is ***pregnancy***. After pregnancy is ruled out, the initial work-up should be based on patient history and physical examination findings. Menstrual periods may cease as a result of faults in the hypothalamus, the pituitary, the ovary or other systems.
- The first tests to perform after pregnancy is ruled out are:
  - Progesterone withdrawal test
  - TSH
  - Prolactin level
- After pregnancy, ***thyroid disease and hyperprolactinemia*** are eliminated as potential diagnoses. The risk of amenorrhea is lower with subclinical hypothyroidism than with overt disease. The treatment of hypothyroidism is simple with thyroid hormone replacement and leads to prompt return of ovulatory menstrual cycles. Hyperprolactinemia is discussed under question 6.
- The remaining causes of secondary amenorrhea are classified as normogonadotropic amenorrhea, hypogonadotropic hypogonadism, and hypergonadotropic hypogonadism; each is associated with specific etiologies.
- ***Progestogen challenge test*** helps evaluate for a patent outflow tract and detect endogenous estrogen that is affecting the endometrium. Medroxyprogesterone acetate-10 mg is given for 5-10 days. A withdrawal bleed usually occurs two to seven days after the challenge test. If she bleeds consider anovulation to be the cause of amenorrhea as is the case in PCOS.

- A negative progestogen challenge test signifies an outflow tract abnormality or inadequate estrogenization. An ***estrogen/ progestogen challenge test*** can differentiate the two diagnoses. The test involves administration of estrogen and progesterone in a sequential manner, e.g., conjugated equine estrogen 0.625 mg per day from day 1 to 21 and medroxyprogesterone acetate 10 mg given in the last 7-10 days.
- A negative estrogen/progestogen challenge test typically indicates an outflow tract obstruction. A positive test indicates an abnormality within hypothalamic-pituitary axis or the ovaries.
- The ***gonadotropin levels*** can further help determine the source of the abnormality.
- Normal or low FSH or LH levels suggest a pituitary or hypothalamic abnormality (hypogonadotropic hypogonadism). MRI of the sella turcica can rule out a pituitary tumor or an empty sella. Normal MRI indicates a hypothalamic cause of amenorrhea.
- Elevated FSH and LH levels suggest an ovarian abnormality (hypergonadotropic hypogonadism).
- Patients younger than age 40 with secondary amenorrhea, and elevated FSH level (>40 IU/L) are considered to have premature ovarian failure. Patients with premature ovarian failure should undergo investigation of the other endocrine organs (particularly thyroid) that have been known to fail along with the ovaries as part of a larger endocrinopathy. A karyotype should be considered in women with secondary amenorrhea at age 30 years or younger to rule out complete or partial deletion of the X chromosome, or presence of any Y chromosome material. Ovarian biopsy and antiovarian antibody testing have not been shown to have clinical benefit.
- Turner mosaic patients have a normal appearance and a history of childbearing but subsequently present with secondary amenorrhea due to ovarian failure. These women are also at risk for cardiac problems and should be investigated for cardiovascular anomalies.

Q.16. What are the principles of management in a case of secondary amenorrhea?

Ans: Management of patients with amenorrhea involves correcting any underlying disorder-for example, weight loss, hypothyroidism or hyperprolactinemia, treatment for anovulation associated with PCOS and replacement of cyclical estrogen progesterone in women with estrogen deficiency (hypergonadotropic or hypogonadotropic) till the normal age of menopause.

Q.17. How will you manage a case of hyperprolactinemia?

Ans: Rule out use of medications (e.g. antipsychotics, antidepressants, antihypertensives, histamine H2 blockers, opiates) which may cause hyperprolactinemia. Medications usually raise prolactin levels to less than 100 ng per mL.

A prolactin level more than 100 ng per mL suggests a prolactinoma, and MRI should be performed.

Microadenomas (smaller than 10 mm) are slow growing and rarely malignant. Treatment of microadenomas should focus on management of infertility, galactorrhea, and breast discomfort. A dopamine agonist helps in relieving symptoms and restores fertility. Bromocriptine is effective, but cabergoline has been shown to be superior in effectiveness and tolerability. Bromocriptine is started in a dose of 2.5mg at bed time to minimize side effects (orthostatic hypotension, nausea, headache, fainting). The dose is slowly increased. Some patients may require a dose of 7.5 to 10 mg per day. Cabergoline is started in a dose of 0.25 mg per day once a week and then increased up to 3 mg weekly as required. The dose can be divided into twice weekly if necessary.

Macroadenomas may be treated with dopamine agonists or removed with transsphenoidal resection or craniotomy, if necessary.

Q.18. What are the causes of normogonadotropic amenorrhea?

Ans: Two common causes of normogonadotropic amenorrhea are outflow tract obstruction and chronic anovulation as is seen in PCOS.

The most common cause of outflow obstruction in secondary amenorrhea is Asherman's syndrome (intrauterine synechiae and scarring, usually from curettage or infection). Other causes of outflow tract obstruction include cervical stenosis and obstructive fibroids or polyps.

Polycystic ovary syndrome (PCOS) is the most common cause of chronic anovulation. The primary etiology of PCOS is unknown, but resistance to insulin is thought to be a fundamental component. PCOS is a diagnosis of exclusion. Important distinguishing features are its peripubertal onset and worsening with weight gain. Thin women are not excluded from having this disorder.

- To diagnose PCOS, any 2 of the following 3 criteria should be present:[13]
  - Oligomenorrhea/amenorrhea
  - Signs of androgen excess
  - Presence of polycystic ovaries on ultrasound (≥ 12 follicles-2-9 mm in size, increased ovarian volume ≥ 10 mL)

The diagnosis of PCOS is primarily clinical, although laboratory studies may be needed to rule out other causes of hyperandrogenism. Other diagnoses should be particularly considered in scenario of sudden onset and rapid progression of hyperandrogenic symptoms. In these cases levels of testosterone and other androgens should be ascertained.

- Significantly elevated testosterone levels indicate a possible androgen-secreting tumor (ovarian or adrenal). Raised DHEAS level is suggestive of adrenal cause.
- Elevated levels of 17-hydroxyprogesterone are diagnostic of adult-onset congenital adrenal hyperplasia.
- Cushing's syndrome is rare; therefore, patients should only be screened when characteristic signs and symptoms (e.g., striae, buffalo hump, significant central obesity, easy bruising, hypertension, and proximal muscle weakness) are present. The test used to detect Cushing syndrome is the dexamethasone suppression test.

Q.19. What are the important aspects of manage-ment of PCOS?

Ans:

- Treatment depends on the presenting complaints of the patient.
- In patient with secondary amenorrhea or oligomenorrhea endometrial protection against hyperplasia is provided via hormonal therapy i.e. cyclical progesterones (10- to 14-days per month) or oral contraceptive pills which cause cyclical endometrial shedding.
- Prevention of obesity and metabolic defects: The primary treatment for PCOS is weight loss through diet and exercise. Modest weight loss (as low as 5%) can lower androgen levels, improve hirsutism, normalize menses, and decrease insulin resistance.[14]
- Insulin sensitizing agents such as metformin can reduce insulin resistance and improve ovulatory function. The usual dose of metformin is 500 mg twice a day or 850 mg twice a day. Most common side effects are gastrointestinal.
- Patients with associated hirsutism require management with antiandrogens- most common being spironolactone and cyproterone acetate.
- Infertility due to PCOS is managed with ovulation induction with clomiphene. In resistant cases laparoscopic ovarian drilling or gonadotropins are needed to induce ovulation.
- The insulin resistance associated with PCOS increases a patient's risk of diabetes mellitus; therefore, testing for glucose intolerance should be considered.

Q.20. What are the causes of Asherman's syndrome?

Ans: Asherman's syndrome describes the occurrence of intrauterine adhesions. Asherman's syndrome mostly affects women who have had dilatation and curettage, especially those who have undergone this procedure postpartum. The endometrium is highly susceptible to adhesions, between week 2 and week 4 postpartum due to injury to the pars basalis of the endometrium.

Other causes of Asherman's syndrome include

- Surgical trauma to the non-gravid uterus (for example, via dilatation and curettage or endometrial ablation) and
- Uterine infection, including genital tuberculosis and schistosomiasis.

Q.21. How will you diagnose and manage a case of Asherman's syndrome?

Ans:

- In presence of above mentioned history, diagnosis is suggested by absence of normal endometrial stripe on pelvic ultrasound and absence of withdrawal bleeding after administration of estrogen- progesterone.
- Hysterosalpingography, hysteroscopy, or sonohysterography can help confirm the diagnosis.
- The lysis of intrauterine adhesions under hysteroscopic guidance is required. Adhesions can be divided with scissors, electrosurgery, or laser energy. If the uterine cavity is obliterated completely, hysteroscopy is done under laparoscopic guidance. The main risks of hysteroscopy include uterine perforation and hemorrhage from uterine vascular damage.
- Long-term treatment with estrogen and progestogen may stimulate regrowth of the endometrium. Prognosis depends on the degree of adhesions present.
- Women who become pregnant after treatment are at high risk of obstetric complications, including miscarriage, premature labor, spontaneous uterine rupture, placenta accreta, intrauterine growth retardation, and postpartum hemorrhage.

Q.22. How will you manage a case of secondary amenorrhea with hypogonadotropic hypogonadism (low serum FSH and LH)?

Ans: The cause could be hypothalamic amenorrhea or pituitary disorder as in Sheehan syndrome.

a. Hypothalamic amenorrhea is associated with abnormalities in GnRH secretion and disruption of the hypothalamic-pituitary ovarian axis. The condition often is caused by excessive weight loss, exercise, or stress.
   - Treatment of hypothalamic amenorrhea depends on the etiology. Women with excessive weight loss should be screened for eating disorders and treated if anorexia nervosa or bulimia nervosa is diagnosed. Menses usually will return after a healthy body weight is achieved.
   - Young athletes may develop a combination of health conditions called the female athlete triad that includes an eating disorder, amenorrhea, and osteoporosis. Menses may return after a modest increase in caloric intake or a decrease in athletic training.
   - In patients with amenorrhea caused by eating disorders or excessive exercise, the use of oral contraceptive pills or combined estrogen-progesterone therapy may decrease bone turnover and partially reverse bone loss; however, neither therapy has been shown to significantly increase bone mass.
   - Bisphosphonates, traditionally used to treat postmenopausal osteoporosis, are possible teratogens and have not been studied as a therapy in women of reproductive age.
   - Adequate calcium and vitamin D intake are recommended for these patients.

b. Sheehan's syndrome occurs due to pituitary necrosis following massive obstetric hemorrhage.
   - The diagnosis is based on characteristic history of massive postpartum hemorrhage and often failed lactation and loss of pubic and axillary hair.
   - Patient will have decreased levels of estradiol, FSH and LH. Serum levels of other anterior pituitary hormones should also be checked.
   - Hormone replacement with estrogen-progesterone helps correct hypoestrogenemia and restores menstrual function.
   - Other anterior pituitary hormones (particularly TSH and ACTH) may also be deficient and require replacement with thyroid hormone and corticosteroid.
   - Pregnancy can be achieved with ovulation induction with exogenous gonadotropins.[15]

Q.23. Discuss the management of secondary amenorrhea due to premature ovarian failure.

Ans: Premature ovarian failure is characterized by amenorrhea, hypoestrogenism, and increased gonadotropin levels (FSH > 40 IU/L) occurring before 40 years of age.

A karyotype should be considered in most women of secondary amenorrhea age 30 years or younger to rule out complete or partial deletion of the X chromosome, or presence of any Y chromosome material which would require removal of gonadal tissue.

Women with premature ovarian failure have an increased risk of osteoporosis due to hypoestrogenism. Therefore estrogen- progesterone replacement is required to correct hypoestrogenism and restore menstrual function. The treatment needs to be continued till the normal age of menopause.

The condition can be associated with autoimmune endocrine disorders such as hypothyroidism, Addison's disease, and diabetes mellitus. Even if initial laboratory tests are normal, periodic screening is required.

Fertility is possible through donor oocyte and in vitro fertilization.

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18 Approaches to Improve the Diagnosis and Management of Infertility

Infertility can be defined as the failure to achieve a pregnancy within 1 year of regular unprotected intercourse in the absence of known reproductive pathology.[1] This condition may be further classified as primary infertility, in which no previous pregnancies have occurred and secondary infertility, in which a prior pregnancy, although not necessarily a live birth, has occurred.

Fecundability is the probability of achieving pregnancy within a single menstrual cycle and fecundity is the probability of achieving a live birth within a single cycle. The fecundability of a normal woman has been estimated to be 20 to 25%.

On the basis of this estimate, about 90% of couples should conceive after 12 months of unprotected intercourse.[2] Infertility affects about 10% to 15% of reproductive-age couples.

CASE 1

A young couple, who was not able to conceive after five years of marriage, consult you for infertility treatment. Elaborate the essential components in the infertility history and what are the specific important investigations in relation to infertility management?

Evaluation begins with a detailed documentation of the history and physical examination of both the partners. Adequate counseling is an integral part of the management.

Both Partners

- Age
- Occupation, occupational hazards
- Family history, e.g. hereditary diseases, cancer, thrombosis, personal health problems
- Current/past regular medications or any history related with tuberculosis, substance abuse (smoking, alcohol, caffeine)
- Allergy
- Previous surgery, previous genital surgery, pregnancies

Female Partners

- Age at menarche
- Menstrual cycle details
- Duration of infertility
- Sexual activity and problems, e.g. dyspareunia, coital frequency.
- Hirsutism, acne, galactorrhea, enlarged thyroid gland.

The physical examination of the female should be thorough with particular attention to height, body weight, body habitus, hair distribution, thyroid gland and detailed pelvic examination.

Male should be thoroughly evaluated by a reproductive medicine specialist, clinical andrologist or uroandrologist for the identification of underlying unrecognized male factors as

prevalence of significant pathology among male partner is as high as 40%.

Q.1. What are the causes of infertility?

Ans: The main causes of infertility are listed below in the Table 18.1.

Table 18.1: Causes of infertility[3]

Infertility	*%*
Female factors (single)	40-55
• Tubal factor	30-40
• Endometriosis	6
• Ovulatory dysfunction	30-40
• Diminished ovarian reserve	8
• Uterine factor	1
Male factor (single)	19
Other causes	7
Unexplained causes	12
Multiple factors (female only)	12
Multiple factors (female + male)	18

Therefore, clinical evaluation of the infertile couple may be grouped into five categories: semen analysis, the postcoital test (PCT), assessment of ovulation, uterine and tubal evaluation, and laparoscopy.[4]

Q.2. In certain group of patients do you think early investigation for infertility is required?

Ans: Few set of patients may not have a long duration of infertility but can be investigated and treated early when

- Age > 35 years
- H/o oligomenorrhea/amenorrhea
- Known or suspected uterine/tubal disease, endometriosis or diminished ovarian reserve
- Suspected or infertile partner
- Expected chemotherapy/radiation therapy of either partner for the underlying disorders

The detailed history, examinations and accurate detection of underlying reproductive abnormalities helps to guide individual management decisions and maximize infertility/ART treatment outcomes.

CASE 2

A 30 years old patient consults you with a normal semen report and patent fallopian tubes and normal uterine cavity on hysterosalpingogram for further treatment, how will you proceed?

Utmost important point is to find out whether this patient is ovulating or not.

Preovulatory follicles produce high levels (200 pg/ml) of estrogen. This sustained level for more than 48 hours causes positive feedback and LH surge. Due to mid cycle LH surge local concentration of prostaglandins and proteolytic enzymes are increased. This event progressively weakens the follicular wall till perforation and extrusion of the oocyte occurs (Fig. 18.1).

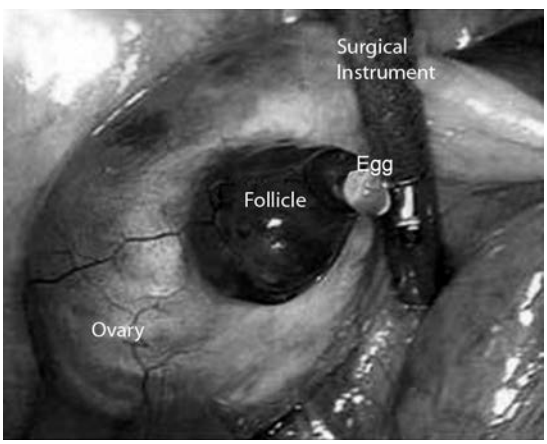


Fig. 18.1: Release of egg through the follicle

There are various methods to diagnose ovulation.

Indirect:

- Menstrual history: regular cycle
- *Evaluation of peripheral or end organ changes*
  - BBT
  - Cervical mucus study
  - Vaginal cytology

Hormone estimation
a. Serum progesterone
b. Serum LH
Endometrial biopsy
Sonography

Direct:
Laparoscopy
Conclusive:
Pregnancy
Often more than one cause is identified in a couple.

Q. 3. How can you document ovulation?

Ans:

1. **Menstrual history:** Regular cycles, mid cycle pain or spotting (Mittelschmerz syndrome), primary dysmenorrhea are strong evidences of ovulation. Five days before and the day of ovulation is called as "*Fertile Window*" of 6 - days. This period remains for six days in women with regular cycles (Fig. 18.2).

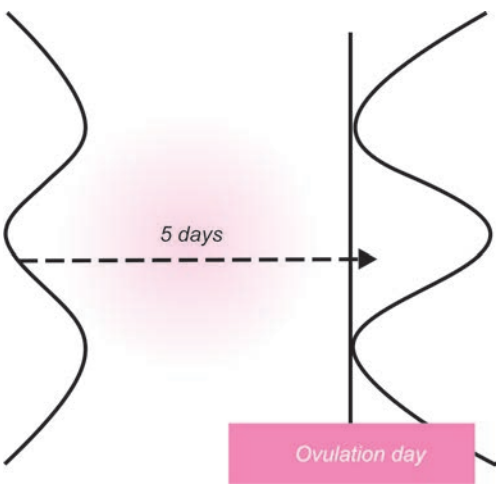


Fig. 18.2: Six-day fertile window

2. **Basal body temperature (BBT):** Ovulatory cycles produce a characteristic biphasic pattern of BBT. Secretion of progesterone occurs after ovulation as corpus luteum secretes progesterone. Due to thermogenic effect of progesterone there is rise of temperature in post ovulatory phase.

   Patient records her oral or rectal temperature each morning before the patient arises; eats or drinks. There is increase of 0.58°F over the baseline temperature of 97 degree to 98.8 degree in the follicular phase. The nadir in BBT coincides with LH surge (Fig. 18.3).
3. **Cervical mucus study:** Ovulatory cervical mucus is thin, profuse, elastic and withstands stretching up to 10 cm (Spinnbarkeit). This can be also assessed by the patients itself which is called *Billings' Test.*
4. **Fern Test:** Cervical mucus and saliva are strongly influenced by progesterone and estrogen. Fern test can be done by both. Sodium chloride levels in the mucus secreted under the influence of estrogen are high around the time of ovulation. These causes crystallization when it dries up on a glass slide (Fig. 18.4).

   Disappearance of fern pattern and elasticity which was present in the mid-cycle is suggestive of ovulation.
5. **Postcoital test:** The PCT provides an assessment of the quantity and quality of cervical mucus, number of motile sperms per high power field, sperm-mucus interactions and the presence of antisperm antibodies. It can be performed after 2 days of abstinence and 2 to 12 hours of intercourse. There is poor correlation between PCT result and pregnancy outcome as its results can be reflected due to poor cervical mucus or abnormal semen parameters. Hence, it is not the standard investigation of infertility now.[5]
6. **Hormones estimation:**
   a. **Progesterone:** Above 3ng/ml (10 nmol/L) on day 21 to 23 of an ideal 28 day cycle confirms ovulation. However, lower values are not necessarily diagnostic of anovulation.[6]
   b. **Luteinizing hormone monitoring:** There is an increase in LH level over 2 to 3 times in preovulatory phase. Ovulation occur 34-36 hours after the onset of the LH surge and 10-12 hours after LH peak.

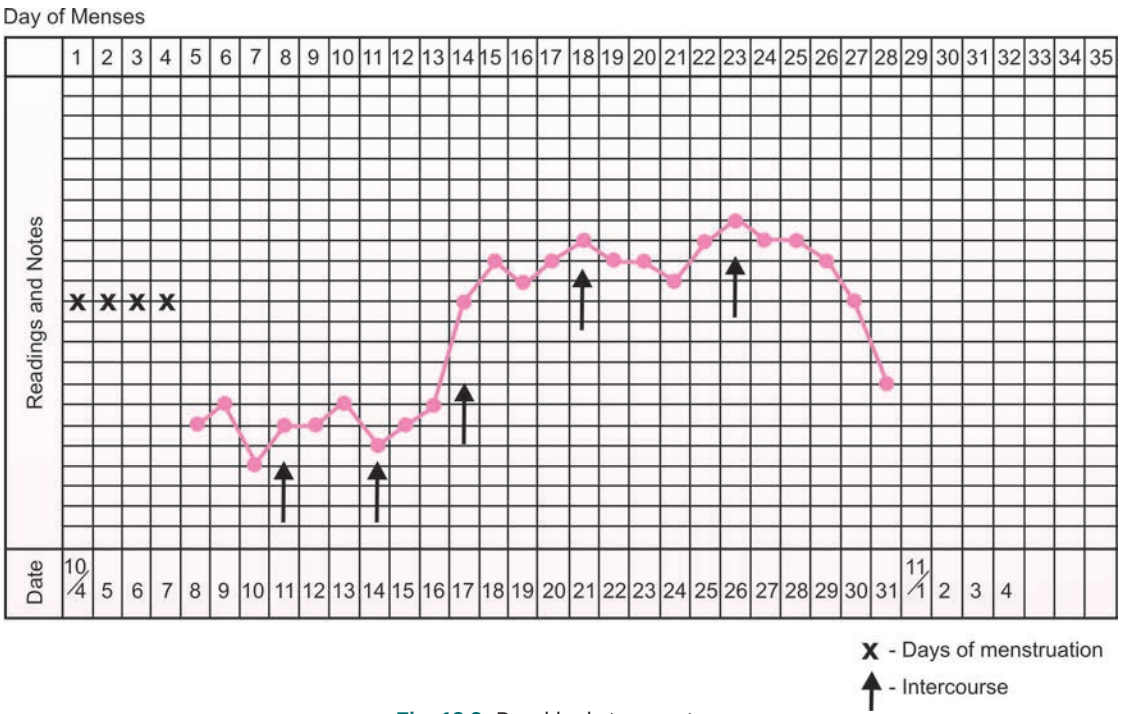


Fig. 18.3: Basal body temperature

Fig. 18.4: Fern test: Cervical mucus/salivary changes

7. **Endometrial biopsy:** Endometrium is biopsied on day 21 to 23 day by endometrial biopsy curette or Karman's canula no 4. Histopathological report of secretory endometrium in the second half of the cycle is diagnostic of ovulation. Endometrial sample should be subjected to AFB stain and culture to rule out tuberculosis and calendar and histological dating to diagnose corpus luteum defect (LPD).
8. **Ultrasound monitoring:** Irregular and decrease in the size of a monitored ovarian follicle and appearance of fluid in cul-de-sac characterizes ovulation.

Q.4. How do you define tubal, paratubal, and peritoneal factors for infertility and what are the diagnostic tests?

Ans: Tubal disease is responsible for 25%-35% of female infertility. Pathology may involve the proximal, distal or entire tube due to previous PID, genital tuberculosis, sexually transmitted disease like gonorrhea or chlamydial infection, endometriotic or previous pelvic or tubal surgery.

The diagnostic tests for tubal infertility are:

- **Detection of infection:** Cervical culture, serum antibodies (IgG) for *chlamydia trachomatis* or endometrial tissue culture for *tuberculous mycobacterium.*

- **Hysterosalpingography (HSG):** HSG has a sensitivity of 85% -100% in delineating uterine anatomy and assessing tubal patency. It is usually performed between 6 to 11 days of cycle by water based soluble contrast medium; Meglumine diatrizoate (Renografin- 60) is rapidly absorbed with no risk of lipid embolism or granuloma formation. However, the resolution of tubal architecture is better with oil based dyes (Ethiodol). It can pick up abnormalities in endometrium like submucosal fibroids, endometrial polyp, uterine septa and synechiae. HSG can cause pain and pelvic infection (1%-3%), and rarely uterine perforation, hemorrhage, collapse and allergic reaction.
- **Laparoscopy:** It directly visualizes all pelvic organs especially assesses the external architecture of the tubes including fimbria. Simultaneously it also detects and treat intramural and subserous uterine fibroids, peritubal and periovarian adhesions and endometriosis.
- **Sonosalpingography:** It can detect tubal patency under ultrasound scanning. With a slow and deliberate injection of about 200 ml of physiological saline mixed with air into the uterine cavity through a Foleys catheter. The saline flow is observed as shower through the fimbrial end and the presence of free fluid in the pouch of Douglas. Saline flow can also be observed through Doppler.

Other diagnostic modalities are:

- **Transcervical fallopscopy:** Transcervical fallopscopy allows direct visualization of tubal ostia and intratubal architecture, abnormal tubal mucosal pattern and even intraluminal debris causing tubal obstruction.
- **Selective salpingography:** Small guide wires are used to permit selective tubal canalization and radiographic visualization under fluoroscopy.

Recent Advances

Virtual hysterosalpingography:[7] With the demand for more accurate imaging methods for identifying the specific cause of female infertility and other gynecologic disorders, Virtual hysterosalpingography is an emerging modality in which aspects of the established technique of hysterosalpingography are combined with the cutting-edge technology of multidetector computed tomography (CT). It is capable of depicting both the external and internal surfaces of the uterus, fallopian tubes, and other pelvic organs, providing high-resolution data for two- and three-dimensional reconstructions and virtual endoscopic views.

Q.5. What are the methodologies available to assess intrauterine pathology and what is its impact?

Ans:

Hysteroscopy: Office hysteroscopy is only recommended by the WHO when clinical or complementary tests (ultrasound, HSG) suggest intrauterine abnormality[8] or after in vitro fertilization (IVF) failure.[9]

Ultrasound: Late follicular phase TVS has proved to be a useful tool for the detection of intrauterine abnormalities such as polyps, synechiae, fibroids and Müllerian anomalies.[10]

Saline infusion sonography: This offers enhanced visualization of the endometrium and better detection of intrauterine pathology than does standard TVS, and may be as effective as hysteroscopy in detecting intracavitary abnormalities.[11,12]

There is some evidence from basic science studies to suggest a detrimental effect of polyps on fertility. Polyps diagnosed prior to commencement of controlled ovarian hyperstimulation (COH) for in vitro fertilization (IVF) should therefore be removed. The management of polyps seen during the course of COH for IVF should be individualized.[13]

MRI: MRI may be used for patients with suspected complex Müllerian anomalies.[14]

CASE 3

A young couple was investigated for infertility abnormality. If on basic work up there is no male factor abnormality, and assessment of ovulation and tubes on laparoscopy were found normal. How will you treat this patient further for infertility?

Most probably we are dealing with a case of unexplained infertility. Unexplained infertility is defined as when couple has failed to establish a pregnancy despite no abnormality detected on completion of the basic work up. This includes history and examination, assessment of ovulation and HSG or laparoscopy for tubal status and the tests for the male partner. Evaluation of a male partner usually includes history, examination and semen analysis.

Various studies have reported that 0 to 26% of infertile couples have unexplained infertility. Unexplained infertility is associated with few following factors:[15]

Table 18.2: Associated factors with unexplained infertility

1. Ovulatory dysfunction
2. Subclinical infection leading to tubal dysfunction
3. Minimal to mild endometriosis
4. Sperm dysfunction
5. Immunological factors
6. Subclinical pregnancy loss
7. Psychological factors

Management of unexplained infertility

These patients require further assessment like estimation of serum prolactin, serum TSH, cervical cultures for *Chlamydia* and *Ureaplasma urealyticum*. The role of diagnostic laparoscopy if not done early is debatable. It may uncover sub serous and pedunculated fibroids, peritubal adhesions and endometriosis. The diagnostic laparoscopy should be performed in women with unexplained infertility even with normal HSG as it may identify and treat endometriosis (Table 18.2).

Treatment of unexplained infertility

The therapy "superovulation and IUI"; aims at increasing the available numbers and proximity of healthy gametes. Superovulation by clomiphene citrate or letrozole with IUI for 3 cycles is followed by COH using gonadotropins and IUI for another 3 cycles.

If both these approaches fail to result in pregnancy or fertilization failure, then IVF with or without ICSI may be considered.

All patients should be assessed for ovarian reserve before enrolling for assisted reproduction.

"Ovarian reserve" simply means the number of eggs the ovary has in reserve. The greater the ovarian reserve, the more time is left on individual's biological clock.

The parameters of assessment for ovarian reserve during infertility evaluation are:

i. Age
ii. D2 FSH
iii. D2 estradiol
iv. Anti Mullerian hormone
v. Antral follicle count
vi. Inhibin B
vii. Clomiphene citrate challenge test
viii. GnRH agonist stimulation test (GAST)
ix. Exogenous FSH ovarian reserve test (EFFORT)
x. Ovarian biopsy

CASE 4

An infertile couple presents to you for evaluation. A semen analysis is ordered on the same day. The sample of 1 cc contains 8 million sperm counts per milliliter, 30% are motile and 5% are of normal morphology. What advice you should give to this couple?

The evaluation of infertile man begins with proper counseling. The confidentiality is maintained and a thorough history and examination

is to be taken. Male factor is solely responsible for 19% of subfertile couples and contributes in another 18% of cases.[16]

Semen collection is the foremost simple and diagnostic investigation for male infertility.

There are few significant points in giving semen samples.

a. Abstinence for 2 to 3 days
b. Delivery to laboratory within 1 hour of collection
c. Keep sample at body temperature (37°C)
d. Masturbation preferred
e. Avoid normal condoms or lubricants

The normal semen value with sperm morphology is important for a conceptual cycle. Normal spermatogenesis depends on adequate gonadotropic stimulation of the testis, proper testicular function and patent and normally functioning seminal ducts (Table 18.3 and 18.4).

Table 18.3: Normal values for a semen analysis[17]

Volume	> 2.0 ml
Sperm concentration	> 20 million/ml
Motility	> 50%
Morphology	> 30% normal forms

Table 18.4: Strict Tygerberg classification[18]

Normal sperm morphology	*Prognosis*
> 14%	Normal fertilization in IVF cycles
4-14 %	Good prognosis
< 4%	Poor prognosis

Accepted definition of semen quality

Normozoospermia: All norma semen parameter defined by WHO.

Oligozoospermia:

- Mild 10 to 20 million spermatozoa/ml
- Moderate 5 to 10 million spermatozoa/ml
- Severe < 5 million spermatozoa/ml
- Extreme < 1 million spermatozoa/ml

Aesthenozoospermia: Reduced total sperm motility or reduced sperm progression

Teratozoospermia: Increased proportion of abnormal forms of spermatozoa

Oligoaesthenoteratozoospermia: All sperm parameters are abnormal

Azoospermia: No sperm in the ejaculate

Aspermia/anejaculation: Ejaculate/ejaculation failure

Q.6. What are the important points while investigating the male partner?

Ans:

History

- Medical (illnesses requiring radiotherapy or chemotherapy)
- Surgical (childhood hernia, undescended testes, varicocele)
- Sexually transmitted infection (Chlamydia, Gonococcus, Tuberculosis)
- Trauma
- Exposure to drugs or toxins
- Family history
- Coital history: Erectile dysfunction/Ejaculatory failure

Examinations

General examination (i.e. height, weight, BP etc)

Secondary sexual characteristics

Genital examination

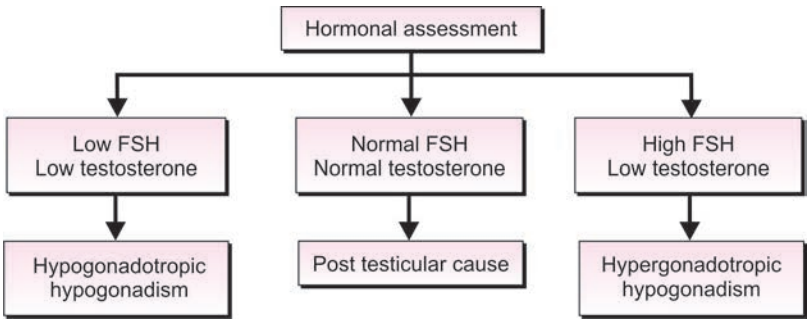
- Testes (volume and consistency)
- Epididymis (volume and consistency)
- Vasa deferens (presence or absence)
- Assess for any abnormalities (e.g. lumps/ varicocele)

Investigations

- Repeat second sample of semen analysis, three months apart.
- Post-ejaculate urine (if retrograde ejaculation suspected).
- Sperm pelleting (Specimen is centrifuged at 2000 rpm and the resulting pellet) examined for sperms before confirming azoospermia.

Endocrine profile: FSH, testosterone, prolactin (Flow chart 18.1)

Flow chart 18.1: Endocrinal assessment of male partner



Genetic tests:
– Peripheral karyotype
– Y micro-deletions
– Cystic fibrosis mutations

Ultrasound scan (if indicated, i.e. abnormal examination)

Management
- Discontinue adverse medication
- Stop smoking. Abstain from alcohol.
- Avoid scrotal heating
- Antioxidant therapy – Vitamin E and selenium to improve mortality
- For retrograde ejaculation – α-sympathomimetic drugs (phenylpropanolamine, imipramine).
- Donor insemination: for azoospermia, severe oligospermia
- For mild/moderate oligospermia:

Intrauterine insemination offers good results where 0.3 ml of washed, processed and concentrated sperms is placed into intrauterine cavity.
- Varicocele repair involves interruption of the internal spermatic vein, despite its widespread use, the therapeutic benefits remain controversial.

For Hypogonadotropic Hypogonadism
- Rule out hyperprolactinemia
- CT/MRI or pituitary fossa
- Drugs: hCG 2000 IU, twice weekly for 6 months/HMG – 150 IU thrice weekly
- For testicular and post-testicular azoospermia, IVF/ICSI either by ejaculation or surgically retrieved sperms.
- Testicular biopsy should not be done for the confirmation of diagnosis.

Q.7a. What is retrograde ejaculation? In which conditions it can occur?

When bladder neck coaptation is not complete, the seminal fluid may travel retrograde into the bladder during periurethral muscular contraction. Patient may present with low semen volume, low motility and sperm concentration.

Retrograde ejaculation is commonly seen in following conditions:
- Patients with diabetes.
- After transurethral surgery iatrogenic surgical damage to the bladder neck innervation.
- Retroperitoneal lymph nodes dissection.
- Spinal cord injuries.
- Alpha adrenergic blockers used as hypertensive disorder.

Urinalysis performed immediately after ejaculation and examined for sperm under the microscope. If sperms are present, specimen is processed further to evaluate concentration, motility and morphology. Sperms can be retrieved from the urine may be used for assisted reproduction.

Q.7b. What is split ejaculate?

Ans: The ejaculate is split in two or more and collected in different jars. First fraction contains majority of the spermatozoa suspended in prostatic fluid. Later fraction of the ejaculate consists of seminal vesicle secretion.

CASE 5

A 26-years-old lady had a past history of vaginal discharge and lower abdominal pain for which she took treatment. She couldn't conceive after two years of married life. On per vaginal examination she had bilateral tubo-ovarian mass and laparoscopy confirm bilateral TO masses with hydrosalpinx. During infertility evaluation all other significant investigations were normal. How will you treat this patient?

There is an adverse effect of hydrosalpinx on fertility. This may cause following effects:

- Hydrosalpinx fluid includes microorganisms, endotoxins, cytokines, oxidative stress and lack of nutrients which are embryotoxic.
- The endometrial receptivity may be reduced as an effect of disturbed expression of the cytokine cascade, which is essential for implantation.
- The presence of excessive fluid in the uterine cavity may also be a mechanical hindrance to implantation.

Cochrane review has shown a significant increase in clinical pregnancy rate with surgical treatment of hydrosalpinx (Peto OR 4.66, 95% CI 2.47 to 10.01). Meta-analysis has shown that patients with visible hydrosalpinx on ultrasound should be encouraged to undergo prophylactic salpingectomy prior to IVF. The meta-analysis from three clinical studies demonstrated superior pregnancy [odds ratio (OR) 1.75, 95% confidence interval (CI) 1.07–2.86] and live birth rates (OR 2.13, 95% CI 1.24–3.65) following salpingectomy compared with no surgical intervention.[19]

Assisted Reproductive Technology (ART)

All treatment or procedures which, include the *in vitro* handling of human oocytes and sperm or embryos for the purpose of establishing a pregnancy. This includes IVF and transcervical embryo transfer, gamete intra-fallopian transfer, zygote intra-fallopian transfer, tubal embryo transfer, gamete and embryo cryopreservation, oocyte and embryo donation and gestational surrogacy. ART does not include assisted insemination (artificial insemination) using sperm from either a woman's partner or sperm donor.[1]

Q.8. What are the other indications of assisted reproductive technologies?

Ans: The indications of ART are:[20]

- Abnormal fallopian tubes- blocked/impaired tubal function or absent tubes following surgery
- Endometriosis affecting tubo-ovarian ovum pick-up function
- Idiopathic or unexplained infertility of >3 years or earlier if women >36 years
- No conception after 3 or 4 IUI cycles
- Male infertility
  - TMC > 1 m-10 m – IVF
  - THC > 10 million in unexplained infertility.
- Cervical or immunologic infertility
- Failure of donor semen insemination
- Failure of ovulation

CASE 6

Few patients cannot conceive by IVF as they require intracytoplasmic sperm injection?

Semen parameters play an important role in the management of infertility. Depending upon the count, motility and morphology of the semen following are the different methods helpful for conception, provided there is no female factor infertility (Table 18.5).

Table 18.5: Sperm count in relation with different methods for conception

Method	*Concentration*	*Motility*	*Morphology*
Natural conception	20 million/ml or more	50% or more with forward progression	30% or > normal forms
IUI	5-15 millions/inseminate	30-50% with forward progression	15% or > normal
IVF	1-5 millions/inseminate	25-30% with forward progressions	5-15% or > normal
ICSI	<2 millions/inseminate	progressive motility	<5% > 95% abnormal sperm

Indications of ICSI

1. Total motile sperm count < 1 million
2. Normal morphology < 4% with TMC < 5 million
3. No or poor fertilization in previous IVF cycle with TMC <10 million
4. No or poor fertilization in previous two IVF cycle with TMC >10 million
5. Epididymal or testicular spermatozoa

Oocytes retrieval is the procedure which requires excellent degree of relaxation. Normally it takes maximum of 10 minutes.

IVF/ICSI procedures are done under anesthesia. There should be minimum exposure of oocytes to the anesthetic agents which accumulates rapidly in follicular fluid during procedure.

Anesthetic drugs used for oocytes retrieval:

1. Fentanyl: 1 to 2 g/kg intravenous
2. Midazolam: 0.05 to 0.1 mg/kg intravenous
3. If required: Propofol 1 to 2 mg/kg may be added

CASE 7

An anovulatory infertile woman was induced ovulation by gonadotropins. What is an ovarian hyperstimulation syndrome?

OHSS is an iatrogenic complication of so called controlled ovarian hyperstimulation. It is directly related with increasing number of stimulated follicles and is hCG dependent. Vasoactive mediators are released from ovaries – PG, cytokines, VEGF, renin, angiotensin, endothelin which causes endothelial injury and vasodilatation leading to 3rd space fluid collection with circulatory dysfunction.

There is variable degree of ovarian enlargement and/or ascites, pleural effusion, oliguria, hemo-concentration, thromboembolism, and electrolyte disturbances which may be life threatening.

Classification (Table 18.6)

Table 18.6: Classification of OHSS

Grade	*Ovarian size*	*Clinical presentation*	*Lab tests*
Mild	5 to 10 cc	Abdomen distension, GI upset	HCV < 45, TLC < 15,000/cc Normal renal function
Moderate	10 to 12 cc	Moderate ascites	Normal renal function
Severe	> 12 cc	Marked ascites Dyspnea Hypovolemia Mild thromboembolism	HCV > 45 TLC > 15.999/cc Impaired renal function
Critical (Life threatening)	Marked enlargement	Tense ascites, hydrothorax Thromboembolism Adult respiratory distress syndrome	HCV (55%), TLC > 25000/mm^3, serum creatinine >1.6 mg%^, creatinine clearance < 50 ml/min.

Causes of OHSS

Cause is unknown. But, women at risk of developing OHSS include:

- Over response to ovulatory drugs.
- Women with polycystic ovaries.
- High estrogen hormone levels and a large number of follicles or eggs.
- Administration of GnRh agonist.
- The use of hCG for luteal phase support.

Management

A. **Mild cases:** Spontaneous recovery occurs within 2-3 weeks (conservative measures and follow-up).

B. **Moderate and severe cases:** Assessment is made after thorough history, examination, and investigations and if patient is stable, outpatient care can be given which involves daily follow-up with restricted activity and daily weight monitoring. Intake (1 liter/day) and output should be monitored.

The patient needs to be hospitalized in case of

If weight gain > 2 lb/day, hemodynamic instability, respiratory comprise, tense ascites, hemo-concentration, renal failure, or decreased oxygen concentration.

Supportive care

The intravascular volume and renal perfusion should be maintained preferrably by intravenous colloids even crystalloids in the form of normal saline with/without glucose can be given total volume replacement may require 1.5-3L of fluids and even albumin infusion is helpful (20%).

Symptomatic treatment

- Peripheral dopamine inhibitor: cabergoline
- Analgesia: paracetamol and opiods.
- Antiemetics: metoclopramide
- Prevention of thromboembolism by anti-coagulant therapy if there is clinical or laboratory evidence

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19 Fibroid Uterus

Fibroids (leiomyomas, myomas) are the most common benign tumours of the uterus arising from uterine smooth muscles. There are a number of long ongoing researches investigating the underlying pathogenesis of these highly prevalent benign tumours linking the latter to high levels of intrinsic aromatase activity, estrogen and progesterone receptors, and genetic predisposition (aberrations in chromosome 3, 6, 7, 10, 12). They are symptomatic in only 50% of cases, manifesting with a multitude of symptoms and complications. Recent developments in the management of fibroids include the advent of minimally/non-invasive procedures (embolotherapy, focused ultrasonic therapy) and modifications of laparoscopic myomectomies.

CASE 1

A 45-year-old lady, Mrs P presented with menorrhagia of 6 months duration. On examination uterus was enlarged equivalent in size to 20 weeks pregnancy. Ultrasound revealed multiple fibroids in the uterus.

Q.1. What are the important points in the history?

Ans: A patient of fibroid uterus can present with the following complaints. The following history should be taken in detail.

1. Age: seen in women of reproductive age group, mostly between 35 and 45 years. They do not occur *de novo* before menarche and after menopause.
2. Parity: more commonly seen in nulliparous or those having one child infertility. Multiparity confers a risk reduction.

Presenting Complaints:

1. Menstrual complaints (Menorrhagia): Specifically ask about menorrhagia, metrorrhagia. Though not a classical symptom, polymenorrhea can be occasionally found due to altered ovarian blood supply on account of associated pelvic congestion.

   Menorrhagia is the most common complaint in symptomatic patients with fibroids. The cause of menorrhagia is:

   a. increased endometrial surface area (normal 15 cm^2)
   b. presence of fibroid restricts normal uterine contractility
   c. pelvic congestion
   d. obstruction by the tumor resulting in dilatation of subadjacent endometrial venous plexus
   e. endometrial hyperplasia due to hyperestrogenism

   In case of heavy menstrual flow enquire regarding use of any hemostatic agent and degree of relief.

2. Dysmenorrhea:
   a. congestive due to pelvic congestion or associated endometriosis or Pelvic inflammatory disease (PID).
   b. Spasmodic when associated with a submucous polyp during attempts of the uterus to expel the submucous fibroid.

   Take any history of relief in symptoms and if so with what drugs–antispasmodics/simple analgesic
3. Pain/heaviness in abdomen: Pain is an uncommon feature of fibroids and if present is due to complications of the tumor (e.g. degeneration, torsion of a pedunculated subserous fibroid, extrusion of the polyp, sarcomatous change, or adhesion with other organs) or associated pathologies (endometriosis, PID).
4. Lump in lower abdomen: The duration of the lump and rate of increase in size of the lump. Obese patients might not be able to appreciate any lump.
5. Pressure symptoms: posterior wall fibroids compress the rectum causing constipation, while cervical and broad ligament fibroids cause retention of urine due to ureteric compression. Ureteric compression can lead to hydronephrosis and pyelitis. Anterior wall fibroids produce urinary symptoms due to direct pressure effect.
6. Infertility
7. Recurrent pregnancy loss (RPL)
8. Something coming out per vaginum: Fibroid polyp with long pedicle may present as some mass coming out of vagina especially on straining.
9. History suggestive of anemia: Easy fatigability, tiredness, lassitude, palpitations, etc.
10. History of any bleeding disorder: Bleeding from other mucosal sites
11. History suggestive of malignancy and distant spread: Significant weight loss, anorexia, jaundice, bone pains, headache, chest pain, hemoptysis.

Menstrual History:

To be taken in detail

- LMP: rule out pregnancy
- Bleeding duration (days), regularity
- Number of pads used per day
- History of passage of clots
- Association with dysmenorrhea
- Young adolescents–menarche and the characteristics of previously normal menstrual cycles.

Obstetric history

- If previous cesarean delivery any mention of fibroid seedling in the operation notes.
- Any complication during pregnancy (red degeneration)/during or following delivery (PPH etc.)
- In history of RPL – sub clinical abortion/early abortion/may be associated with submucous fibroid
- History of use of OCPs

Past history

- Any chronic medical/surgical illness which may preclude surgical management
- Any treatment sought for the above complaint and any relief with that
- History of prior medication (including hormones) or any procedure if she underwent in the past
- History of long-term intake of anticoagulants (warfarin, aspirin) or tamoxifen which can lead to menorrhagia

Personal history

- Smoking: associated with a lower risk of fibroids

Q.2. What are the important points on examination?

Ans: General Physical Examination

- General Condition
- Built and nutrition: fibroids are more often found in obese women

- Pallor and severity
- Vitals: Pulse rate, blood pressure, respiratory rate–evaluate the degree of anemia and need for immediate transfusion of blood products.
- Lymphadenopathy
- Thyroid
- B/L breasts

Systemic examination: This is important for anaesthesia fitness prior to planning surgery.

If the patient has other co-morbid medical problems, the patient can be planned for non surgical modalities for treatment of fibroid.

Per abdominal Examination

1. Inspection: Contour of the abdomen, uniform/unequal distension, any scar marks
2. Palpation:
   - Description of the mass if present: size (corresponding to weeks of a gravid uterus), condition of overlying skin (tender, warm, fixity to mass), mobility–sideways and vertical, confirm pelvic origin (inability to reach the lower limit of the mass), consistency, margins of the mass (well defined/vague), surface regularity (smooth/irregular).
   - Any other associated organomegaly
   - Presence of free fluid
   - B/L renal angles for any mass/tenderness (large fibroids can compress ureter and can cause hydronephrosis
3. Percussion: The swelling will be dull on percussion.

Local Examination

- External genitalia whether healthy or not
- If currently bleeding, the severity of menorrhagia

Per-speculum examination

- Look for cervix and vagina for any associated pathology
- Presence of clots in the vagina, bleeding seen through the cervical os
- Any descent of cervix, cystocele, rectocele
- Any polyp protruding through or arising from cervix

Mrs P's per-vaginal examination (p/v) findings were as follows:
Cervix was firm and regular, pointing downwards, uterus anteverted size corresponding and equivalent to 20 weeks pregnant uterus, irregular, firm, mobility present from side to side, non-tender. Cervical movements transmitted to the mass

In any case of lump abdomen, it is important to differentiate a uterine mass from an adnexal mass by the following points:[3]

- Uterus will not be felt separate from the uterine mass
- Movements of the mass felt per abdomen are transmitted to the cervix and vice versa in case of a uterine mass
- No groove will be felt between the mass and the uterus in contrast to an adnexal mass where a groove is found between the adnexal mass and uterus
  (The above 3 points may not hold true for a subserosal pedunculated fibroid)
- ***Hingorani's sign***: examination of the patient in Trendelenburg position results in upward displacement of the adnexal mass and one can lucidly elicit the groove between the uterus and an adnexal mass.

Q.3. What are the causes of uterine enlargement? What is the differential diagnosis?

Ans:

1. Pregnancy: It must be ruled out in patients with history of amenorrhea/overdue periods prior to investigating other gynecological causes.
2. Uterine fibroid
3. Adenomyosis:
   a. Patients are often multiparous with complaints of menorrhagia and dysmenorrhea.

   b. It usually does not exceed 14 weeks in size.
   c. The uterus on P/V may be slightly soft and tender. Diagnosis can be confirmed on USG which shows localized or diffuse loss of endomyometrial junction with presence of subendometrial cysts. In the latter case, it is important to rule out endometrial cancer and it is here where an MRI has a crucial role. *Treatment is hysterectomy after which the diagnosis is confirmed on histology*.
4. Myohyperplasia: Clinical presentation simulates that of fibroid uterus and diagnosis is confirmed on histology.
5. Pyometra, hematometra: History and examination will be suggestive of causes conducive to cervical stenosis, e.g. Cervical cancer, tubercular endometritis, previous cervical amputation. Diagnosis is confirmed on sonography. Management consists of drainage of the intrauterine collection along with a cervical/endometrial biopsy followed by appropriate treatment of the underlying cause.
6. Malignancy of uterus:
   a. Uterine sarcoma
   b. Sarcomatous degeneration of a pre-existing neglected fibroid
   c. Endometrial cancer: As it usually presents in its early stages, such marked enlargement of the uterus is rarely seen.

Q.4. What investigations should be ordered in the above patient?

Ans:

1. Hemoglobin,
   Complete blood count (CBC) with peripheral smear (especially in menorrhagia/anemia and also as a part of pre-operative work up if planned for surgery)
2. USG pelvis: For mapping, number and size of fibroids. Trans-abdominal sonography (TAS) may not identify fibroids less than 2 cm in size. Findings on USG include[4]
   a. uterine contour irregularity and enlargement are the most common findings
   b. hypoechoic heterogeneous well-defined lesions within the myometrium causing distortion of uterine outline, any protrusion into the endometrial cavity.
   c. degenerative changes can take on different echogenic patterns such as irregular central anechoic areas seen in cystic degeneration or bright highly echogenic areas with distal shadowing seen in calcific degeneration.
   d. hydroureter or hydronephrosis in cases of large/broad ligament fibroids
3. Pap smear
4. Endometrial aspiration and Endocervical curettage (ECC): Mandatory in patients with history of irregular bleeding PV to rule out associated endometrial pathology.
5. IVP: Recommended in cases of large subserosal fibroids, cervical and lower uterine segment fibroids, and broad ligament fibroids to see for relation of ureter and any signs of compression as cervical and broad ligament fibroids may displace the ureter.
6. Investigations for PAC work-up prior to surgery: Complete blood count, blood sugar, kidney function tests, chest X-ray, ECG, urine routine and microscopy.

Q. 5. Classify the different types of fibroids.

Ans:

Fibroids are classified according to their anatomical location[1-3]

1. Body of uterus
   a. intramural/interstitial (75%)
   b. subserous (15%)
      i. true subserous
      ii. broad ligament fibroid (pseudo)
      iii. wandering/parasitic
   c. submucous (5%)
      i. sessile
      ii. pedunculated/polyp

2. cervical
   a. anterior
   b. posterior
   c. central – produces "Lantern on Dome of St. Paul's appearance" due to uterus sitting on top of the expanded cervix.
   d. Lateral
3. Intravenous leiomyomatosis–polypoid intravascular projections into the veins of the parametrium and broad ligament.
4. Leiomyomatosis peritonealis disseminata – benign nodules replace peritoneal deciduas on subperitoneal surface of the uterus and other pelvic and abdominal viscera due to a reparative process.

Q.6. How can one distinguish between true and false broad ligament fibroids?

Ans:

	True	*False*
Origin	Arise from the muscle fibers in parametrium	Arise from the lateral wall of the uterine body/ cervix and bulge between layers of the broad ligament
Uterine artery	Lies beneath and on the inner side (medial) of the tumor	Uterine artery is displaced outwards and upwards
Ureter	Displaced inwards- lies medial to the tumor	Displaced outwards towards the pelvic wall- lies lateral to the tumor

Q.7. What complications can be anticipated in a patient with fibroid uterus?

Ans:

1. Degenerations
   a. Hyaline degeneration (most common)
   b. Atrophic degeneration
   c. Fatty degeneration
   d. Calcific degeneration
   e. Red degeneration – in mid-pregnancy and puerperium (explained later)
2. Vascular changes – telangiectasis and lymphangiectasis inside the myoma
3. Necrosis and infection – seen in submucous fibroid polyps
4. Sarcomatous change – Leiomyosarcoma follows less than 0.1% of fibroids. It is suspected when there is sudden enlargement of a fibroid, fibroid along with postmenopausal bleeding, or recurrence of a fibroid polyp after its removal.
5. Torsion of subserous pedunculated fibroid
6. Hemorrhage – It can be intracapsular or intraperitoneal due to rupture of surface veins of a subserous fibroid.
7. Rare paraneoplastic complications – polycythemia, thromboembolism, hypoglycemia, hypokalemia.

In the above patient Mrs P, ultrasonography revealed multiple fibroids in the uterus. How will you manage her?

As the above patient is 45 years and has completed her family, the best treatment would be hysterectomy, which can be performed either by laparotomy or laparoscopy.

Q.8. What are the indications of treatment of fibroids?

Ans: Asymptomatic fibroids less than 12 weeks don't require treatment but must be followed up regulary at 6 monthly intervals.

Indications for treatment:

1. asymptomatic fibroid > 12 weeks in size
2. abnormal uterine bleeding
3. pain and pressure symptoms
4. urinary tract symptoms or obstruction
5. infertility after excluding other causes
6. recurrent pregnancy loss

7. rapid growth (defined as a gain of 6 weeks or more in gestational size within a year or less)
8. growth after menopause

Q.9. What are the various treatment modalities?

Ans: Treatment needs to be individualized depending on presentation age, parity etc.

1. Medical management
2. Non invasive procedure: Magnetic resonance imaging guided focused ultrasound surgery (MRgFUS)
3. Minimally invasive techniques
   a. Uterine artery embolization
   b. Myolysis
4. Surgery
   a. polypectomy
   b. hysteroscopic resection
   c. myomectomy – open/laparoscopic
   d. Hysterectomy- Total abdominal hysterectomy/ Non descent vaginal hysterectomy/ laparoscopic assisted vaginal hysterectomy/ Total laparoscopic hysterectomy

Q.10. What is the role of medical management in a patient with fibroid uterus?

Ans: Medical therapy can be used for either one of the following two purposes (Refer Table 19.1):

Temporary palliation	*As an alternative to surgery*
a. To improve menorrhagia	a. Perimenopausal women
b. Correct anemia before surgery	b. Women medically unfit for surgery
c. To minimize size and vascularity and reduce blood loss during surgery	c. Women unwilling to undergo surgery
d. To facilitate laparoscopic surgery/allow use of a transverse incision	
e. Temporary postponement of surgery	

Magnetic resonance imaging guided focused ultrasound surgery (MRgFUS)[6,7]:

It is a non-invasive procedure which destroys myoma tissue using ultrasonic energy but still in the research phase.

Selection criteria includes:

1. fibroids between 4 and 10 cm size
2. completed family
3. perimenopausal age group
4. maximum depth of subcutaneous tissue to fibroid < 12 cm
5. fibroids clearly visible on MRI

Procedure: It is a non-invasive outpatient procedure that uses high intensity focused ultrasound waves to ablate the fibroid tissue. This method of tissue destruction is thermal ablation. During the procedure, an interventional radiologist uses magnetic resonance imaging (MRI) to provide a three-dimensional view of the targeted tissue, allowing for precise focusing and delivery of the ultrasound energy. MRI also enables the physician to monitor tissue temperature in real-time to ensure adequate but safe heating of the target. The procedure is FDA approved for treating uterine fibroids. Immediate imaging of the treated area following MRgFU helps the physician determine if the treatment was successful. Symptoms abate within 3 months of the procedure.

Complications: Minor skin burns, worsening menorrhagia, and non target sonification of uterine serosa.

Q.11. What is the role and indications of uterine artery embolization in the treatment of fibroid uterus?

Ans:

Indications: Symptomatic uterine fibroids in women who have completed child bearing but are unfit for surgery (morbid obesity, diabetes mellitus, multiple medical problems) or not willing to undergo surgery.

Table 19.1: Various drugs available for treatment of fibroids[5]

Drug	*Dosage*	*Advantages*	*Disadvantages*
Antifibrinolytics	Tranexamic acid: 1-4 gm/day during days of heavy flow	• Significant reduction in the amount of blood loss • Improvement of anemia	• No effect on the size of the fibroid
GnRH agonist	Goserelin (Zoladex): 3.6 mg every 28 days for 3-6 months, subcutaneous	• 40-60% reduction in size of fibroids • Reduction of intraoperative blood loss	• Hypoestrogenic side effects limits its use to no more than 6 months • Rebound increase in size after discontinuation of therapy • Loss of surgical planes during surgery • Small seedling fibroids may be missed during surgery and reappear later • Expensive
GnRH antagonist	Cetrorelix, Ganirelix	• Quicker response to therapy (2-4 weeks) • No flare up effects	• Needs further evaluation
Antiandrogens	Danazol: 200-400 mg PO/day for 6-12 months Gestrinone	• Decreases fibroid volume and bleeding • No hypoestrogenic S/E • Fibroids do not regrow after discontinuation of therapy	• Androgenic side effects: acne, hirsutism, hoarse voice, altered libido, decreased breast size, headaches
Progesterone antagonist	Mifepristone: 25-30 mg/day for 3-6 months	• 25-75% reduction in size of fibroid • Amenorrhea and improves Hb levels • No bone loss	• Endometrial hyperplasias develop on long-term use • S/E: hot flushes, joint pains, deranged LFTs
Selective progesterone Receptor modulator	Asoprisnil	• Suppresses menstruation • Improves Hb level • Inhibits growth of the fibroid • No effect on ovulation or endometrial proliferation	• Further evaluation required
Aromatase inhibitors	Fadrazole	• Under trial	• Under trial
Progesterone IUDs	Mirena	• Reduces blood loss • Reduction of size of the uterus • Improves Hb level due to suppression of menstruation • Also provides effective contraception • Effective for 5 years	• Expensive • Not suited for uterus > 12 weeks size • Can't be used where the uterine cavity is distorted

Procedure: It is performed by an interventional radiologist under deep sedation or local anesthesia. Percutaneous single femoral artery catheterization is done through which bilateral uterine arteries are catheterized and occluded with polyvinyl alcohol particles (PVA, 500-710 um diameter) to produce ischemic necrosis of the fibroid. The procedure is followed by parenteral antibiotics.

Advantages:

1. least invasive procedure which avoids surgery
2. shorter hospital stay and recovery
3. success rate between 85 and 95%
4. 50% reduction in uterine size after 6 months
5. fewer incidence of major complications

Disadvantages:

1. Not suitable for women desirous of preserving their fertility but conclusive data is still lacking regarding its safety.
2. Can only be performed in a setting with an interventional radiologist.

Complications: They are seen in 1-5% of procedures.

1. Abdominal cramps
2. Post-embolization syndrome: Results from necrosis of the fibroid and release of inflammatory mediators. Patients complain of fever, nausea, vomiting, anorexia and malaise.
3. Chronic vaginal discharge
4. Target organ embolization: uterine infection, sloughing of the fibroid, sexual dysfunction
5. Non target organ embolization of ovary: menopausal symptoms, amenorrhea
6. Chances of emergency hysterectomy in 1% in case of infected fibroids, severe post-embolization syndrome, procedural failure
7. Complications in subsequent pregnancy: spontaneous abortions, placental insufficiency, preterm delivery, PPH and uterine rupture

Contraindications:

1. Acute pelvic infection
2. Uncontrolled coagulopathy
3. Contrast allergy
4. Immunocompromised patient
5. Malignancy
6. Undiagnosed pelvic mass
7. Pedunculated subserosal fibroid- can cause peritonitis and bowel adhesions
8. Adenomyosis – poor response to UAE
9. Pregnancy
10. Arteriovenous malformations

Q.12. What is myolysis?

Ans: Laparoscopic procedure which destroys the myoma employing either laser, cryotherapy, or electrosurgical energy. High recurrence rates and extensive adhesion formation limits its use.

Ideal candidates are perimenopausal women having symptomatic fibroids between 3 and 10 cm or uterine size less than 14 weeks.

ACOG criteria for hysterectomy for leiomyomata

Confirmation of Indication:

1. Asymptomatic leiomyomata of such size that they are palpable abdominally (12 weeks) and are a concern to the patient
2. Excessive uterine bleeding evidenced by *either* of the following:
   a. Profuse bleeding with flooding or clots or repetitive periods lasting more than 8 days
   b. Anemia due to acute or chronic blood loss
3. Pelvic discomfort caused by myomata (a/b/c)
   a. Acute and severe.
   b. Chronic lower abdominal or low back pressurec.
   c. Bladder pressure with urinary frequency not due to urinary tract infection.

Actions Prior to Procedure:

1. Confirm the absence of cervical malignancy
2. Eliminate anovulation and other causes of abnormal bleeding
3. When abnormal bleeding is present, confirm the absence of endometrial malignancy
4. Assess surgical risk from anemia and need for treatment
5. Consider patient's medical and psychologic risks concerning hysterectomy

Contraindication:
1. Desire to maintain fertility, in which case myomectomy should be considered
2. Asymptomatic leiomyomata of size less than 12 weeks' gestation size determined by physical examination or ultrasound examination

Q.13. What are the indications of emergency hysterectomy for uterine fibroid?

Ans:
1. uncontrolled bleeding from the fibroid
2. intraperitoneal hemorrhage
3. torsion in older patients.

Q.14. What precautions must one take during hysterectomy of cervical fibroids?

Ans: There are greater chances of inadvertent injury to the ureter, bladder and uterine vessels in this case. The principle to be followed is enucleation followed by hysterectomy to minimize injury to the ureter. Alternatively, one can also give preoperative GnRH analogues 3 months prior to facilitate surgery.

Q.15. How do fibroids affect the course of pregnancy?

Ans:
1. Abortions/recurrent pregnancy loss due to:
   a. interference with enlargement of the uterus
   b. initiation of abnormal uterine contractions
   c. inefficient placentation
2. Placental abruption
3. Preterm labor
4. IUGR- due to
   a. defective implantation of the placenta
   b. poorly developed endometrium
   c. reduced space for the growing fetus and placenta
5. Malposition and malpresentations: contributing factors are-
   a. distortion of shape of the uterine cavity
   b. prevention of head engagement
6. In coordinate uterine contractions leading to dysfunctional labour and greater incidence of Cesarean section.
7. Abnormal uterine action – may lead to
   a. retained placenta
   b. PPH
   c. delayed involution
8. Obstructed labor – seen with cervical and broad ligament fibroids
9. Fetal anomalies
   a. Limb reduction
   b. Congenital torticollis
   c. Head deformities

Q.16. What changes can occur in a fibroid during pregnancy?

Ans:
1. increase in size and vascularity of fibroids
2. torsion of subserous fibroids
3. infection in puerperium
4. red/carneous degeneration: It is common in mid-pregnancy due to rapid growth of the fibroid leading to ischemic necrosis and release of inflammatory mediators. Patients present with fever, nausea, vomiting and acute abdominal pain. Examination reveals localized tenderness over the fibroid. Management is conservative consisting of bed rest and analgesics. There is no role of surgery.

Q.17. What is to be done for fibroids encountered during cesarean section?

Ans: Fibroids encountered during surgery should be left untouched (but mentioned in detail in the peroperative notes and discharge ticket) due to risk of excessive blood loss. Surgery, if required, can be taken up 3 months after delivery. Conditions where emergency myomectomy may be required during pregnancy or cesarean section are:
1. Intractable pain
2. Removal of a pedunculated subserosal fibroid at the time of CS

3. Large fibroid hindering uterine repair
4. Fibroid interfering with delivery of the fetus from the uterus
5. Incarcerated fibroid
6. Rapidly enlarging fibroid having compressive symptoms

CASE 2

A 24 years old lady, Mrs R married for three years, seeking treatment for primary infertility presents with a lump lower abdomen equivalent to 16 weeks of pregnant uterus.

Q.18. What are the causes of infertility in a patient with fibroid uterus?

Ans:

1. Uterine factors:
   a. Difficult sperm transport: Due to distortion and elongation of the uterine cavity and hinderance with rhythmic uterine contractions
   b. Defective nidation: Due to congested and dilated endometrial venous plexus. Atrophy and ulceration over a submucous fibroid interfere with nidation.
2. Tubal factors:
   a. Cornual block due to position of the fibroid
   b. Elongation of the tube over a large subserosal fibroid
   c. Associated salpingitis
3. Ovarian: Anovulation
4. Peritoneal: Endometriosis
5. Idiopathic.

Q.19. What are other gynecological diseases associated with fibroid uterus?

Ans:

1. Anovulation and multiple follicular ovarian cysts
2. Endometrial hyperplasia
3. Endometrial carcinoma (3%)
4. Endometriosis/adenomyosis (30%)
5. Salpingo-oophoritis (15%)

List the important investigations to be performed in the above patient.

1. Husband semen analysis – to evaluate the male partner for infertility
2. Hysterosalpingography – rule out tubal block and to see if the fibroid is distorting the endometrial cavity

(All other investigations which have been described previously will remain the same).

Q.20. How will you manage the above patient Mrs R?

Ans: After excluding other causes of infertility myomectomy should be planned either by laparoscopically or by laparotomy.

Q.21. What are the various types of myomectomy?

Ans: Myomectomy procedures:

1. Laparotomy (Abdominal myomectomy)
2. Hysteroscopic myomectomy: suited for submucous fibroids/polyps
3. Laparoscopic myomectomy: particularly for removing pedunculated subserosal fibroids and small subserosal fibroids not growing too deeply into the uterus. The fibroids are morcellated and suctioned out through the laparoscope.

Newer modifications of laparoscopic myomectomy:[9-11]

a. *Laparoscopy assisted myomectomy:* Combines laparoscopy with 2-4 cm abdominal incision done for myoma more than 8 cm or in deep myoma requiring extensive morcellation and uterine repair in layers. The advantage is reduced operating time and reduced need for extensive laparoscopic experience.
b. *Laparoscopy assisted transvaginal myomectomy:* Done for extensive and deeply infiltrating fundal and posterior wall fibroid. Laparoscopy is done to confirm the size, location and number of myoma. Intra-

myometrial vasopressin is injected. Posterior colpotomy is done to deliver the myoma and uterus. After myoma removal, uterine reconstruction is performed by conventional suturing transvaginally. Uterus is replaced back into its anatomical position and colpotomy repaired. Final laparoscopic survey done and peritoneal lavage given.

c. *Robot assisted laparoscopic myomectomy with the Da Vinci surgical system:* Use of robot assisted technology overcomes the challenges encountered with uterine incision, enucleation, repair and extraction that are seen with conventional laparoscopic myomectomy. This provides surgeons with improved dexterity and precision coupled with advanced imaging and allows endoscopic approach to be more accurately modeled after open surgical technique.

d. *Laparoscopic myoma coagulation [myolysis] and cryosurgery:* Blood supply of the fibroid is coagulated using ND-YAG laser or with long bipolar needle electrode. The main advantage is no regrowth of the myoma. However, risk of uterine rupture in future pregnancy has been reported. In cryomyolysis, myoma is frozen with liquid nitrogen delivered with a special probe. The efficacy of this technique need to be determined by further trials.

Q.22. What are the ACOG criteria for myomectomy in infertility patients?

Ans:

1. Patients in the reproductive age group and desirous of future fertility
2. Unexplained infertility with distorted uterine cavity due to fibroid
3. Unexplained RPL
4. Fibroid in lower part of the uterus and likely to complicate delivery

ACOG criteria for myomectomy in infertility patients

Leiomyomata in infertility patients, as a probable factor in failure to conceive or in recurrent pregnancy loss

In the presence of failure to conceive or recurrent pregnancy loss:

1. Presence of leiomyomata of sufficient size or specific location to be a probable factor
2. No more likely explanation exists for failure to conceive or recurrent pregnancy loss

Actions Prior to Procedure:

1. Evaluate other causes of male and female infertility or recurrent pregnancy loss
2. Evaluate the endometrial cavity and fallopian tubes, e.g. hysterosalpingogram
3. Document discussion that complexity of disease process may require hysterectomy.

Q.23. How will you proceed for a myomectomy (laparotomy)?

Ans:

- Surgery is planned in the postmenstrual phase
- Optimal Hb status and adequate arrangement of blood prior to surgery (at least 10 gm%) should be ensured.

The patient is counseled regarding the following points:

1. The patient may require hysterectomy in case of excessive haemorrhage.
2. Chances of pregnancy after myomectomy: 40-60%
3. Chances of recurrence/persistence of fibroid after myomectomy: 30-50%
4. Risk of re-laparotomy after myomectomy: 20-25%
5. Chances of persistence of menorrhagia after myomectomy: 1-5%

Steps of myomectomy:

1. Induction of the patient, appropriate position, clean and drape

2. After the abdomen is entered, uterine anatomy is identified (is often distorted) by noting position of the round ligaments. The adnexa are also noted and ureters are identified
   a. Prevention of intraoperative hemorrhage:
      i. Occlusion of uterine artery (through a transparent area in the broad ligament around the cervix at the level of lower uterine isthmus) and ovarian artery (around the infundibulopelvic ligament through the same hole in broad ligament)- either tourniquet or Bonney's myomectomy clamp can be used. It is important to release the tourniquet every 30 min as prolonged occlusion of blood supply leads to ischemic necrosis of tissues and release of histamines which can result in shock.
      ii. Vasopressin injection over the fibroid: 20 U of vasopressin diluted in 20 ml of NS
      iii. Controlled hypotensive anesthesia (less popular): Sodium nitroprusside or NTG is used to maintain mean BP 60 mm Hg and the patient is placed in Trendelenburg position.
   b. A longitudinal incision is given over the most prominent part of the fibroid and deepened till the plane between the capsule and fibroid is reached. All myomas should be removed through a single incision. Posterior wall fibroids are also removed through an anterior incision by transcavitary approach. ***Incision is not given on the posterior surface to avoid adhesions which may impede future fertility.*** Another advantage of an anterior incision is easy accessibility to clinical suspicion of imminent scar dehiscence during pregnancy by eliciting scar tenderness. The fibroid is separated from the capsule by sharp and blunt dissection. The fibroid is removed by myoma screw. A cut section is done and the specimen is sent for histopathology
   c. Myometrial dead space is closed in layers. It is important to maintain hemostasis and at the same time ensure patency of the endometrial cavity if the cavity has been opened. The latter can be done either by inserting a dilator through the cervix in the uterine cavity or staining the endometrium using methylene blue prior to surgery.
   d. Abdomen is closed in layers.

Q.24. What is Bonney's hood operation?

Ans: It is done to remove a large fundal fibroid. A low transverse incision is made on the myoma over the anterior uterine surface. After removal of the fibroid, the capsule is trimmed and is sewn over the anterior uterine wall. This procedure minimizes adhesion formation.

Q.25. How is myomectomy performed for a central cervical fibroid?

Ans: After incising the peritoneum of the uterovesical pouch and dissecting the bladder down, hemisection of the uterus is done from above downwards to reach the fibroid which is then enucleated. The dead space is obliterated without closing the cervical canal followed by repair of the bisected uterus.

Q.26. What are the advantages and disadvantages of laparoscopic myomectomy?

Ans:

Advantages:

1. Shorter hospital stay
2. Lower morbidity
3. cosmetically better

Disadvantages:

1. Requires expertise
2. laparoscopic myomectomy is limited to patients with fibroid size less than 8 cm or less than 4 fibroids .

3. high recurrence rates (35%)
4. greater adhesion formation
5. Greater chances of rupture in pregnancy

Q.27. What postoperative advice will you give to a patient after myomectomy?

Ans: Because fibroids can grow back, it is best to try to conceive as soon after a myomectomy as is safely possible. It is recommended that patients should wait 4 to 6 months after surgery to allow the uterus to heal before pregnancy. It should also be mentioned in the discharge slip regarding entry into the endometrial cavity which mandates an elective cesarean section in the subsequent pregnancy at 37 completed weeks of pregnancy.

CASE 3

A 38 years old multiparous lady attends the Gynae OPD with menometrorrhagia and severe dysmenorrhea for last three months and mild pallor. On examination there was a polyp seen through cervical os about 3 centimeters diameter

Q.28. How can you explain metrorrhagia in this patient?

Ans:

1. Ulceration of submucous fibroid polyp
2. Bleeding from the torn vessels of the sloughing base of the polyp
3. Associated endometrial cancer.

Differential diagnosis:

- **Polyp**
  1. Benign – Mucous polyp, Fibroid polyp
  2. Malignant – *De novo* or secondary change
- **Chronic inversion of the uterus**

Diagnosis:

1. Sound test: It is used to differentiate a fibroid polyp from chronic inversion. If a uterine sound is passed all around between the pedicle and the cervical os, it is a polyp. It cannot be passed in case of chronic inversion.
2. USG: It confirms the presence of uterine polyps. Mucous polyps can be differentiated from fibroid polyps by the fact that the former are hyperechoic whereas the latter appear hypoechoic on USG.
3. Saline infusion sonohysterography: confirms the presence of uterine polyps in case of doubt.
4. HSG: shows a filling defect
5. Hysteroscopy: It carries the advantage of being a combined diagnostic and therapeutic procedure.

European Soceity of Hysteroscopy Classification of Submucous Fibroids (depending on the degree of myometrial extension of the fibroid)

Type 0	Submucous polyps lying entirely in the endometrial cavity
Type 1	< 50% extension into the myometrium
Type 2	> 50% extension into the myometrium

Q.29. How should a fibroid polyp be managed?

Ans: The management depends on the following factors:

1. Age of the patient
2. Desire for future fertility
3. Associated uterine pathology
4. Location of the polyp
   1. Polyp confined to the cavity
      a. Hysteroscopic resection of the polyp with endometrial sampling (expertise needed).
      b. Hysterectomy with the polyp *in situ*
   2. Polyp lying in the cervical canal
      a. Thin pedicle: Polypectomy with endometrial sampling
      b. Thick/inaccessible pedicle: Vaginal myomectomy/hysterectomy
      c. Uterine preservation not desired: Hysterectomy with the polyp *in situ*

Pre-operative criteria for vaginal myomectomy:

1. Uterine size less than or equal to 16 weeks
2. Good uterine mobility

3. Adequate vaginal access
4. Intramural/subserosal myomas
5. Absence of adnexal pathology

3. Big fibroids lying in the vagina: The polyp is removed by morcellation followed by a transfixation suture on the pedicle and removal of redundant pedicle distal to the ligature.

Q.30. What are the contraindications of hysteroscopic resection of submucous fibroid?[12]

Ans:

1. Endometrial cancer
2. Local infection
3. Extensive intramural component
4. Severe/persistent menorrhagia leading to severe anemia

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Asmita Muthal Rathore

20 Prolapse Uterus

With increased lifespan of women, the problems of pelvic floor dysfunction are increasing and becoming major health issue. Though, generally not life-threatening, they significantly impair physical functioning, emotional well-being and the quality of life. The lifetime risk of undergoing surgery for prolapse or urinary incontinence for a woman is 11%.[1]

This chapter will discuss the clinical evaluation and management of few cases of pelvic organ prolapse. The traditional goal of treatment to restore normal pelvic anatomy does not necessarily return to normal function of pelvic organs and therefore evaluation of women should also focus on specific symptoms and the degree to which they affect quality of life. The definitive treatment of prolapse is nearly always some sort of surgery but should be performed only if the condition is causing symptoms. If the prolapse is incidental or it is not certain that the patients symptoms are attributable to it, the operation is best deferred.[2]

CASE 1

A 42-year-old Mrs X, Para 3 presents to gynecology outpatient department with complaint of mass descending per vaginum for one year and difficulty in initiating micturition.

Q.1. What details will you ask in history?

Ans: The history taken in detail can give us useful information regarding etiology of prolapse, especially the treatable factors and also helps us in making management decisions.

- History of presenting complaints – should include duration of prolapse, rate of increase in severity, any bladder and bowel complaints. Irreducibility of prolapse indicates long-standing nature of the problem and is due to congestion, edema and hypertrophy of the tissues.
- History of precipitating factor–like chronic cough, constipation, any abdominal swelling should be elicited. They need to taken care of before surgical treatment is instituted so as to reduce risk of recurrence.
- Obstetric history—the most common aggravating factors are birth injury and postmenopausal tissue atrophy. A detailed obstetric history should elicit factors like pregnancies at short intervals, prolonged labor, big babies, and lack of perineal exercises. Parity of the patient, desire to preserve fertility should be noted as it will affect the choice of treatment option.
- Menstrual history—postmenopausal state should be noted as deficiency of estrogen around menopause results in weakening of connective tissue and aggravation of prolapse. Any associated menstrual abnormality may need further evaluation and may modify choice of treatment.
- Other symptoms—the presence of white discharge, metrorrhagia or postcoital bleeding

may be due to decubitus ulcer but should be appropriately evaluated. It is vital to assess the urinary tract, defecatory or sexual dysfunction. History of any other associated problems should be asked to get overall picture of womans health status.

- Treatment History—any treatment in past especially in form of pessary or surgery and its results should be noted.

Q.2. What are the common urinary symptoms in prolapse and their mechanism?

Ans: The woman with prolapse may present with variety of urinary symptoms.

- Difficulty in initiating micturition is common problem in women with large cystocele. It is difficult to empty the bladder and the difficulty increases with straining as bladder base and trigone descend below the level of urethra. She can empty the bladder only after reducing the mass digitally.
- Frequency and dysuria—symptoms suggestive of cystitis can be seen as incomplete emptying of bladder leads to increased risk of cystitis.
- Stress urinary incontinence may be present if prolapse is associated with descent of urethrovesical junction.
- Rarely retention of urine can also be seen.

Q.3 What important points will you note in examination of this woman?

Ans:

- The general examination—should note general condition of patient and assess mental status, body mass index, nutritional status. Since many women will most likely need surgical intervention, presence of anemia, any lymphadenopathy should be looked for.
- The abdominal examination—should focus on hernial sites, any abdominal mass or free fluid in abdomen.
- The pelvic examination is most important to assess severity of prolapse and plan surgical procedure. The goal is to objectively assess the anatomy of pelvic floor and organs and to attempt to correlate symptoms with anatomic findings. Local examination should be performed in dorsal lithotomy position.
  - Inspection of external genitalia for any lesions, rashes, etc. should be done. The perineum should also be inspected for any evidence of old healed perineal tears, integrity of perineal body.
  - Eliciting stress incontinence—the bladder should be full if there is history of stress incontinence and any leakage of urine on coughing should be noted. If present, then Bonneys test should be performed by elevating bladder neck with index and middle fingers on either side which should stop leakage of urine on stress.
  - Examination of prolapse—the degree of prolapse should be assessed after maximum straining.
    - Look for evidence of hypertrophy of cervix, congestion, edema, decubitus ulcer, keratinization, infection or vaginal atrophy.
    - Note the degree of descent of cervix, anterior and posterior vaginal wall and quantify the degree of support using POPQ system.
    - Identify the specific anatomic defects—that can be addressed with surgical intervention. The dominant prolapse is considered to be first hernia to descend or the most dependent part of prolapse and provides key clue about where most significant fascial damage is located.[3]
  - Bimanual pelvic examination is done to note direction of uterus, size and mobility of uterus and any adnexal mass and tenderness. The levator tone should be assessed.

Q.4. How do you look for tone of levator ani muscle?

Ans: The levator tone is assessed by palpating vaginal wall at 5 and 7 o' clock position about 2-4 cm above hymen. The woman is asked to squeeze her vaginal muscles as though she is holding gas or stopping urine flow. The strength is graded from 0 to 5 using modified oxford scale [4] as follows:

- Grade 0 –no discernible pelvic floor contraction
- Grade 1 –a flicker under finger.
- Grade 2 – a weak contraction or increase in tension without any discernible lift or squeeze
- Grade 3 – a moderate contraction with partial lifting of postvaginal wall and squeezing of finger, contraction > grade 3 is visible.
- Grade 4–good pelvic contraction causing elevation of postvaginal wall against resistance and indrawing of perineum.
- Grade 5 – strong contraction of pelvic floor against strong resistance.

Levator muscles should also be palpated for tenderness or spasm. The integrity of the pudendal nerve is tested by eliciting anal and bulbocavernosus reflexes. The anal reflex is elicited by gently stroking perianal skin which results in contraction of external anal sphincter and in bulbocavernosus reflex, the bulbocavernosus and ischiocavernosus muscles contract in response to tapping the clitoris.

Q.5. What are the different classifications of prolapse and their advantages?

Ans: Though there are many classifications, the one traditionally used is Shaw's classification and now widely recommended worldwide is the the Pelvic Organ Prolapse Quantification system [POPQ] [5] which objectively quantifies the prolapse.
Shaw's classification – This is the simplest and most widely used in the past.

It classifies prolapse in four stages and uses ischial spine as reference point.

- First degree-descent of uterus below ischial spine but cervix remains within the introitus.
- Second degree–descent of cervix up to introitus
- Third degree–descent of cervix outside introitus.
- Fourth degree–entire uterus prolapses outside the vulva.

POPQ system–It is approved by International Continence Society in 1995 and more accurately quantifies pelvic support findings. It allows accurate quantification for scientific comparisons and is thus reproducible. In this system the positions of 9 sites are measured in cm in relation to hymen (negative number for proximal and positive number for distal) and recorded in grid form (Fig. 20.1). These 9 sites are as follows:

1. Aa–point 3 cm proximal to urethral meatus on anterior vaginal wall
2. Ba–the most distal portion of upper anterior vaginal wall
3. C–cervix or vaginal cuff
4. D–posterior vaginal fornix
5. Ap–point 3 cm proximal to hymen on post vaginal wall
6. Bp–most distal position on posterior vaginal wall

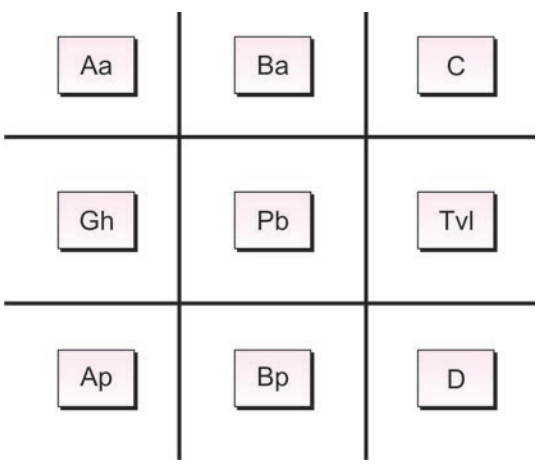

Fig. 20.1: POPQ staging

7. Gh–the diameter of genital hiatus (measured from middle of external urinary meatus to posterior midline of hymen).
8. Pb–the width of perineal body (measured from posterior midline of hymen to the midanal opening).
9. Tvl–total vaginal length (greatest depth of vagina in cm after reducing the prolapse).

It should also be recorded if the measurements were taken in lithotomy or standing position and whether straining or traction was applied.

Based on measurements at above 9 sites the prolapse is staged from 0-4 according to most distal position of prolapse -

- Stage 0–no prolapse is demonstrated.
- Stage I–the criteria for stage 0 are not met but the prolapse is >1cm above the hymen.
- Stage II–within 1 cm of hymen (i.e., the quantification value is > -1 but < +1)
- Stage III–more than stage II but 2 cm less than total vaginal length [i.e., quantification value > +1 but < + (TVL-2)].
- Stage IV–complete eversion of genital tract [ie, quantification value ≥ + (TVL-2)].

Q.6. How will you perform POPQ staging and what is the stage of prolapse in your patient?

Ans: Women is placed in lithotomy position. Ayres spatula is used for measurements and grid with 3 columns and rows is drawn and labeled with patients name.

- First measurement of genital hiatus and perineal body is completed and entered in grid.
- Then speculum is inserted and Tvl is measured with spatula.
- Points C and D are next measured during maximal Valsalva's maneuver.
- Lastly points Aa, Ba, Ap and Bp are measured.

The severity of prolapse in my patient is Stage 4 with leading point C, [lithotomy position with straining] with decubitus ulcer.

The quantification in my patient is as follows (Fig. 20.2)

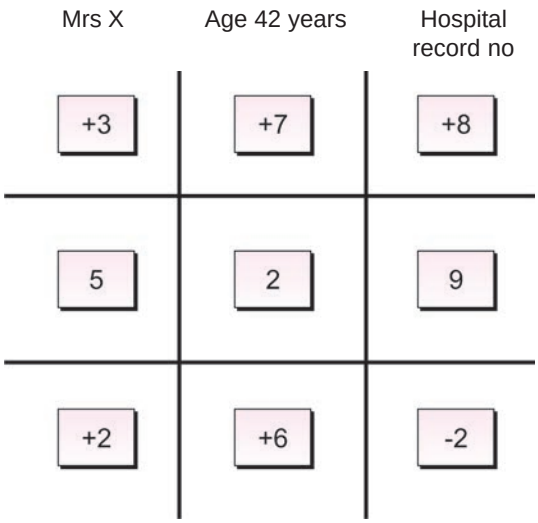

Fig. 20.2: POPQ staging of Mrs X

Q.7. What is differential diagnosis of prolapse uterus?

Ans: The common differential diagnosis of prolapse uterus are:

- Gartner cyst or anterior vaginal wall cyst may look similar to cystocele but is not reducible.
- Congenital elongation of cervix—though congenital, elongation may many time present for the first time after childbirth. It is identified by deep fornices and long infravaginal portion of cervix.
- Fibroid polyp coming out of vagina may look like prolapse but can be diagnosed by rim of cervix felt all around the tumor and associated menstrual complaints.
- Chronic inversion can also mimic prolapse.

Q.8. How will you investigate your patient?

Ans: The woman should have–

- Baseline assessment - of her general condition by having complete hemogram, routine urine analysis.
- Urine culture and sensitivity—It is mandatory to rule out urinary tract infection (UTI).

- Other investigations—should be directed by presence of associated factors like X-ray chest in women with chronic cough.
- Complete preoperative assessment for anesthesia—should be done in women planned for surgical treatment which will include blood sugar estimation, renal function tests, ECG and chest X-ray or any other investigation as advised by anesthesiologists.
- Special investigations—in woman with urinary, defecatory or sexual dysfunction further evaluation by appropriate consultation and investigations like urodynamic studies should be done.

Q.9. What is decubitus ulcer and how will you manage it?

Ans: The decubitus ulcer is benign and is present on dependant part. It is usually an ischemic process due to venous stasis resulting in tissue anoxia. The decubitus ulcer is treated by keeping the prolapse reduced, which will restore circulation and help in healing. Prolapse can be kept in reduced position by packing. Packing with glycerin-acriflavin may help if tissues are hypertrophied and edematous.

In an atrophic vagina, application of estrogen cream CEE 0.625 mg/day for 2-3 weeks will help in tissue vascularisation and improve healing power of tissues, but should be stopped at least 2 weeks prior to surgery.

If hospitalization is not possible for regular packing, option of insertion of pessary for short duration can be considered.

Q.10. How will you treat your patient?

Ans: Since my patient is 42 years of age, completed her family and symptomatic with prolapse interfering with her normal life, I will offer her surgical treatment.

Q.11. What are the objectives of surgical treatment of prolapse?

Ans:

- The aim of surgery is to restore the normal anatomy, to maintain or restore visceral and sexual function.
- The reconstruction of normal supports and normal vaginal length with its axis directed towards S3-S4 is important.
- Correct identification of deficiency whether central or lateral and strength of supporting ligaments will rationalize the choice of surgical treatment.
- Woman's wish for preserving sexual, menstrual and childbearing function will also influence choice of operation.

Q.12. What is DeLancey's classification of supports of uterus?

Ans: De Lancey[6] has classified supports of uterus in three levels:

Level I – apical support by uterosacral ligaments, Mackenrodt's ligament and paracolpium

Level II – midvaginal support due to lateral attachment to levator fascia

Level III – lower vaginal supports by perineal body or fusion of distal urethra to pubic bone.

Q.13. What are different surgical options in your patient?

Ans: In my patient surgeries which can be performed are:

Vaginal hysterectomy with site specific repair of anterior and posterior vaginal wall defects: The removal of uterus will permit better reconstruction of supports and thus reduce risk of recurrence. The uterus which may be site of unsuspected disease will be removed. Site specific repair will reconstruct the pelvic supports.

Manchester operation: It has advantage of preserving menstrual and childbearing potential. The sexual function may also be better after Manchester operation than after vaginal hysterectomy. The possibility of future surgery for

recurrence or other uterine pathology should be explained to the woman.

Hysteropexy: Uterine preservation in cases of uterovaginal prolapse was previously only considered if future fertility was a particular concern. However, today some women are inclined to retain uterus or cervix in an attempt to prevent change in postoperative sexual function. Sacrospinous ligament fixation with uterine conservation can be done vaginally and sacral hysteropexy which uses the same principles as sacral colpopexy and graft placement, can be performed by laparotomy or laparoscopy.

Q.14. What is site specific repair? What are the common sites of specific defects?

Ans: The specific defects in connective tissue network of pelvis are identified and the anatomic corrections of specific defects are performed in individual woman instead of midline placations in all women. The common sites for defects are:

Anterior vaginal wall: The main support to anterior vaginal wall is due to pubocervical septum which is attached superiorly to pericervical ring and cardinal ligaments, to arcus tendinous fascia of pelvis (ATFP) laterally and pubic tubercle on each side inferiorly. The common defects identified in this support are- central defect in pubocervical septum, paravaginal defect on one or both sides due to detachment of pubocervical septum from ATFP or transverse apical defect due to detachment of pubocervical septum from pericervical ring.

Posterior vaginal wall: The postvaginal wall is supported by rectovaginal septum which is attached superiorly to pericervical ring and uterosacral ligaments, laterally to levator fascia and inferiorly to perineal body. The common sites of injury to this septum are-transverse apical defect due to detachment from pericervical ring or uterosacral ligaments, midvaginal defects may be central or lateral due to injury or attenuation of levator fascia and inferior defect due to detachment from perineal body or there may be disruption of perineal body.

Q.15. How do you diagnose site specific defects?

Ans: The site specific defects can be diagnosed by clinical assessment and extesive dissection during surgery.

Clinically these can be identified by examining a woman in lithotomy position during straining and with help of ring forceps, Sims speculum and Bivalve Cusco's speculum. Look for rugosities of vagina which should correlate with with pattern of fascial breaks found during surgery.[3]

- Anterior vaginal wall defects can be midline, paravaginal or transverse apical. To assess them, posterior vaginal wall is retracted by Sims single bladed speculum and anterior vaginal wall inspected.

  Midline defect is suspected if midline bulge is noted when the lateral sulci and apex of vagina are supported with ring forceps.

  The paravaginal defects appear as blunting or descent of lateral sulcus on either side with straining. Bilateral paravaginal defects are assessed by opening the blades of ring forceps and supporting both lateral sulci. Unilateral paravaginal defects are assessed by supporting each sulcus to the sidewalls separately with closed ring forceps. The transverse defects are seen as distinct bulging out of anterior fornix which is smooth and without rugosities.
- Apical defects are seen in patients with uterine prolapse and are due to detachment of pericervical ring. The can be evaluated by using an open bivalve speculum that is withdrawn slowly while patient is straining when posterior and lateral walls seen bulging with downward mobility of cervix.
- Posterior vaginal wall defects are evaluated while supporting anterior vaginal wall and apex with Sims speculum and gradually withdrawing the single bladed speculum over posterior wall. Upper posterior wall prolapse appears as bulging down of posterior wall of vagina and cul-de-sac and are associated with apical and posterior entroceles. They are best evaluated by

doing rectovaginal examination and palpating for breaks and thickness of rectovaginal septum.

The clinical value of determining the location of defects is limited as most women have mixture of defects and the correlation between clinical and intraoperative findings is also not reliable.[7,8] The reproducibility of clinical examination is poor within the same examiner and in between different examiners.[9]

The specific defects become evident only during the intraoperative dissection. Thus irrespective of clinical findings, the extensive dissection should be performed during surgery to identify the defects. After complete dissection inspection is started for fascial defects keeping in mind the normal anatomy. The fascia is whitish, fibrous and in different plane from underlying visceral fascia. Irrigation with saline may make the color difference obvious. Careful inspection reveals the torn edges. The ability to recognize fascial defects is acquired during careful dissection and observation.

Q.17. How does traditional pelvic floor repair (anterior colporrhaphy and posterior colpo-perineorrhaphy) differ from site specific repair?

Ans:

- The traditional prolapse surgery did not emphasize on entire connective tissue network but incorrectly thought as organ specific prolapse, e.g. cystocele, rectocele, etc. and operations focused on reinforcing attenuated tissues surrounding these organs. The support for pelvis is not from ligaments and fascia but from the network of connective tissue that interwines as it surrounds organs.
- In surgical correction of prolapse by site specific repair, the portions of this entire network are used to restore the continuity and support the uterus, bladder, rectum, vagina. The prolapse is considered as hernia and the defects are repaired using nonabsorbable material and use of meshes if the defects are large.

1. The traditional anterior colporrhaphy involves polication of vesicovaginal fascia in the midline after dissection of vagina from bladder using absorbable or delayed absorbable suture material. There is only one midline repair. It does not expose or identify the white line and thus if the woman has a paravaginal defect, this midline plication may aggravate it resulting in recurrence. The site specific repair involves extensive dissection of vaginal wall and complete exposure of pubocervical fascia/septum from ATFP. The specific defects are identified and accordingly repair is performed using nonabsorbable suture material. The repair sites may be multiple depending on defects.
2. In posterior colporrhaphy, the epithelium of postvaginal wall is dissected and underlying endopelvic fascia of rectovaginal septum is plicated in the midline using chromic catgut, sometimes from vaginal apex to perineal body and levator muscles. Though this corrected midline bulge, it did not correct incomplete emptying and caused dyspareunia in many cases. In site specific the recto-vaginal septum is exposed and various defects are identified. There might be multiple suture line in rectovaginal septum after repair and they may be transverse, vertical in midline or laterally. The defects are repaired using nonabsorbable suture material.

Q.18. How do you identify and repair entero-cele during surgery?

Ans: The enterocele is identified by per speculum examination done under anesthesia just before surgery. The posterior lip of cervix is held by allis forceps and speculum is inserted in posterior fornix. The speculum is gradually withdrawn, when a bulge in upper third represents enterocele in which cough

impulse may be present. During surgery it is diagnosed after extensive dissection of posterior vaginal wall and identified by peritoneal sac and preperitoneal fat. Unidentified enterocele is common cause of recurrence and efforts should be taken to identify and repair it at the time of primary surgery.

- Repair during vaginal surgery-
  - Uterosacral ligament suspension—At the time of vaginal hysterectomy, enterocele should be dissected free, a high ligature of the peritoneum done by a purse string suture incorporating uterosacral ligaments drawing the cul-de-sac and uterosacral ligaments together and redundant peritoneum excised. The vaginal cuff is attached to cardinal uterosacral ligament complex to avoid descent of vaginal apex.
  - Mc call culdoplasty—It is a technique for enterocele repair useful when uterosacral ligaments are strong. It consists of rows of internal and external sutures. The internal suture is applied using nonabsorbable suture material and passes through one uterosacral ligament, then peritoneum of cul-de-sac as high as possible to obliterate enterocele sac and then passing through other side uterosacral ligament. The external suture uses delayed absorbable suture material and passes through vaginal wall on one side, ipsilateral uterosacral ligament, peritoneum of cul-de-sac and then uterosacral ligament of other side, finally coming out through other side vaginal wall. These sutures are tied in the end of surgery after all repairs are completed. It can be used as prophylaxis as well treatment of enterocele at the time of vaginal hysterectomy and also for vault prolapse.
- Repair during abdominal surgery—The enterocele can be repaired abdominally by Halbans technique or Moschcowitz operation.
  - Halbans Technique—The closure of cul-de-sac is done by sewing posterior vaginal wall to the rectum back to front from its most caudal to most cephalad position in parallel rows.
  - Moschcowitz technique—The cul-de-sac is closed with sequential concentric purse string sutures placed from caudal post cul-de-sac to the level of uterosacral ligaments incorporating peritoneum over the sacrum.

Q.19. What are the common intraoperative complications of prolapse surgery and how can they be prevented?

Ans: The common intraoperative complications include hemorrhage and injury to bladder and rectum.

- Hemorrhage can be reduced by identifying correct tissue planes and morbidity due to hemorrhage can be reduced by raising preoperative hemoglobin of the woman and arranging adequate blood during surgery.
- The injury to bladder and rectum can be reduced by correct technique. Bladder sound may be used if there is difficulty in identifying bladder margins. Intraoperative per rectal examination will help to avoid rectal injury.

Q.20. What is the postoperative care for your patient?

Ans: Postoperative care of woman includes postoperative fluid management, adequate analgesia and monitoring for vital signs and bleeding. The prophylactic antibiotics should include broad spectrum antibiotics covering anaerobic organisms also. The most commonly used regimen is amoxicillin + clavulanic acid 1.2 gm and metronidazole 500 mg perioperatively in prophylactic doses. The duration of postoperative catheterization should be minimum depending on extent of bladder dissection and type of surgery

performed. Woman should be ambulated after effect of anesthesia wears off. The perineal hygiene should be taken care of.

Q.21. Is hysterectomy necessary for treatment of prolapse?

Ans: No, but generally forms a part of prolapse surgery in older women who have completed family, as retention of uterus with significant degree of prolapse compromises the long-term operative results as cervix limits access to structures of paracolpium that are necessary to achieve proper proximal suspension of vaginal vault. However, many women are now opting for uterine conservation to maintain normal sexual function after surgery.

Q.22. What is role of meshes and grafts in prolapse surgery?

Ans: Although various grafts, bolsters and synthetic meshes can be valuable tools in prolapse surgery they should be used cautiously and selectively.

They are rarely required in primary surgery and not always in repeat surgery. Even in advanced prolapse, fascia (which does not atrophy like muscles) is present in most cases. It may be scarred or retracted but can be identified by meticulous dissection by proper technique. They should not be used as substitute for extensive dissection and meticulous technique. Although the use of grafts has the potential to improve the quality of life, the overzealous use of grafts and meshes may produce side effects due to exposure and erosion. Cost is a limiting factor.

The use of grafts and meshes for supporting large defects in site specific repairs especially in repeat procedures for failed prolapse surgey is likely to become standard of care. The use of commercially available kits for nonsite specific transvaginal mesh-graft repairs where very large pieces of mesh are placed to provide support without site specific approximation of anatomic defects is recently introduced. These large mesh grafts can be used in any of the vaginal compartments and are tunneled to the site where they are to be used via a transobturator, transgluteal, suprapubic, or combined approaches. Though early reports appear favorable, long-term reports are not yet available.

Despite their increasing use, great controversy exists over their use of synthetic mesh grafts especially when packaged delivery-system kits produced by medical devise manufacturers and FDA has issued public notification regarding complications that can be associated with transvaginal placement of surgical mesh in repair of pelvic organ prolapse and stress incontinence.[10] Continued research on graft use in pelvic reconstructive surgery is needed and patient need to be informed about the unique risks associated with graft use.

Q.23. What are common causes for failed prolapse surgery?

Ans: The common reasons for failure or recurrence of prolapse surgery can be any of the following:

- Wrong choice of surgical procedure
- Poor surgical technique
- Omission to recognise and treat enterocele
- Shortening of anterior vaginal wall
- Inherent weakness of supports
- Pregnancy and delivery following operation.

Q.24. What is role of laparoscopic surgery in treatment of POP?

Ans: The techniques used abdominally for pelvic organ prolapse can also be performed laparoscopically with advantage of minimally invasive techniques. Most transabdominal procedures suspend vaginal apex but do not deal effectively with distal half of vagina or perineum. With laparoscopy, surgeons are repairing not only apical supports but all compartments of pelvic floor using synthetic mesh grafts. Laparoscopic sacral

colpopexy is the most commonly performed procedure. Other procedures which are performed laparoscopically include sacral hysteropexy/cervicopexy, uterosacral colpopexy/hysteropexy, anterior and posterior vaginal wall support procedures using mesh. The laparoscopic approach is associated with similar surgical outcomes in expert hand and have advantage of less blood loss, less postoperative hospitalization. The disadvantages include longer operating time, higher costs and deep learning curve.

Robotic assisted laparoscopic surgery is devised to shorten learning curve associated with traditional laparoscopic surgery for prolapse. Current literature on this approach is limited and there is need for more data to substantiate the results.

Q.25. What is the role of conservative management in prolapse?

Ans: Definitive management of prolapse is surgery. However, some women may not be willing for surgery and some may be very high risk for anesthesia though advances in anesthesiology is making it a rare situation.

Insertion of pessary is one option for such women. Pessary is a palliative treatment providing only symptomatic relief. The pessaries of many shapes are available but ring pessary is the most commonly used. It is important to fit correct size of pessary as too small ring may be expelled and too large a ring may cause discomfort and difficulty in passing urine. The size of pessary is assessed by doing pervaginal examination and measuring the distance of subpubic angle from apex of posterior fornix by an examining finger. Postmenopausal women may require application of local estrogen to prevent erosion by pessary. The pessary should be changed every 3-6 months to allow inspection of vaginal mucosa and reducing risk of infection.

Pelvic floor exercises–Kegels exercises aim at increasing the tone of pelvic floor muscles. They are unlikely to reduce prolapse but may reduce progression from early stages or prevent recurrence after surgery. They are useful only in milder degree of prolapse and need to be continued for prolonged time.

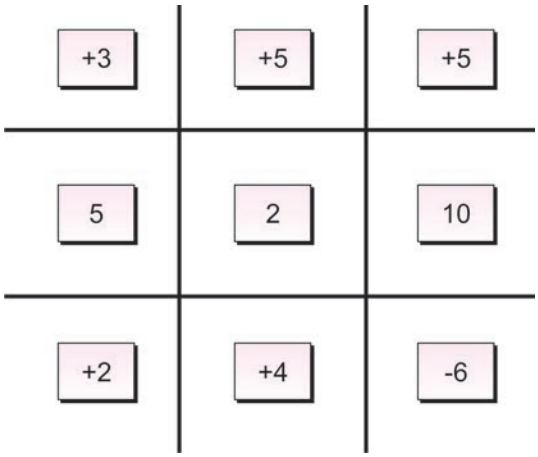

Fig. 20.3: POPQ staging of Mrs Y

CASE 2

27-year Mrs Y, Para 2 presents with third degree uterovaginal prolapse. How will you proceed?

History: The detailed history should be taken with special emphasis on poor nutrition, poor intrapartum care, early return to activity after delivery, any other factors suggestive of congenital weakness of tissues like hernia, prolapse rectum, etc. as prolapse at such a young age is not very common. Any urinary or bowel symptoms should be asked to help in planning treatment.

General examination should specifically look for spina bifida and other neurological problems which may contribute to prolapse in young woman. Local examination should assess degree of cervical descent, elongation of cervix and whether it is supra or infravaginal, sites of anterior and posterior vaginal wall defects, tone of pelvic floor muscles.

POPQ staging of my patient is –Stage III Ba, lithotomy with straining

The quantification is as follows (Fig. 20.3).

Q.26. How will you treat your patient?

Ans: Taking into consideration young age and parity of the woman the preservation of future fertility is important. Unless the problem is severe, the women should be advised to complete the childbearing so that definitive treatment can be offered. Ring pessary provides temporary relief, permits intercourse and can be offered till she completes childbearing after thorough counseling.

The definitive treatment in this case is surgical. Various operations which can be considered are-

Manchester operation: It is appropriate in young woman with any degree of prolapse. Though uterus is conserved, there may be some effect on future childbearing in form of increased incidence of infertility, midtrimester abortions, preterm delivery and cervical dystocia and this should be discussed with the woman.

Q.27. What are the main components of Manchester operation?

Ans: The main components of Manchester operation are:

- Dilatation and curettage done first to rule out any associated endometrial pathology.
- Anterior colporrhaphy
- Amputation of cervix
- Anterior plication of Mackenrodts ligament and other paracervical tissues in front of cervix
- Sturmdoffs suture to cover amputated cervix
- Repair of enterocele and posterior colpoperineorrhaphy if necessary.

The intraoperative complications include bleeding and injury to surrounding structures. The postoperative complications include bleeding, infection on short term and recurrence of prolapse on long-term.

Q.28. What are the other operations which can be performed in this woman?

Ans: ***Shirodkars modification of Manchester operation:*** In this vaginally performed operation, after giving circular incision on cervix, vaginal flaps are dissected. After bladder dissection, the pouch of Douglas is opened, uterosacral ligaments are dissected, detached from its cervical attachment, brought anteriorly and crossed in front of cervix. Enterocele is then repaired by excising and closing peritoneum and obliterating the space by approximation of uterosacral ligaments. The anterior colporrhaphy and postcolpoperineorrhaphy is then performed. The advantage of this operation over Manchester is that amputation of cervix with its effect on childbearing is avoided and opening of cul-de-sac allows better repair of enterocele. It may not be suitable for women with elongation of cervix.

Sling operations: In young or nulliparous woman with prolapse there is congenital weakness of supporting tissues and these abdominal operations aim at supporting weak ligaments by various natural or synthetic slings. The point of attachment of slings and material used as sling varies with technique. The enterocele if present should be repaired by Moschowitz or Halban technique. They do not affect future fertility. They should be avoided when there is procidentia, infected hypertrophied cervix, marked elongation of cervix.

Vaious types of sling operations are as follows-

- **Khannas operation:** The sling is made of mersilene tape and is attached posteriorly to cervix, passes retroperitoneally to be attached to anterior superior iliac spine. Vaginal delivery is allowed.
- **Shirodkars sling operation:** The sling is prepared from fascia lata or mersilene tape. It is attached to cervix posteriorly at one end and follows the course of uterosacral ligaments retroperitoneally to be attached to the intervertebral disc between L5 and S1. It is difficult technically. The woman can have vaginal delivery.
- **Purandares sling operation:** The sling is fashioned from two strips of anterior rectus sheath which remain attached at one end and

other end goes along course of round ligaments through internal inguinal ring to get attached to anterior lip of cervix. The woman can deliver vaginally but there can be a problem if she need LSCS and incision should be made above the level of attachment of strip. The disadvantage is that it relies on intrinsic strength of rectus sheath which may not be good in woman developing prolapse at young age.

Sacrospinous fixation with uterine preservation: A unilateral sacrspinous fixation with uterus in place may be beneficial and does not prohibit subsequent childbirth.

Sacral hysteropexy: It can be performed by open laparotomy or laparoscopy and uses mesh, which is attached to sacrum at one end and posterior or both anteroposterior suface of uterine isthmus on other. Burch operation may be performed concomitantly.

CASE 3

35-year Mrs Z, Para 3 comes with abdominal swelling during coughing and mass descending per vaginum since 2 years. She has undergone abdominal hysterectomy for fibroid uterus 3 years back and has developed above symptoms one year after previous surgery. How will you proceed?

History: The details of previous surgery like indication, technique especially method of vault suspension should be found out. Any pathology like chronic cough, constipation that may predispose to recurrence should be ruled out. Any associated urinary symptoms if present should be asked for.

Examination: General examination should note general health of woman, any evidence of connective tissue disorder like hyperelasticity of joint, etc. This woman has midline subumbilical incision with incisional hernia and vault prolapse. On local examination -

POPQ stage was Stage IV C, lithotomy with straining, with quantification as follows (Fig. 20.4).

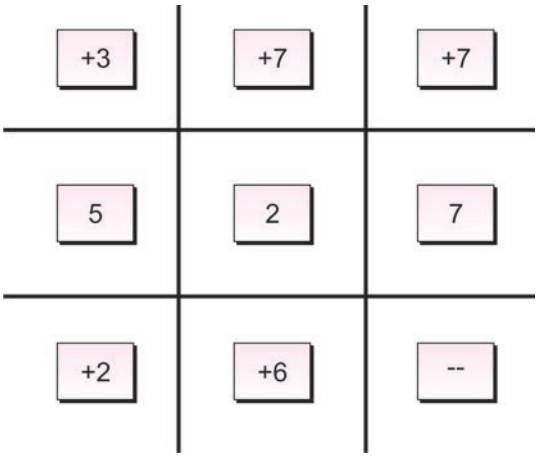

Fig. 20.4: POPQ staging of Mrs Z

Q.29. How will you investigate and manage her?

Ans: Since this woman has developed incisional hernia along with vault prolapse the connective tissue disorders should be ruled out in addition to routine work up for prolapse.

Treatment: This woman needs treatment for incisional hernia as well as vault prolapse both of which is surgical and can be combined in single sitting by coordinating with surgeons.

The first choice of surgery in this woman would be.

Abdominal sacrocolpopexy with hernia repair: Taking into account need for incisional hernia repair, young age of woman and possibility of inherent weakness, abdominal sacrocolpopexy with hernia repair will be choice of surgery in this woman.

Technique: After opening the abdomen, the two limbs of a Y-shaped mesh are attached to anterior and posterior vaginal walls after dissection of bladder and rectum. The peritoneum is dissected in front of sacrum and the other end of the mesh is attached to the anterior longitudinal ligament of first sacral vertebra. The mesh is peritonealized to avoid bowel entrapment. A culdoplasty by Halbans or Moschowitz technique is done as essential part of operation. Repair of incisional hernia is done using appropriate technique.

Intraoperative complications: are unusual and include injury to bowel, bladder, ureter, nerves and hemorrhage. Hemorrhage from presacral vessels may be life threatening and should be controlled with pressure, sutures, clips, bone wax and sterile thumbtracks as last resort. Postoperative complications like infections can occur as with all abdominal operations. Commonest long-term complication is erosion of mesh which may need removal by abdominal or vaginal route.

The advantage of this operation is that it provides surest and strongest correction for prolapse in young women with more strenuous activity. It provides good vaginal length. The disadvantage is longer operative time and longer recovery time.

The success rate of abdominal sacral colpopexy is higher than sacrospinous fixation The reoperation rates were 33% in vaginal group and 16% in abdominal group.[11]

Q.30. What are the other surgical options for treatment of vault prolapse?

Ans: The other surgeries that can be performed for treatment of vault prolapse are

Vaginal: Generally vaginal route is preferred for primary repair as it has advantage of less operating time, less morbidity and permits better visualization and repair of anterior and posterior vaginal wall defects.

- Sacrospinous vaginal fixation–After extensive dissection and site specific repair of anterior and postvaginal wall defects the vaginal apex is attached to sacrospinous ligament on one or both sides. The sacrospinous ligament is identified by its attachment to ischial spine and exposed by dissecting pararectal pillars. The nonabsorbable suture material is used and the vault is attached to ligament about 2 cm away from ischial spine to avoid injury to pudendal vessels and nerve. In unilateral fixation, the vagina is pulled to one side but rarely cause dyspareunia. Injury to pudendal vessels and nerves can occur. It is durable and strong surgical correction of vaginal vault prolapse. It is safer and require less operative time.
- High uterosacral ligament suspension–It was introduced by Richardson and based on main concept that endopelvic fascia surrounding vagina does not attenuate but breaks at specific points. This procedure identifies fascial defects, reduces enterocele sac, closes defects and resuspends vagina at original level I support of uterosacral ligaments. Though primarily used vaginally, it can also be performed abdominally or laparoscopically. The main risk during this procedure is of ureteric injury and cystoscopy should be performed after the vaginal procedure.
- **Laparoscopic colposuspension–**The techniques used abdominally can also be performed laparoscopically with advantage of minimally invasive techniques and have similar results in expert hands.
- **Obliterative procedures**–In very old women who are poor risk for surgery and no longer sexually active, obliterative procedures like partial colpocleisis is an option but is rarely used with increasing safety of anesthesia techniques. In this operation vaginal mucosa on anterior and posterior wall are removed and cut edges of denuded vaginal walls are stitched together with interrupted delayed absorbable sutures after turning inward uterus and cervix. Since there is no support aggressive perineorrhaphy is done. Complete breakdown and recurrence can occur. Postoperative stress incontinence is reported in about 30% cases. Early postoperative complication are hematoma and infection. In cases of vault prolapse, colpectomy with colpocleisis can be done.

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Latika Sahu

21 Vesicovaginal Fistula

Every minute, a woman dies in pregnancy or childbirth, and for every woman who dies, 20-30 others will survive but with morbidity, one of which is obstetric fistula.[1]

Vesicovaginal fistula (VVF) is a subtype of female urogenital fistula (UGF). VVF is an abnormal fistulous tract extending between the bladder and the vagina that allows the continuous involuntary discharge of urine into the vaginal vault.

CASE 1

Mrs X, 19-year-old woman delivered her 1st dead born child 1 month back at home conducted by an untrained dai, come to the Gynecology OPD with complains of urine leak per vaginum since 8th postpartum day.

Q.1. What is important to elicit in history?

A. Age and socioeconomic status of the woman– In poor young woman there is increased incidence of cephalopelvic disproportion and VVF due to:
   - Pelvic bone immaturity.
   - Reduced birth canal size before age 18.
   - Reduced inlet, midplane, outlet dimensions.
   - Late onset of puberty.
   - Malnutrition.
   - Net "Low" gynecological age. (Chronological age – age at menarche).
   - Younger age at marriage and teen age pregnancy.[2]

B. Duration of labor—Prolonged labor especially in 2nd stage can lead to VVF and urine leak per vaginum.
   Vesicovaginal fistula is seen in women following obstructed labor. So, history suggestive of obstructed labor to be extracted from the patient.

C. Any other complication intrapartum and postpartum—postpartum hemorrhage and sepsis are associated with poor tissue healing and make the patient prone for developing VVF.

D. Voiding urine per urethra apart from the leakage—Depends on the site and size of fistula. Patients with small fistulas may void normal amounts of urine and notice only slight position-dependent drainage. Alternatively, they may have leakage only at maximal bladder capacity. Those with larger fistulas may not void transurethrally and may have total incontinence.

E. Amount of leakage—The size and site of fistula determines the amount of leakage.

F. Other common comorbitities associated with obstetric fistula-like
   Gynecologic—Amenorrhea, PID.
   Musculoskeletal—Lower limb contracture 2^{o} to nerve damage.
   Neurological—Footdrop from sacral and perineal nerve compression, Neurogenic bladder dysfunction
   Dermatologic—Ammmonical dermatitis,Vulvar excoriation.

Examination

General examination

Height

Weight

BMI

Pallor

Features of malnutrition

Per abdomen examination

Any organomegaly

Palpable mass

Surgical scar

Per speculum examination: Any pooling of fluid in the vagina that is noted should be sent for analysis if the diagnosis is unclear. Next, perform a careful speculum exam that allows visualization of the entire anterior vaginal wall to identify the fistula tract. In many cases, the fistula is grossly visible.

Determine the location of the fistula in relation to the vaginal apex and bladder trigone and assess the quality of surrounding tissue (e.g. presence of inflammation, edema, or infection), tissue mobility; accessibility of the fistula to vaginal repair; and association of a rectovaginal fistula. Fistulas near the vaginal apex may require a more complicated abdominal approach, and those close to the trigone may be associated with increased risk of ureteral injury during repair.

If the fistula is particularly small, no tract may be apparent. In such cases, bimanual exam with careful palpation of the anterior wall may help locate the fistula (e.g. when there is a surrounding zone of induration).

If no fistula is noted despite highly suspicious signs and symptoms and careful examination, a simple office test can be performed. Using a catheter, fill the bladder with a dyed solution such as normal saline with indigo carmine and repeat the pelvic exam with a half-speculum to visualize the anterior wall. Ask the patient to cough and bear down, and identify the fistula by visualizing urine leakage.

If this test fails to locate the fistula, do ***tampon test of Moir*** (*described later*)

Per vaginal examination: Digital examination will give better idea of fistula than speculum examination. Assessment of tissue mobility; accessibility of the fistula to vaginal repair; determination of the degree of tissue inflammation, edema, and infection, scarring; can be better assessed by digital examination.

On Examination of Mrs X: Short statured, malnourished, anemic, anxious looking.

Per abdomen: Nothing significant.

Per Speculum examination: Vaginal rugosities present , urine seen leaking from anterior vaginal wall. Single fistulous opening of 2 cm size over middle portion of anterior vaginal wall .Tissue around opening shows puckering.

Per vaginal examination

Uterus well involuted, bilateral fornices free, the fistula margin feels indurated, inflamed, a ~2 × 2 cm opening felt over midanterior vaginal wall, no induration/fixity to underlying bone, no mass/tenderness around the opening.

Per rectal examination –

Nothing significant.

Since the fistula is seen clearly diagnosis of VVF is made.

Q.2. How will you manage this patient?

Ans: The principles of management of obstetric VVF in this case are:

A. *Catheterization*—Foley's for 6 -12 weeks.

Advantages—Viable treatment during first 90 days +/-.

Avoid urine flowing through fistula.

Promotes spontaneous closure of fistula.

B. *Surgery*—After 12 weeks.

C. *Rehabilitation*—Stretching and mobilizing limbs.

Physiotherapy of lower limbs, foot.

Psychological and emotional counseling.

Employment skill building.

Q. 3. What is the preferable method of surgical repair in this patient?

Ans: Flap-splitting technique is the preferable method for repair of this patient with an obstetric VVF.

Important points to remember in this repair

- *In case of fibrosis, the edges have to be freshened*
- Her fistula is in her midvagina, it is usually easier to suture the first layer transversely.
- Avoid diathermy if bleeding, especially near the walls of her vagina and bladder, because it destroys tissue, and reduces the blood supply.
- If it is low (juxtaurethral) near vesicourethral junction, suture it longitudinally
- Check the patency of the repair done by instilling colored fluid into bladder. If it leaks, insert more sutures, or take them out and start again.
- For the first two layers use '0' delayed absorbable sutures.
- Close the intermediate layer (if you have been able to define it) with interrupted sutures, and eliminate all dead space.
- Close the vaginal wall with interrupted sutures.
- If possible, place the line of sutures transversely. Otherwise place it whichever way the edges lie easiest.
- Try to arrange the sutures on the three layers so that they don't immediately overlie one another. Check again that the repair does not leak.

Numerous surgeons have found this procedure as efficacious as the Latzko technique. It has better applicability for large VVFs while not foreshortening the vaginal vault.

An asymmetric J incision in the anterior vaginal wall can be given whereby the lower curve of the J loops around the fistula site. This modification enables the surgeon to advance one flap over the fistula repair and prevent overlapping suture lines.

Martius grafts require in cases where fistula closure is tenuous. Tension-free closure of viable tissue, avoidance of overlapping suture lines, and continuous postoperative bladder drainage were factors considered crucial to success. Success rates ranged from 90-100%.

Q.4. What is the ideal time for repair of obstetric VVF?

Ans: The obstetric VVF requires 3 months time for recovery of local tissue before surgical intervention. The traumatic fistula should be repaired immediately and repair can be attempted if recognized within 48 hours.

Q.5. What is the size of VVF can be best repaired with flap-splitting technique?

Ans: Most small (<4 cm) VVFs can be repaired with a flap-splitting technique. large (>4 cm) VVFs are complicated by increased rates of vaginal stenosis and atresia when repaired in this manner. Full-thickness Martius grafts to preserve vaginal depth may be considered as an adjunct to transvaginal flap-splitting surgery for the repair of large vaginal fistulas.

Q.6. What postoperative care you will give to the patient after obstetric VVF repair?

Ans: Catheters left in place. Urinary 2 weeks.

- Clamped for short periods to accustom the bladder to distention.
- Confined to bed rest for 2 weeks.

Good nursing care to avoid bedsores

- Abstain from intercourse for >3 months.
- Contraceptive counseling.
- Advise future deliveries to be cesarean.[3]

Q.7. What is the surgical management of urinary incontinence after obstetric fistula repair?

Ans: Urinary incontinence after obstetric fistula repair:

- >25% of women still incontinent after fistula repair.

- Most common in women who had a bladder neck/juxtaurethral fistula, urethral-vaginal fistula.
- Second operation can be done to repair using a combination of urethralization (urethral lengthening), plus fibromuscular sling of rectus fascia.[3]
- Postfistula stress incontinence has been controlled by modified needle suspension procedure.

Q.8. What are the medical consequences of fistula?

Ans: Left untreated, fistula can lead to frequent ulcerations and infections, kidney disease and even death. Some women drink as little as possible to avoid leakage and become dehydrated.

Q.9. How does fistula occur in a case of obstructed labor?

Ans: By reduced blood supply due to tissue necrosis caused by prolonged labor during childbirth.

Unattended obstructed labor can last for up to six or seven days, although the fetus usually dies after two or three days. During the prolonged labor, the soft tissues of the pelvis are compressed between the descending baby's head and the mother's pelvic bone. The lack of blood flow causes tissue necrosis and create a vesicovaginal fistula.

Q.10. What is the ideal way of managing a case of obstructed labor to prevent VVF?

Ans: In a case of obstructed labor a FISTULA is going to form:

1. When labor is long enough to kill the baby.
2. After craniotomy.
3. When there is gross intrauterine infection .

If you suspect a fistula is goint to form:
Insert an indwelling silastic catheter and start continuous closed drainage.

Ensure a high fluid intake so as to reduce the risk of infection.

Mobilize her early, always keeping the bag below her bladder.

After 7–10 days put her into the Sims' position and examine her anterior vaginal wall with a Sims' speculum.

If her bladder is still bruised or necrotic, leave the catheter in and only remove it when later examinations show it is healthy. *If you use a latex catheter, change it every 7 days.*

If she develops a VVF, continue catheter drainage for 3 weeks, unless the fistula is so big that the balloon falls into her vagina. If it is very small, drain her bladder for 6 weeks. If you can keep her bladder empty, it may close spontaneously.

If a large area of sloughing tissue causes a persistent foul discharge, debride the dead tissue under general anesthesia.

If her pubic bone is exposed, it will be infected (osteitis), so give her a broad spectrum antibiotic and rectal metronidazole 1 g twice daily. Touch her with weak clorhexidine.

As soon as her VVF develops and her vulva is exposed to urine, wash her vulva and perianal area twice daily with soap and water. Twice daily zinc and castor oil ointment will keep her vulva healthy and reduce smell.

Q.11. What is the epidemiology of obstetric VVF?

Ans: There are certain countries in South Asia, specifically Bangladesh, and in sub-Saharan Africa, such as the Sudan, Ethiopia, Chad, Ghana, and Nigeria, where fistula prevalence is reported to be high.[4] In 2002, the UNFPA conducted a 6-month needs assessment in 9 African countries, and estimated that there could be up to 1 million women living with fistulas in Nigeria alone, and that incidence rates could be as high as 2 to 3 per 1000 women in countries with high maternal mortality rates.[4]

In developing countries, mostly in African countries:[5]

- Estimates of 2-7 million women affected.
- Estimates of >75,000 new cases each year.
- Estimates of 3-5 cases per 1000 pregnancies.
- Limited indigenous surgical repair capability.
- Cultural and religious worldviews serve to perpetuate the status quo:
  - "whatever will be, will be"
  - "the will of God (Allah)"
- Women currently have neither the education, resources, nor rights to change the underlying causes of fistula.

Q.12. What are the etiologies of VVF?

Ans: Frequencies and the causes of VVF reflect the culture and geography. Kelly showed that in England, 95% of the VVFs occurred with non-obstetric causes.[6]

Direct causes:

- **Obstetric:** In Nigeria, 98% of the VVFs were secondary to obstructed labor.[6] Obstructed labor can occur in an android pelvis, malnutrition, orthopedic disorders including rickets, and hydrocephalus contribute to dystocia. Fistulas may be caused by forceps, destructive instruments used to deliver stillborn infants, or surgical abortion.
- **Surgery:** The most common cause of fistula in developed countries is trauma associated with *pelvic operation*, and the operation most often involved is total abdominal hysterectomy and the most common indication is benign leiomyoma. The overall incidence of urinary tract injuries during pelvic surgery is estimated to be 0.33%. *Cystotomy and VVF account for more than three-fourths of the injuries*. The etiology of VVF at the time of hysterectomy is the result of an unrecognized bladder laceration at the time of dissecting the bladder off the cervix. *Even cystotomies that are repaired have a risk of fistula formation*.[7]

A fistula may also arise from avascular necrosis secondary to crush injury or erosion of a vaginal cuff suture into the bladder.[7]

A fistula may also follow an uncomplicated operation as the result of a pelvic hematoma that ruptures into the bladder postoperatively.

Devascularizing the bladder or vaginal cuff could lead to fistula formation and can be minimized with mobilization of tissue planes.

Placement of **transobturator** *midurethral slings* are touted as being less likely to cause bladder injury. However, recent reports have documented VVF following trauma to the bladder with trocar placement and with the presence of a foreign body in the bladder; the latter may be caused by directly placing the tape through the bladder or erosion of the material into the bladder wall.[8]

Predisposing Factors for Bladder Injury

- Coexisting pelvic pathology,
- Distortion of normal anatomy,
- Previous pelvic surgery, adhesions

Radical pelvic surgery for extensive disease. Indeed, the incidence of bladder injury during radical hysterectomy is three times higher than with simple hysterectomy.

Other Risk Factors

- History of pelvic irradiation
- Cesarean section
- Endometriosis
- Prior pelvic inflammatory disease
- Diabetes mellitus
- Concurrent infection
- Vasculopathies
- Tobacco abuse.
- ***Malignant disease of the pelvic organs is the 2***nd ***most common cause in developed countries. Carcinoma cervix is the common malignancy associated with VVF.***
- ***Radiation-induced*** fistulas are commonly associated with treatment for carcinoma of the

cervix or other pelvic malignancies. Fistulas may appear during the course of radiotherapy (usually from necrosis of the tumor itself) or after treatment is completed. Late fistulas arise secondary to endarteritis obliterans within the first 2 years. It is essential to rule out recurrent malignancy with biopsies.

- ***Trauma*** (Road traffic accidents, Sharp object injury),
- ***Infections*** such as tuberculosis, schistosomiasis, syphilis, and lymphogranuloma venereum, HIV.
- ***Congenital VVF*** is usually associated with other genitourinary anomalies.
- ***Foreign body***- There are case reports of VVFs caused by vaginal foreign bodies, direct trauma from masturbation or automobile accidents, bladder calculi, forgotten vaginal pessaries.
- ***Female Genital Mutilation*** Vesicovaginal fistula occurs when there is introital stenosis secondary to female *circumcision*, Symphysiotomy, the use of postpartum vaginal caustic agents, and self-inflicted "Gishiri cuts" also have a role.
- ***Sexual trauma*** through coerced vaginal penetration and even consensual sexual intercourse have been reported to have led to VVF.
- ***Urethrovaginal fistulas*** may occur postpartum and are associated with operative vaginal delivery, after surgery for urethral diverticulum, anterior vaginal wall prolapse, or urinary incontinence, and after radiation therapy. *Pressure necrosis resulting in an urethrovaginal fistula can occur with a prolonged indwelling transurethral catheter*. Urethrovaginal fistulas may also be congenital.
- In rare instances, spontaneous vesicouterine fistulae were reported following uncomplicated vaginal birth after cesarean section.

Indirect causes—Low status of women in society

- Poverty and gender discrimination—malnutrition, contracted pelvis,
- Culture/tradition—early marriage and conception, female circumcision, health seeking practice
- Limited access to medical services.

Q.13. When do women typically present after various antecedent events?

Ans: Women typically present within specific intervals after the various antecedent events (pelvic surgery, childbirth, radiation therapy) with a primary complaint of constant, painless urinary incontinence.

- If the fistula is related to traumatic childbirth, most patients experience urine leakage within the first 24 to 48 hours.
- Following pelvic surgery, symptoms usually occur within the first 30 days.
- In contrast, radiation-induced fistulae develop over a much longer interval secondary to progressive devascularization necrosis, and may present 30 days to 30 years after the antecedent event.

Q.14. What are the preventive measures for obstetrics fistula?

Ans:

Primordial prevention—Girls' education**.**

- Women's empowerment**.**
- Increase the marriage age.
- Nutritious diet since childhood.

Primary prevention

Making family planning available to all who want to use it. It would reduce maternal disability and death by at least 20 percent.

Follow strategy to make motherhood safer.

Skilled attendants at all births and emergency obstetric care for those women who develop complications during delivery would make fistula rare.

Secondary prevention

- Early recognition of cephalopelvic disproportion and prevention of obstructed labor.
- LSCS in indicated cases.

- Avoidance of difficult forceps and destructive operations.
- Catheter drainage for 14 days in prolonged or obstructed labor.

Q.15. What are the various ongoing projects available worldwide for prevention of obstetric fistula? What is the Campaign to End Fistula?

Ans: Two projects available worldwide.

- Women's dignity project (WDP) work on obstetric fistula in eastern Africa has two main themes:
  - Poverty, which precludes access to care, and
  - Power of society to reject, banish and isolate

In 2003, UNFPA[9] and its partners launched the first-ever global campaign to end fistula. This includes interventions to:

- Prevent fistula from occurring.
- Treat women who are affected.
- Renew the hopes and dreams of those who suffer from the condition. This includes bringing it to the attention of policy-makers and communities, thereby reducing the stigma associated with it, and helping women who have undergone treatment return to full and productive lives.

The Campaign currently covers more than 40 countries in sub-Saharan Africa, Asia and the Arab region.

CASE 2

Mrs Y, 48-year-old multiparous woman presented to you with H/o one previous cesarean section, H/o undergoing total abdominal hysterectomy for cervical fibroid uterus, 15 days back in a private hospital, H/o urine leak for 3 days.

Q.16. What is important to elicit in history?

Ans: Enquire from the patient operative details as per her records and postoperative period.

A. Intraoperative findings

An unrecognized injury to the bladder resulting in urinary extravasation.

Theoretically, with early recognition, it may be possible to avert the formation of a VVF.

B. Postoperative period

Excessive postoperative abdominal pain, distention or paralytic ileus, or both.

Hematuria and symptoms of irritability of the bladder, and prolonged postoperative fever and increased white blood cell count are common findings in a posthysterectomy fistula. The patient may experience recurrent cystitis or pyelonephritis with costovertebral angle tenderness; Flank, vaginal, or suprapubic pain; Abnormal urinary stream.

The most common presenting feature of VVF is continuous leakage of urine from the vagina. Urinary leakage may make the patient a social recluse, disrupt sexual relations, and lead to depression, low self-esteem, and insomnia.

The leakage of urine may cause irritation of the vulva and vagina mucosa, perineum and usually produces a foul ammoniacal odour. Phosphate encrustations may be noted in more neglected cases. These crystals serve to further irritate what can be already compromised tissue.

C. Voiding urine perurethal apart from the leakage and the amount of leakage.

D. Some patients report exacerbation during physical activities, which can sometimes lead to erroneous diagnosis of uncomplicated stress incontinence. If the fistula is small, intermittent leakage with increased bladder distention or physical activity may be noted.

E. Other patients may complain of vaginal discharge or hematuria (vesicouterine fistula).

F. If there is concurrent ureteric involvement, the patient may experience constitutional symptoms (such as fever, chills, and flank pain) or even gastrointestinal symptoms.

Obstetric history: Parity, mode of deliveries, last delivery, sterilized or not.

Menstrual history: Regular cycles or not. H/o dysmenorrhea.

Past history: H/o Surgeries (other than cesarean) in past, history suggestive of endometriosis, history suggestive of PID, H/o radiotherapy in past, H/o any malignancies, H/o any medical disorders.

Mrs X had intraoperative history of cervical fibroid enucleated to facilitate hysterectomy. Bladder was pulled up due to adhesions of previous cesarean section. Continuous bladder catheterization for 2 days, discharged after 8 days. She noted urine leakage from vagina after 12 days of surgery. C/o persistent urine leaking from vagina, using pads daily and not able to pass urine normally, no H/o Fever, chills and rigor but C/o itching and soreness over vulva.

Per Abdomen examination

Inspection—condition of scar of hysterectomy, any other scars/dilated veins

Palpation—Organomegaly,

Renal angles free or not mass over the scar, Free fluid.

Local examination –The aim of local examination is to know regarding VVF:

- The precise anatomical situation.
- The number and size of the fistula.
- Tissue condition, tissue loss, scarring and infection.
- Vaginal accessibility.
- Mobility or fixity to bone.
- Local ulceration/excoriation over vulva, perineum needing prior treatment.

Per speculum –look for urine leaking through vagina. Patient smelling of urine, size and site of fistula, condition of tissue around fistula.

Per vaginal examination— feel induration/fixity to underlying bone—Any mass/tenderness around the opening.

Per rectal examination—Any associated recto-vaginal fistula.

On examination of Mrs Y—nothing significant in general examination.

Per speculum examination

Showed sodden vulva and a single fistula of 4-5 mm size in the anterior vaginal wall near the apex. Tissue around opening showed puckering.

As her fistula size is small she should be investigated further to confirm diagnosis of VVF.

Q.17. How will you diagnose bladder or ureteral injury during surgery?

Ans: Intraoperative assessment for bladder or ureteral injury may be performed by:

- Administering indigo carmine intravenously and closely observing for any subsequent extravasation of dye into the pelvis.
- Cystourethroscopy to assure bilateral ureteral patency and absence of suture placement in the bladder or urethra.
- Alternatively, intraoperative back-filling of the bladder with methylene blue or sterile milk before completing abdominal or vaginal surgery also may help detect a bladder laceration.
- Retrograde filling of the bladder also can be used during surgery to better define the bladder base in more difficult dissections.

Q.18. What are the guidelines to follow intra-operatively during pelvic surgery to minimize VVF formation?

Ans: A summary of these guidelines follows.[10]

- Adequate exposure of the operative field.
- Minimize bleeding and hematoma formation. The closure of dead space at the anterior vaginal wall upon completion of an anterior colporrhaphy will prevent hematoma formation. This technique employs intermittently incorporating pubocervicovaginal fascia with the vaginal mucosal layer as the vaginal wall is sutured.
- Widely mobilize the bladder from the vagina during hysterectomy to diminish the risk of suture placement into the bladder wall. A minimum of a 1 to 2 cm margin of dissection of

the bladder from the vaginal cuff should be developed prior to cuff closure.

- Dissect the pubocervicovaginal endopelvic fascia between the vagina and the bladder in the appropriate plane. Dissection may be easier with a sharp technique compared to a blunt technique; the key is to prevent trauma and separation of bladder wall fibers as the bladder is mobilized off the anterior vaginal wall.
- If scarring is present at the pubocervicovaginal fascia and dissection is difficult, consider performing an intentional anterior extra-peritoneal cystotomy. This technique enables the surgeon to assess the anatomic boundaries of the bladder wall with digital palpation.
- If scarring is present at the pubocervicovaginal fascia and dissection is difficult, consider employing an intrafascial technique of hysterectomy to best dissect the endopelvic fascial plane.
- Intraoperative retrograde filling and emptying of the bladder or mild traction on a temporarily placed small Foley catheter inserted into the fistula itself are helpful to optimally identify anatomical planes and reveal intraoperative bladder lacerations.
- Consider supracervical abdominal hysterectomy instead of total abdominal hysterectomy (TAH) in difficult cases. The incidence of UGF (urogenital fistula) formation is lower for supracervical versus total hysterectomy.
- If an intraoperative bladder injury does occur, widely mobilize the bladder from the underlying structures (fascia and vagina, cervix, or uterus). In doing so, the surgeon can effect a VVF closure under no tension.
- For repairing a cystotomy at the trigonal area, a transverse closure is preferable over a vertical one. Vertical closure would be more likely to produce ureteral obstruction because the ureteral orifices would be drawn inward toward each other. Ureteral catheters should be considered in repair of a cystotomy involving or encroaching on ureteric orifices.
- Consider performing cystourethroscopy when performing pelvic surgery. Cystourethroscopy to assure bilateral ureteral patency and the absence of suture placement in the bladder or the urethra has been advocated by some authors as a standard for all pelvic surgery.

Q.19. What is the ideal position for examination (EUA) and also for VVF repair?

Ans:

Lawson position: This position is ideal for proximal urethral and bladder neck fistulas. The patient is placed in a prone position with the knees spread and ankles raised in the air and supported by stirrups. Combining it with reverse Trendelenburg positioning enhances visualization with this technique.

Jack knife position: This is ideal for proximal urethral and bladder neck fistulas. The patient is placed in a prone position with the hips abducted and flexed and the table jackknifed.

Dorsal lithotomy position: Dorsal lithotomy position with standard Trendelenburg positioning provides excellent access for repair of a high VVF.

Knee chest position: To visualize retropubic fistulas.

Sim's position : The patient on the left side and chest, the right knee and thigh drawn up, the left arm along the back.

Q.20. Classify VVF.

Ans: Classification according to site-

A. High fistula
   a. Juxtacervical
   b. Vault (indirect, vesicouterine)
B. mid vaginal fistula
C. Low fistula-
   a. juxtacervical.
   b. bladder neck–urethra intact,
      - urethral involvement-segmental (partial bladder neck loss)

- Circumferential vesicourethral fistula (complete bladder neck loss).

D. Urethrovaginal fistula–a small fistula below the bladder neck is also incompetent.

E. Massive vaginal fistula encompasses all three levels and often includes one or both ureters in addition.

Posthysterectomy fistulas are usually supra-trigonal, medial to both ureteral orifices, and lie within the vaginal vault at the vaginal cuff.

Fistulas from obstetric causes may be located more distally, typically are larger, and are more commonly associated with a urethral injury.

Classification according to size:

- Small <2 cm
- Medium 2-3 cm,
- Large 4-5 cm,
- Extensive >6 cm

Obstetric vesicovaginal fistulae usually are *categorized* according to their *cause*, *complexity,* and *site of obstruction*. In contrast, *gynecologic fistulae* are generally classified as *simple or complicated*.

These levels may have important implications for the surgical approach and prognosis. For example, simple vesicovaginal fistulae are usually uncomplicated surgical cases with good prognosis. Complicated vesicovaginal fistulae, on the other hand, can challenge even highly practiced and skilled gynecologic surgeons and are associated with a high rate of recurrence.

Table 21.1: Classification of vesicovaginal fistulae

Classification	*Description*
Simple	• Fistula is less than 2 to 3 cm in size and near the cuff (supratrigonal) • Patient has no history of radiation or malignancy • Vaginal length is normal
Complicated	• Patient has had previous radiation therapy • Pelvic malignancy is present • Vaginal length is shortened • Fistula is greater than 3 cm in size • Fistula is distant from cuff or has trigonal involvement • Associated with scarring. • Involving the urethra, vesical neck or ureter. • Associated with intestinal fistulas. • Previous unsuccessful attempts at repair.

Contd...

Q.21. How will you differentiate VVF from ureterovaginal fistula? What are the tests performed to differentiate?

Ans: To differentiate variety of fistula—single or multiple vesicovaginal, urethrovaginal, or ureterovaginal fistulas and fistula formation between the urinary tract and the cervix, uterus, vagina or vaginal cuff. The following tests can be done:

- **Tampon test of Moir/Three swab test-** Bladder is filled with sterile milk/methylene blue (100-250 ml) in retrograde fashion using a small transurethral catheter.
- Placement of three swabs/tampons in tandem in the vaginal vault and observation for staining of the tampons by methylene blue may help to identify and locate fistulas.
- The patient is asked to do exertional maneuvers, including stair climbing, jumping in place, walk, cough, do deep knee bends for twenty minutes. After that tampons are removed and examined.
- Staining of the apical tampon would implicate the vaginal apex or cervix/uterus; staining of a distal tampon raises suspicion of a urethral fistula.
- If the tampons are wet but not stained, oral phenazopyridine (Pyridium) or intravenous indigo carmine then can be used to rule out a ureterovaginal, ureterouterine, or uretero-cervical fistula.

- Evidence of staining or wetting of a tampon should then prompt the physician to proceed with additional diagnostic testing prior to proceeding with definitive management.
- Indigo carmine dye can be given intravenously and if the dye appears in the vagina, a fistula is confirmed.

Double-dye test: Give the patient oral phenazopyridine (Pyridium), fill the bladder with the blue-tinted solution, and insert a tampon. The presence of blue staining suggests vesicovaginal or urethrovaginal fistula, while red staining (Pyridium) suggests ureterovaginal fistula.

Q.22. What are the relevant investigations you like to do for this patient?

Ans: Laboratory Studies

- vaginal vault fluid collection—tested for urea, creatinine, or potassium concentration to determine the likelihood of a diagnosis of VVF as opposed to a possible diagnosis of vaginitis.
- Once the diagnosis of urine discharge is made, identify its source.
- Cystourethroscopy may be performed, and the fistula(s) may be identified.
- Urine C/S- if positive results should be treated prior to surgery.
- Biopsy of the fistula tract/urine microscopy if suspicious of malignancy.

I**maging Studies**- Radiologic studies are recommended prior to surgical repair of a vesicovaginal fistula to fully assess the defect and exclude the presence of multiple fistulae.

- IVU/IVP - Necessary to exclude ureteral injury or fistula because 10% of VVFs have associated ureteral fistulas. If suspicion is high for a ureteral injury or fistula and the IVU findings are negative, then retrograde ureteropyelography should be performed at the time of cystoscopy and examination under anesthesia.
- A Tratner catheter can be used to assist in evaluation of an urethrovaginal fistula.
- Renal ultrasound shows calyceal dilatation and ureteric duplication.
- Transvaginal ultrasound—can help in diagnosis of urethral fistula associated with diverticulum.
- MRI and CT scan can display renal anatomy and in the pelvis may delineate extravasation and associated abscess formation.
- Cystography
- hysterography can demonstrate vesicouterine fistula.

Q.23. What are the diagnostic procedures for VVF?

Ans: Diagnostic procedures are:

- Cystoscopic examination with a small scope (e.g. 19F) may be used to identify VVF in the bladder or urethra, to determine the number and location and proximity to ureteric orifices, and to identify and remove abnormal entities such as calculi or sutures in the bladder.
- Water cystoscopy may be inadequate in the face of large or multiple fistulas.
- A cystoscopic examination using carbon dioxide gas may be used with the patient in the genupectoral position. With the vagina filled with water or isotonic sodium chloride solution, the infusion of gas through the urethra with a cystoscope produces air bubbles in the vaginal fluid at the site(s) of a UGF (flat tire sign).
- Combined vaginoscopy—cystoscopy: Andreoni et al describe their technique of simultaneously viewing 2 images on the monitor screen (both cystoscopic and vaginal examinations).[11] They used a laparoscope and clear speculum in the vagina and a regular cystoscope in the bladder to enhance visualization and identification of VVFs. Transillumination of the bladder or vagina by turning off the vaginal or bladder light source allows for easier identification of the fistula in the more difficult cases.
- Color Doppler ultrasonography with contrast media of the urinary bladder may be considered

in cases where cystoscopic evaluation is suboptimal, such as in those patients with severe bladder wall changes like bullous edema or diverticula. Color Doppler ultrasonography demonstrated a VVF in 92% of the patients studied by Volkmer and colleagues using diluted contrast media and observing jet phenomenon through the bladder wall toward the vagina. [12]

- Fistulograms: A targeted fistulogram may be indicated if conservative therapy is planned, including expectant management, continuous bladder drainage, fulguration, or fibrin occlusion.
- In patients with a history of urogenital malignancy, biopsy of the fistula tract and urine cytology is warranted.

Q.24. What is the role of cystoscopy in the diagnosis of VVF?

Ans: ***Relatively insensitive in the diagnosis of VVF***, cystoscopy should be performed to visualize the fistulous tract, assess its location in relation to the ureters and trigone, assure bilateral ureteral patency, and exclude the presence of a foreign body or suture in the bladder.

Best combined with vaginal examination under anesthesia, with or without retrograde bladder filling. In case of larger fistula, distention of the bladder with fluid for viewing is possible only when the fistula is occluded with finger or vaginal tampon.[13]

Q.25. What are the various management options?

Ans:

- Conservative management
- Medical Therapy,
- Surgical therapy.
- Non-surgical interventions.

Q.26. How will you manage this patient Mrs Y?

Ans: After confirmation of diagnosis, conservative management by putting the patient on an indwelling Foley's catheter, examine the patient every 2 weeks and plan for surgery after 6-12 weeks once the tissue condition is optimal for surgery.

Q.27. What is conservative management?

Ans: Conservative therapy should be reserved for simple fistulae that are less than 1 cm in size, diagnosed within 7 days of the index surgery, lacking associated carcinoma or radiation, and subject to at least 4 weeks of constant bladder drainage.

Persistent, large, or complex fistulae are best treated surgically.

If VVF is diagnosed within the first few days of surgery, a transurethral or suprapubic catheter should be placed and maintained for up to 30 days. Small fistulas (<1 cm) may resolve or decrease during this period if caution is used to ensure proper continuous drainage of the catheter.

In 1985, Zimmern concluded that if the fistula is small and the patient's vaginal leakage of urine is cured with Foley placement, the fistula has a high spontaneous cure rate with a 3-week trial of Foley drainage. He also noted that in general, if at the end of 30 days of catheter placement the fistula has diminished in size, a trial of continued catheter drainage for an additional 2-3 weeks may be beneficial. Finally, Zimmern concluded that if no improvement is observed after 30 days, a VVF is not likely to resolve spontaneously. Under these circumstances, prolonged catheterization only increases the risks of infection and offers no increased benefit to fistula cure.[14]

Q.28. What are the medical management options?

Ans: Medications

- Estrogen replacement therapy–in the postmenopausal patient may assist with optimizing tissue vascularization and healing. Oral hormone replacement therapy/estrogen replacement therapy (HRT/ERT) alone has been

found to suboptimally estrogenize urogenital tissue in 40% of patients.

- Treatment with estrogen vaginal cream is recommended for patients with VVFs who are hypoestrogenic. A 4-6 week treatment regimen prior to surgery is commonly recommended. It may be used alone or in combination with oral HRT/ERT. Dosages range from 2-4 g placed vaginally at bedtime once per week. Alternatively, the patient may place 1 g vaginally at bedtime 3 times per week.
- Corticosteroid and nonsteroidal anti-inflammatory therapy is theorized to minimize early inflammatory changes at the fistula site. However, its efficacy has not been proven. Because it also carries potential risks for impairment of wound healing, when early repair is planned, cortisone is not recommended for the treatment of VVF.
- Acidification of urine to diminish risks of cystitis, mucus production, and formation of bladder calculi may be a consideration, particularly in the interval between the diagnosis and surgical repair of VVF. Vitamin C at 500 mg orally 3 times per day may be used to acidify urine. Alternatively, methenamine mandelate at 550 mg plus sodium acid phosphate at 500 mg 1-4 times per day also can be administered to achieve urine acidification.
- Urised is effective for control of postoperative bladder spasms. It is a combination of antiseptics (methenamine, methylene blue, phenyl salicylate, benzoic acid) and parasympatholytics (atropine sulfate, hyoscyamine sulfate).
- Sitz baths and barrier ointments, such as zinc oxide preparations, can provide needed relief from local ammoniacal dermatitis.

Q.29. How will you plan surgical therapy?

Ans: The associated ureteric fistula is usually dealt at the same sitting while the intestinal fistula may require some operation for fecal diversion. Both components of a double fistula should only be repaired simultaneously if it can be done without tension. The genital malignancy should get biopsy first to prove the absence of disease locally.

Q.30. What are the preoperative care required?

Ans: Perineal care.

- Frequent pad changes to minimise inflammation, edema and vulval irritation.
- Zinc oxide ointment or vaseline application locally is helpful in the treatment of perineal and vulval dermatitis.
- Three sterile urine cultures must be present, obtained on a sterile Sim's speculum
- Catheter drainage.

Q.31. What preoperative local assessment will you perform before fistula repair?

Ans: This is best done 1 to 3 days before the repair, so that you know what to expect and are not obliged to repair a patient immediately after you have assessed her.

- How big is the fistula?
- How far it is from her urethral orifice?
- What is the state of the surrounding tissues? Are they soft and friable, or soft and healthy? Mildly, or severely fibrosed?
- Is her urethra stenosed or obstructed?
- Is her vagina narrowed, or almost obliterated by scar tissue?
- Does she seem to have 'lost her urethra'?

It is easy to repair if a fistula is: (1) Less than 1 cm in diameter. (2) More than 2.5 cm from her urethral meatus. (3) Not significantly fibrosed.

Q.32. How will you decide the route of approach to surgery?

Ans:

- In low fistula (urethral and juxtaurethral)-vaginal approach (face down or jack knife position)

- Circumferential loss of bladder neck-combined abdominovaginal approach. Lithotomy Trendelenburg position.
- Midvaginal fistula –transvaginal approach.
- High vaginal fistula (post hysterectomy fistula or in a juxtacervical position)—abdominal or vaginal approach.

Q.33. What should be the position of patient during surgery?

Ans: This is critical and depends on the skill of the anesthetist, and surgeon's personal preference.

1. If anesthetist is skilled, patient can lie on her front, her thighs abducted as far as possible, and her legs supported in double lithotomy stirrups. Bandage her legs to the poles, have her buttocks clear of the table, and an overtable just below her. Tilt her 5° head- down, and raise the table to a convenient height to let you see into her vagina.
2. If anesthetist is less skilled, patient can lie on her back in the exaggerated lithotomy position, with a steep (30°) head-down tilt, her buttocks well over the edge of the table, and her shoulders supported by shoulder rests.

Q.34. What anesthesia should be used?

Ans: If patient is lying prone, use general anesthesia, intubate her, use relaxants, and control her ventilation. Put a pillow under her chest, and another smaller one under her pubis; make sure that her abdomen is free. Don't rely on spontaneous ventilation, because she will not ventilate adequately.

CAUTION! No patient should lie prone under general anesthesia, and be expected to breathe spontaneously. Hypoxia, cardiac arrest, brain damage, and death may follow.

Q.35. What are the surgical options?

Ans:

1. Surgical closure should be the first option.
2. Urinary diversion is required when primary surgical closure of fistula is not possible.
   a. external diversion like ileal conduit
   b. internal diversion like ureterosigmoidostomy, colpocleisis.

Q.36. What is the ideal time to repair a VVF of gynecological cause?

Ans: The timing of repair should be dictated by the overall medical condition of the patient and the tissue quality surrounding the fistula. While the emotional status of the patient should not be underestimated, it also should not play a dominant role in the decision process of when to repair a VVF.

Traditionally, an interval of 3 months was recommended between the index surgery and fistula repair, with a delay of up to 1 year when the fistula was radiation-induced. A one-year interval for radiation-induced fistulas is recommended to ensure full resolution of tissue necrosis. However, little data support these recommendations.

Today most experts recommend an individualized approach, delaying the surgery until inflammation and infection of the surrounding tissue have resolved. The use of estrogen, antibiotics, or steroids to facilitate healing during this period also has been recommended. Comparable success rates have been reported for early and late repair of surgery-induced fistulae based on these principles.

Margolis and Mercer simply recommend delaying surgery until inflamed and infected tissue has been treated and the infection and inflammation have resolved.[15]

Q.37. What is the role of Antibiotic prophylaxis in VVF repair?

Ans: Patients given prophylactic antibiotic therapy will have fewer urinary infections and will require less antibiotic therapy postoperatively.

Q.38. What is the debate on the fistula tract excision—To excise or not to excise?

Ans: Debate continues about whether resection of the fistulous tract is necessary. Some experts believe

that wide resection increases the size of the fistula and, therefore, the risk of recurrence. They also maintain that the fibrous tissue surrounding the fistula helps to reinforce the surgical repair. Proponents of fistulectomy counter that resection of the fistula and exposure of healthy tissue optimizes wound healing and improves surgical success rates. Comparable success has been reported for both techniques.

In their experiences, Vasavada, and Margolis and Mercer[15] note that routine excision of the fistula tract is not mandatory. They emphasize the risks of increasing the size of the fistula tract with attempts to resect it. Additionally, these surgeons contend that the fibrous ring of the fistula may add to the strength of the repair and prevent postoperative bladder spasms.

Elkins and Thompson state that a small fistula may be resected, but large tracts should only be freshened. They warn of the risk of overexcising fistula edges, thereby causing an increase in the size of the fistula. They point out further risks of intracystic bleeding and blood clot formation from the mucosal edge of the bladder with fistula resection. Subsequent blockage of the catheter postoperatively would then increase the risk of failure of the VVF repair.[16]

It is preferable to have an individualized approach, with minimal resection of the fistulous tract to simplify the procedure and minimize associated complications, including recurrence.

Q.39. What are the methods of de-epithelialization?

Ans: De-epithelialization of the fistula tract can be accomplished by various techniques. Screw curette is one method. In 1977, Aycinena described the use of a common type of screw to strip away or curet the epithelial lining of small VVFs. He then simply allowed spontaneous healing to occur. Seven patients were reported in this series, all of whom were treated successfully. Experts in the field caution that this procedure is efficacious only in the smallest of VVFs.

Other methods used to de-epithelialize the fistula tract include electrocoagulation and sharp knife dissection.

Q.40. What is Saucerization?

Ans: The original Marion Sam's technique may be used for very small fistula, particularly for residual fistula after previous surgery. A bevelled cut through the vagina to the small visceral aperture should clear scar tissue to allow healthy tissues for apposition.[13]

Q.41. What are the available techniques of repair?

Ans: The best chance for a surgeon to achieve successful repair is by using the type of surgery with which he or she is most familiar.

Techniques of repair include:

1. The vaginal approach
2. The abdominal approach
3. Electrocautery
4. Fibrin glue
5. Endoscopic closure using fibrin glue with or without adding bovine collagen
6. The laparoscopic approach, and
7. Using interposition flaps or grafts.

Q.42. What are the determinants of successful repair?

Ans: The literature documents excellent success rates for both the vaginal and abdominal approaches if the following general surgical principles are followed:

1. Complete preoperative diagnosis
2. Exposure
3. Hemostasis and closure of dead space
4. Mobilization of tissue
5. Tissue closure under no tension
6. Watertight closure of bladder with any cystotomy repair

7. Timing to avoid infection and inflammation of tissue
8. Adequate blood supply at area of repair, and continuous catheter drainage postoperatively.
9. Preservation of vaginal vault caliber and pliability.

Q.43. What are the advantages of vaginal approach?

Ans: Advantages of vaginal approach are:

- Minimal blood loss
- Low postoperative morbidity
- Shorter operative time, and shorter post-operative recovery time.
- Additionally, the vaginal approach obviates bowel manipulation, reducing operative morbidity, particularly in patients with radiation-associated fistulas.
- Angioli et al emphasize that the absolute contraindications for vaginal repair of VVF are the concomitant presence of fistulas with other abdominopelvic organs, such as ureters and small and large bowel, and multiple VVFs. [10]

Q.44. What are the indications of abdominal approach?

Ans: Absolute indications for abdominal approach include:

- the need for concomitant abdominal surgery, such as augmentation cystoplasty and ureteral reimplantation;
- the inability to adequately expose the fistula vaginally;
- a complex presentation of VVF involving the ureters, bowel, or other intraabdominal structures; and
- involvement of the VVF with ureteric orifices.

Abdominal approach is preferred in following conditions:

- When ureteroneocystostomy is needed or a need for ureteral reimplantation.
- Complex fistula.
- Multiple in number,
- When there is concurrent uterine or bowel involvement
- Multiple operated fistula with significant scarring.
- Radiation-induced fistula.
- Relative position of ureters to the fistula is seen as problematic.
- When omental flap is to be used.
- When a very large fistula or high and inaccessible or a contracted bladder may require bladder patching or augmentation with sigmoid colon, caecum or ileum.

Q.45. In which type of fistula abdomino-vaginal approach is required?

Ans: In circumferential fistula (circumferential loss with the anterior bladder wall completely adherent to the body of the pubis).

- In Massive fistula .

Q.46. What are the essential steps in the management of radiation-induced fistulas?

Ans: The essential steps in the management of radiation-induced fistulas are:

- Exclusion of the diagnosis of recurrent malignancy.
- Avoidance of surgery during acute necrosis
- Diversion of fecal stream in case of concomitant rectovaginal fistula.
- Increasing the blood supply with the use of grafts/flaps.
- Proper closure of fistula.

Q.47. What is Bonney's principle for repairing any fistula?

Ans: Bonney described 6 general principles which should be adhered to when repairing any fistula.[17]

1. The tissue to be repaired must be healthy. In case of urinary fistula the urine should be rendered sterile and the area free of infection. Slough due to irradiation, trauma or infection must be separated to leave clean healthy surface.

2. There must be adequate exposure of the affected area and the tissue surfaces surrounding the defect.
3. There must be no tension on the suture lines when the fistula is closed.
4. Meticulous hemostasis is essential throughout the operation to avoid hematoma formation and to facilitate healing.
5. Infection must be guarded against or it will jeopardize healing.
6. The urinary incontinence may be difficult when a bladder fistula affects the region of bladder urethral junction. This is a vulnerable area in relation to urinary control and for this reason it is not only important to close the fistula but also to reinforce the area with adjacent fascia and muscle including the anterior fibers of pubococcygeous muscle when necessary, thus reducing the risk of postoperative stress incontinence.

Q.48. How will you improve exposure during surgery in vaginal approach?

Ans: Exposure can be improved by:

- Suturing of the labial folds to the ipsilateral thigh provides improved visibility of the vaginal vault.
- Episiotomy incision afford greater exposure in the vaginal repair of fistulas that were located high in the vaginal vault.
- Duhrssen incision is a deep vaginoperineal incision or extended episiotomy initially proposed for usage in other types of vaginal surgery. Its application to fistula surgery was recommended by Mackenrodt in 1894.
- In 1893, Schuchardt introduced a parasacral incision as an extension of a Duhrssen incision, whereby a deep vaginoperineal incision is carried cephalad to the vault apex and then posteriorly toward the tip of the coccyx.
- Schuchardt's paravaginal incision is performed by incising the posterior vaginal wall in a direction angled toward the ischial tuberosity, going through the levator ani and the coccygeus muscle, to ultimately gain access into the ischiorectal fossa. Hemorrhage is an expected complication encountered using this technique.
- Catheterization of the fistula tract: Exposure and access to a VVF can be facilitated by catheterization of the fistula with a bulb catheter, such as a Fogarty catheter. An uninflated catheter may thread the fistula where the bulb is inflated, and then traction is placed on the catheter to draw the VVF into the field. A small VVF may be probed first with a lacrimal duct probe and dilated with cervical dilators to permit placement of a pediatric catheter/ureteral bulb catheter.

Q.49. How will you perform low tension closure?

Ans: Low-tension closure—The critical issue of closure of suture lines without any tension is a tenet of surgical repair of VVF. The methods are:

- Extensive vaginal wall dissection and mobilization from the underlying vesicovaginal endopelvic fascia.
- Lateral radial or circumferential relaxing incisions. The relaxing incisions are the full thickness of the vaginal wall without extension into the endopelvic fascia. The margins are not reapproximated; instead, they may be sutured in running fashion for desired hemostasis. A significant danger to performing lateral relaxing incisions is further devascularization of the vaginal tissue.
- An alternative approach that avoids this potential complication is to employ vascularized flaps or grafts at the site of fistula repair, such as a Martius bulbocavernosus fibromuscular pedicle with or without an intact skin patch.

Q.50. What is the standard surgical procedure for posthysterectomy VVF as in Mrs Y?

Ans: Latzko (1942) partial colpocleises procedure is the standard for repair of simple post hysterectomy VVFs. Alternately fistulectomy with flap-splitting closure can be done.==

- **Latzko partial colpocleisis:** This technique, first reported in 1942, remains a common procedure, with success rates of 90 to 100%.
- The colpocleisis technique applied a transverse closure of the vagina beneath the fistula defect.
- Disadvantage: Formation of a symptomatic diverticulum between the bladder and cervix if fistula occurs following subtotal hysterectomy.
- Two prerequisite conditions: First, adequate preoperative vaginal vault length must be present because the vagina is shortened by 1.5 cm. Second, the fistula must be located at the vaginal apex "so that the posterior margin of the fistula and the scar of the vaginal vault coincide."
- Advantages of the Latzko procedure include simplicity of technique, high success rate, low morbidity, no impairment in bladder capacity, short operative time, low intraoperative and postoperative morbidity, and low risk of ureteral injury, even with fistulas lying close to the ureteral orifices.
- Latzko technique: Make a circumferential incision in the vagina approximately 2 cm from the fistulous tract. Mobilize the vagina and close it over the fistulous tract, with delayed absorbable suture in a double layer, without disturbing the bladder mucosa. The vaginal mucosa is then closed, completing the repair. The vaginal wall in contact with the bladder becomes the posterior vesical wall and eventually is reepithelialized with transitional epithelium.

Other Procedures

- **Fistulectomy technique—**Fistulectomy with a flap-splitting closure, begin by resecting the fistulous tract to expose healthy tissue at the wound margins. Then close the defect in a multilayer fashion, beginning with the bladder mucosa, bladder serosa, pubocervical fascia, and vaginal mucosa. Be careful to avoid tension on suture lines. In addition, create a fascial flap to prevent apposition of the incision planes and reduce the risk of recurrence.

Vaginal cuff excision

- Technique: The vaginal mucosa is denuded circumferentially for a radius of 3-5 mm from the vaginal cuff, including the fistula. This incision is then extended obliquely to the bladder wall so as to resect the fistula tract and vaginal cuff scar in a funnel-shaped specimen. The defect is closed in 4 layers.
- Intravenous indigo carmine and cystoscopy is used to ensure bladder and ureteral integrity.

Abdominal approach—The abdominal approach may be facilitated by cystoscopically-guided placement of a catheter through the fistulous tract to assist in subsequent identification and dissection.

To begin, make a vertical skin incision to optimize visualization and allow mobilization of an omental flap, if necessary. Expose the bladder and perform a high extra peritoneal cystotomy to visualize the fistulous tract. Place ureteral stents if the fistula is in close proximity to the ureteral orifice.

Extend the bladder incision to the fistulous tract and completely excise it following mobilization of the vagina. Then close the vagina and bladder with interrupted, delayed absorbable suture in a double layer. Transpose an omental flap between the vaginal and bladder incisions.

- Exposure: As with the transvaginal approach, exposure with the transabdominal approach can be augmented with the use of traction sutures and with catheterization of the fistula with a Fogarty catheter.
- The classic positioning of the patient for abdominal procedures is supine, with Trendelenburg orientation. However, modifying this by flexing the patient's hips and abducting and supporting her legs in stirrups is wise. Simultaneous access and examination of the vaginal vault may assist with laparotomy procedures.

- The choice of incision may include suprapubic, Pfannenstiel, or midline vertical.
- Transvesical extraperitoneal technique: In 1885, Trendelenburg introduced this method of vesicovaginal repair. With the patient placed in a steep Trendelenburg position, a transvesical incision is performed to visualize the fistula. The bladder mucosa adjacent to the fistula is circumscribed and removed. The bladder is dissected off the vagina and the bladder, and vaginal defects are closed separately.
- Transperitoneal technique: It was developed by von Dittel in 1803 for the repair of VVFs.
- Transvesical transperitoneal suprapubic method: In 1913, Legueu combined both the Trendelenburg and the von Dittel techniques, whereby the peritoneal cavity is accessed by laparotomy and a sagittal incision is made in the bladder. This cystotomy incision is extended to the fistula. The bladder is mobilized off the vagina, and the bladder and vaginal defects are closed separately.
- Extravehicular transperitoneal procedure: Margolis and Mercer[15] and O'Conor and Sokol find this method of great benefit when the bladder is densely adhered to the endopelvic fascia and underlying structures (e.g. lower uterine segment, cervix, anterior vaginal wall).
- O'Conor and Sokol technique (1951): Intraperitoneal or transperitoneal technique for the suprapubic repair of trigonal and supra-trigonal VVFs. Success rates 85%.

Q.51. What are the procedures for complex fistula repair?

Ans: Among the complex fistula are radiation-associated cases and difficult repairs.

- The *transperitoneal approach* is preferred because it allows for the addition of interposition grafts. Advantages of this technique are high success rate, optimum surgical access to the fistula and ureters, and the ability to add an interposition graft with this procedure.

Technique: The posterior wall of the bladder is dissected free as much as possible. The bladder then is bivalved at the dome. This incision is extended posteriorly to the level of the fistula. The fistula tract and scarred and necrotic tissue are resected. Dissection of the posterior wall of the bladder from the underlying endopelvic fascia and vagina is completed. The bladder and vagina are closed in separate layers. Commonly, peritoneal or interposition grafts are added.

- Vesical autoplasty
- Gil-Vernet and colleagues presented a bladder wall flap procedure in 1989 as an alternative technique for the repair of complicated VVF. The approach may be transvesical, extraperitoneal, or transperitoneovesical.

Advantages are the capability of repairing large VVFs without compromising bladder capacity, a low-tension closure, direct and easy identification, and preservation of the submucosal ureteral portion.

Technique: The fistula tract is completely excised. The bladder wall is carefully mobilized off the endopelvic fascia and vaginal wall. The vaginal defect is closed with a single-layer closure. A bladder flap is constructed to close the bladder defect. The anterior margin of the flap is drawn down over the bladder defect to meet the caudal margin of the bladder defect. It is sutured in place with 3-0 catgut through the submucosal and muscular layers in interrupted fashion with sutures not less than 10 mm apart.

- Bladder mucosal autologous grafts
- The use of autologous bladder mucosa grafts was first introduced in 1947 as a technique designed for urethral reconstruction.

Simplicity of technique, high success rates, lack of the need for interposition grafts, and decreased patient morbidity were notable advantages to this procedure. Re-epithelialization of the denuded mucosa donor site is believed to occur spontaneously over the following 4-6 weeks.

Technique: Bladder mucosa is denuded circumferentially at the fistula site at a distance of 1 cm. The fistula tract and vaginal wall are left undisturbed. A free bladder mucosal graft is sharply dissected from its underlying muscularis layer at the edge of the anterior cystotomy margin. This graft of mucosa is then secured over the fistulous tract with interrupted 4-0 chromic catgut sutures that are placed into the superficial muscularis at a distance of 2-3 cm.

Q.52. How will you suture bladder opening?

Ans: The bladder is closed with a 2-0 chromic/vicryl suture in continuous running fashion beginning at the apex and extending through the full muscle layers and imbricated with a second layer with interrupted 1-0 chromic/vicryl sutures.

Q.53. What are the newer techniques of VVF repair?

Ans: The newer techniques are:

- *Laparoscopic approach*: Laparoscopic repair has been reported with comparable results, but requires advanced skills with endoscopic suturing and knot tying.
- This technique involves cystoscopy, catheterization of the fistula tract, dissection of the bladder from the vagina, laparoscopic cystotomy, excision of the tract, adequate dissection of the bladder from the vaginal wall, cystotomy, and colpotomy closure with interposition of a flap of healthy tissue.[18]
- Melamud and colleagues reported their successful attempt in the repair of a VVF in a 44-year-old woman. Their approach was a minimally invasive laparoscopic approach using the DaVinci *robotic system*. In their technique they added fibrin glue between the bladder and vagina to separate the suture lines.[19]
- *Transurethral suture cystorrhaphy (TUSC):* This technique offered multiple advantages including minimal intervention, outpatient setting, reduced operating time, and reduced morbidity.[20] Essential to the technique are suprapubic visualization with a shorter scope such as an arthroscope, large-caliber sheaths used transurethrally to allow passage of relatively large curved needles, self-righting needle driver, and adequate fulguration of the fistula tract and the surrounding bladder mucosa.

Q.54. Which type VVF get benefit from interposition graft/flap placement?

Ans: Multiple operated fistulas, post-irradiation fistulas, post-surgical fistulas more than 4 cm in diameter or large tissue loss fistulas (large obstetric fistulas) often are complicated with marked tissue devascularization, necrosis, and cicatrization and will get benefit from flap placement.

In cases with a high risk of recurrence, such as complex or large fistulae, a Martius fat-pad graft should be interposed between the closure layers to promote vascularization and reduce the risk of recurrence.

Q.55. What are the various interposition grafts or flaps available for vaginal approach?

Ans:

1. *Martius flap:* Martius first described his procedure in 1928 as a technique used in VVF repair. He isolated the bulbocavernosus muscle and its overlying fibroadipose tissue as a pedicled graft for VVF repair. The fibroadipose tissue possessed sufficient blood supply and strength for success. Its application today extends to numerous types of vaginoplasties performed for urethral, vaginal, and rectal disorders that include VVF, vaginal scarring and atresia, urethrovaginal fistulas, and rectovaginal fistulas. The dual blood supply to this tissue and the bulbocavernosus muscle (dorsally via internal pudendal artery and ventrally via external pudendal artery) enables the surgeon

the choice of using a flap with a superior or inferior base. Various modifications of Martius' original procedure have been published. Success rates range from 85-100%.

Complications of classic Martius graft technique: There is risk of hemorrhage because it requires a deep plane of dissection to isolate the bulbocavernosus muscle. Mild dyspareunia over the graft site is a potential complication.

The graft is obtained through a vertical incision over the labium majus. It is separated from the underlying vestibular bulb and bulbocavernosus muscle and then tunnelled beneath the labium minora and through the paracolpium to finally reach and overlay the 2-layer bladder closure. It is secured at its distal end with 4-corner stay sutures. The vaginal wall is closed using interrupted chromic or Vicryl sutures, and then the labial incision is closed. A Penrose drain is placed at the bed of the graft and brought out at a lateral site if any persistent bleeding is noted. This drain is then removed on the third to fifth postoperative day. Perform cystoscopy prior to and following the procedure to exclude ureteral compromise.

2. *Gracilis muscle flap:* The predominant application for this flap is in total vaginal reconstruction following pelvic exenteration.
   The gracilis muscle reaches to cover the medial portion of the groin, the vulva, the perineum, and the lower abdomen. Its major blood supply is a branch of the profunda femoris entering the upper one-third of the muscle. This dominant vascular pedicle is the point of rotation for the flap and supports the entire muscle and overlying skin island.
3. *Peritoneal flap:* Peritoneum is mobilized carefully from the posterior bladder wall and brought down to reach beyond the fistula site and be secured over the fistula repair suture line with 2-0 polyglycolic sutures. Closure integrity is assessed with indigo carmine. Vaginal packing is used.

Q.56. What are the interposition grafts or flaps used in abdominal approach VVF repairs?

Ans: Abdominal approach interposition grafts or flaps are:

1. *Omental J flap:* Omentum, with its rich lymphatic and vascular supply, is ideal as an interposition graft. The omentum may be mobilized off the transverse colon, and ligation and division of the short gastric branches may be required. The omentum can be mobilized on the right gastroepiploic artery from the transverse colon. Absorbable sutures must be used at the distal omentum in order to avoid contact of permanent suture at the bladder.
   A number of surgeons have performed VVF repair with an omental J flap under laparoscopic technique and have found it to be a good alternative to the traditional abdominal approach.
2. *Peritoneal flap:* As with transvaginal approach, peritoneal flaps may be used during a transabdominal approach to provide an additional layer between the bladder and vaginal cuff at the time of repair of a VVF.
   In an effort to decrease the likelihood of VVF formation, it has been suggested as a technique to be used at the time of repair of both incidental and intentional cystotomies that occur during simple and complicated pelvic surgeries.
3. *Rectus abdominis muscle flap:* Kanavel first described using a flap isolated from the rectus abdominis muscle for repair of a space of Retzius defect in 1921.
   In 1965, Banerji published his experience with rectus abdominis musculofascial pedicle grafts in the treatment of 7 patients with VVFs. All of the fistulas resulted from obstetric trauma. Of 7 patients, 4 were cured.
4. *Autologous bladder mucosa interposition graft:* A site is selected at the bladder dome for harvesting of the donor mucosal graft. The graft is dissected from the muscularis and interposed

between the bladder and vaginal walls so that the mucosal surface faces the vagina. The bladder wall is then closed over the graft using 5-0 continuous catgut. The anterior cystotomy is closed in 2 layers with 3-0 interrupted chromic sutures.

Vyas and colleagues report of a 91% success rate using mucosal autografts for repair of VVF. A transabdominal approach was used for fistulae above the trigone and a combined abdominal and vaginal approach for fistulae involving the trigone.

5. *Free supporting graft:* Moharram and El-Raouf report their 100% success rate in the repair of urogenital fistulas in 26 women using a retropubic transvesical approach with placement of a support graft from the anterior abdominal wall fat.[21]
6. *Human dura mater interposition graft:* In a prospective study of 11 patients with VVF, Alagol and colleagues used solvent dehydrated, gamma-radiated human dura mater. They reported a 100% success rate. Surgical technique included a transvesical extraperitoneal approach.[22]
7. *Broad ligament flaps:* Plastic reconstruction technique for the repair of mega vesicovaginal fistulae resulting from obstetric complications.[23]
8. Placement of a *cadaveric biomaterial graft* also has been reported, reducing the need for complicated flap procedures.

Q.57. How do interposition flaps/grafts increase the success rate of VVF repair?

Ans: Interposition flaps or grafts/Rotated vascularized pedicle flaps increase success by enhancing granulation tissue formation, increasing neovascularity to the area, and obliterating dead space. They also provide a barrier layer between the bladder suture line and the vaginal suture line.

Q.58. What postoperative care to be given after VVF repair?

Ans:

1. *Bladder drainage:* Urethral drainage is done via 16-18 Foley's catheter. One hourly urinary output charting should be maintained. It is usually 70-100 ml/hr with good hydration. Continuous bladder drainage postoperatively is vital for successful UGF repair. A large-caliber catheter minimizes the potential for catheter blockage by blood clots, mucus, and calcaneus deposits.

Type and duration of catheter drainage: For fistulas involving the lower portion of the bladder trigone, bladder neck, or urethra, transurethral bladder catheters should not be used. A large suprapubic catheter for an average of 3 weeks (upto 60 days in certain cases) preferable to minimize excess tension on the suture line and to ensure nonobstructed continuous drainage.

In post hysterectomy VVF repairs, both transurethral and suprapubic catheters may be placed. The urethral catheter may be discontinued **by fourteenth day (7-14 days)**. If vesical integrity is noted 2 weeks later on a cystogram, the suprapubic catheter may be removed. Surgeries to repair pelvic radiotherapy-associated VVFs require longer periods of drainage.

The ***suprapubic drainage is done when:***

- Abdominal approach is used.
- Large vesicovaginal fistula is repaired via vaginal approach.
- Urethal reconstruction is done.

The basic aim is to ensure a continuous drainage so that bladder does not become overdistended.

Urethal catheter is removed in 2 weeks and suprapubic catheter should be clamped for every one hour and residual urine should be checked

after voiding, if it is less than 30cc suprapubic catheter can be removed.
2. Alternate day *urine sample* should be sent for culture and sensitivity.
3. *Perineal care* to keep the area clean.
4. Acidification of urine to diminish risks of cystitis, mucus production, and formation of bladder calculi is a consideration for patients with an indwelling catheter.
5. *Estrogen replacement therapy* in the postmenopausal patient may assist with optimizing tissue vascularization and healing.
6. *Control of postoperative bladder spasms:* Urised is effective for control of postoperative bladder spasms.
7. *Antibiotic therapy:* The use of antibiotic therapy postoperatively is controversial. Many physicians administer oral antibiotic prophylaxis to patients with VVF postoperatively until the Foley catheter is discontinued.

   Others check closely for the development of a urinary tract infection and administer antibiotic therapy when urine cultures are positive for bacterial growth. Close follow-up and prompt evaluation for any urinary tract infections and antibiotic therapy, when indicated, are mandatory.

   Antibiotics are administered for 14 days starting preoperatively on the day of surgery.
8. *Minimizing valsalva maneuvers:* Stool softeners and a high-fiber diet postoperatively minimize valsalva maneuvers in the patient.
9. *Examinations:* Avoid pelvic and speculum vaginal examinations during the first 4-6 weeks postoperatively because the tissue is delicate.
10. *Pelvic rest:* Prohibit coitus and tampon use for a minimum of 4-6 weeks. Some advocate strict pelvic rest for 3 months.

Q.59. What are the available methods of non-surgical interventions in VVF?

Ans: The available methods of non-surgical interventions are:

- *Electrocautery*
  - Reported a 73% cure rate with electrocoagulation. The fistulas that can be successfully managed with electrocautery as the sole treatment modality should be small in size (either pinhole openings or bladder mucosal dimples).
  - Details of the technique include both vaginal and cystoscopic routes and fulguration with a Bugbee electrode and placement of a large Foley catheter for a minimum of 2-3 weeks.
  - Care should be taken to use low-current settings in order to minimize the potential of thermal damage and enlargement of the fistula.
- *Fibrin glue*
  - Occlusion therapy using fibrin glue is considered useful and safe for intractable fistulas. Fibrin glue facilitates healing by recruiting macrophages and providing a semisolid support structure rich in growth and angiogenic factors. This system continues to support the fibroblast to connective tissue transition.
  - Fibrin occlusion of a VVF was first developed by Pettersson and associates in 1979. The VVF was incurred following surgery and radiotherapy and was cured with the first attempt.
- *Electrocautery and endoscopic closure* using fibrin glue and bovine collagen
  - Morita and Tokue published a case report of successful closure of a radiation-induced and markedly fibrosed VVF measuring 5 mm. They buttressed the fibrin glue in the fistula tract between collagen cushions at the proximal and distal sites of the fistula to prevent its mechanical disruption by the efflux of urine from the bladder.[24]
  - Technique: After performing electrocoagulation of the fistula, a cystoscope was introduced transurethrally into the bladder, and 1 mm of bovine collagen was injected

submucosally under direct visualization around the fistula opening. Fibrin glue was injected transvaginally into the fistula tract. A second application of 1 mm of bovine collagen was then injected transvaginally into the vaginal mucosal layer around the fistula tract. A transurethral Foley was used for 3 weeks.

– *Laser welding:* Dogra and Nabi reported their success in the repair of a 3-mm VVF in the supratrigonal area of the bladder. They used a Nd-YAG laser to fulgurate the fistula opening and the full tract. A transurethral catheter was used for 3 weeks. The authors emphasize that the Nd-YAG laser has the advantage over electrocoagulation of precise and accurate destruction of the areas involved.[25]

Q.60. What is the palliative treatment available if surgical repair is not possible?

Ans: Use in the vagina of a sponge tampon tucked into a length of Paul's tubing draining into a bag may provide socially acceptable temporary continence. Every movement squeezes a small amount of urine out of the bottom of the sponge, within the lumen of the Paul's tubing.[13]

Q.61. If VVf is associated with RVF (recto-vaginal fistula) which one should be repaired first?

Ans: A bladder fistula heals better if not bathed in feces during recovery. Preliminary loop ileostomy or transeverse colostomy should be performed and then it is better to treat the urinary fistula first as avoidance of suture line tension is essential.[13]

Q.62. What are the complications of fistula surgery?

Ans: *Intraoperative complications:* Creation of another fistula

Ligation of/injury to the ureter

Failure to achieve complete closure of fistula.

- *Postoperative complication:* Most important complication is breakdown of the repair. This usually occurs about 7-10 days after operation.

Blocked Catheter

Infection, anuria, hemorrhage, thromboembolism new-onset incontinence after anatomical closure of fistula

Death- Very rare. The documented fatality rate for fistula surgery ranges from 0.5 to 1 percent in sub-Saharan Africa.

Preoperatively, patients should be informed of the possibilities of sexual dysfunction or dissatisfaction, and the progression of preexisting urge and/or stress incontinence symptoms.

Abdominal approach procedures carry additional risks of abdominal and pelvic adhesions. Vaginal approach procedures carry increased risks of dyspareunia, tenderness at the site of the donor Martius graft, and diminished vaginal length and caliber.

Careful screening and management before surgery is vital, as women with fistula tend to be malnourished and may be more susceptible to disease. Postoperative care and close long-term follow-up to manage both the surgical and medical problems that may occur is also essential.

Q.63. What are the causes of dribbling of urine in the postoperative period?

Ans: If patient complains of dribbling in the postoperative period, the reason can be:

- Breakdown of repair
- Leakage by the side of catheter due to incompetent internal sphincter.
- Overflow incontinence following blockage of catheter.

Q.64. How will you manage postoperative intravesical hemorrhage?

Ans: Intravesical hemorrhage threatens the integrity of the repair by obstruction of the catheter and overdistention of the bladder; gentle attempts to evacuate the clots can be made by transurethral bladder irrigations. If these are not successful, then immediate suprapubic cystotomy has to be

performed to remove the clots and suture the bleeding points in the bladder mucosa.

Exclusion of the urothelium from the actual suture line diminishes the risk of hematuria, but in some cases this is unavoidable. In such cases combination of suprapubic and urethral drainage is preferred. Urethral catheter preferably a Jaques or McCarthy "whistletip"catheter which will facilitate the evacuation of any clot that may form. Gentle irrigation should be continued until the efflux is clear. Early diuresis, if necessary with frusemide or similar agent is desirable.

Q.65. How will you manage postoperative ureteral obstruction?

Ans: If patient exhibits signs of ureteral obstruction (persistent fever, abdominal distention, pain and tenderness), an excretory urogram should be performed immediately. If complete ureteral obstruction is diagnosed, either the repair can be broken down or T tube can be placed in the ureter for drainage or ureteroneocystostomy can be performed or percutaneous nephrostomy can be done.

Q.66. What is the prognosis of VVF?

Ans: Recent advances have improved the success of VVF repair—a challenge that can test even the most experienced gynecologic surgeon. For example, it now is apparent that some small uncomplicated fistulae respond to conservative treatment. Further, in selected cases, laparoscopic repair can eliminate the need for complicated laparotomy.

Vesicovaginal fistula presentation and prognosis vary, depending on location and size of the defect, as well as coexisting factors such as tissue devascularization and previous radiation. However, surgical repair is associated with a high cure rate if it is performed by an experienced surgeon.

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Saritha Shamsunder, Meenakshi Garg

22 Abnormal Uterine Bleeding

Normal menstrual cycle is defined as occurring at an interval of 28 days (±7 days) with an average duration of 4 to 7 days and mean menstrual blood loss of 35 ml (range 31-80 ml). **Abnormal uterine bleeding (AUB)** is defined as any change in the frequency of menstruation, duration of flow or amount of blood loss. AUB is defined as **dysfunctional uterine bleeding (DUB)** when palpable pelvic pathology or underlying medical causes have been excluded. AUB is responsible for 20-30% of the visits to Gynecology Out Patient Department amongst women in the reproductive age group and 69% in a peri or postmenopausal age group.[1]

Types of Abnormal Uterine Bleeding (AUB)

- *Menorrhagia* – excessive or prolonged bleeding at regular intervals.
- *Polymenorrhea* –bleeding at intervals of less than 21 days.
- *Oligomenorrhea* – bleeding at intervals of 35 days or more with scanty flow.
- *Metrorrhagia* – irregular acyclical bleeding.
- *Menometrorrhagia* – prolonged and excessive bleeding at irregular intervals.
- *Postmenopausal bleeding* – bleeding per vaginum at least 12 months after the cessation of regular menses, or unscheduled bleeding after use of hormone replacement therapy (HRT) for 12 months or more.[2]

Five different problem cases of AUB are discussed in this chapter.

CASE 1

History

A young unmarried nulliparous 15-year-old girl gives history of irregular cycles since menarche with weakness and fatigue.

Examination findings

- *Pallor ++*
- *Tachycardia ++ BP 100/60,*
- *No lymph nodes*
- *No petechiae palpation*
- *Per abdomen – soft, liver and spleen not palpable*
- *Local examination – bleeding per vaginum present ++*
- *Per rectal examination – uterus was normal size, no adnexa mass.*

Q.1. What are the important points in history and examination in a patient of puberty menorrhagia?

Ans:

A. **History**

1. Age at menarche.
2. Duration and amount of bleeding to know the severity of problem.
3. Cycle length and regularity, to ascertain whether cycles are ovulatory or anovulatory.
4. History of preceding amenorrhea indicates anovulatory cycle or incidental pregnancy in a sexually active female.

5. History of sexual activity should be taken discretely in the absence of parent/guardian.
6. Dysmenorrhea – spasmodic dysmenorrhea (pain during menstruation) without an organic cause is seen in 5-10% of young girls and is associated with ovulatory cycles. Congestive dysmenorrhea (premenstrual pain relieved by flow) due to endometriosis or PID although rare, but could occur in this age group. Anovulatory cycles are painless.
7. History of easy bruisability/prolonged bleeding from wounds, heavy bleeding after any surgery/dental procedure, h/o of nosebleed which lasted for more than 10 min or required medical attention to stop is suggestive of coagulation disorder.
8. History of fever/cough/night sweats/chest pain is suggestive of tuberculosis.
9. History of weight gain/acne/excessive hair growth or unwanted hair is suggestive of PCOD.
10. History of weight gain/cold intolerance/fatigue/lethargy/constipation is suggestive of hypothyroidism.

B. **Examination**

General physical examination – important findings to be noted:

- Pallor to know severity of bleeding.
- Lymphadenopathy is suggestive of tuberculosis or hematological causes like leukemia or lymphomas.
- Thyromegaly–as hypothyroidism could be a cause of menorrhagia.
- Petechiae/ecchymosis/gum bleeding are suggestive of a coagulation disorder.

Per abdominal examination:

- Splenomegaly is present in a patient of ITP, hepatosplenomegaly in a patient of leukemia.
- Abdomino-pelvic mass – could be due to fibroid, estrogen secreting ovarian tumor (although rare).

Per rectal examination should be carried out to assess:

- Uterine size, position, consistency mobility, tenderness.
- Adnexal masses.

Per rectal examination is essential to rule out less common causes like associated pregnancy, fibroid, uterine or ovarian tumor.

Q.2. How will you investigate a patient of puberty menorrhagia?

Ans: Essential investigations

1. Urine pregnancy test – **pregnancy should be ruled out in every case of uterine bleeding which is irregular in the reproductive age group**.
2. Complete hemogram and peripheral smear.
3. Bleeding time, clotting time.
4. Prothrombin time and partial thromboplastin time.
5. Erythrocyte sedimentation rate, Mantoux test, chest X-ray to rule out tuberculosis.
6. Thyroid function test – if symptoms are suggestive of hypothyroidism.
7. USG pelvis to note the endometrial thickness, look for fibroid and any adnexal mass.

Special investigations

1. Menstrual blood for PCR tuberculosis – can be sent if there is strong suspicion of tuberculosis.
2. Endometrial assessment by endometrial aspiration should **ONLY** be considered in obese girls with persistent anovulatory cycles for 2-3 years despite treatment to rule out chances of endometrial cancer (risk in women aged under 30 years the estimate is less than 0.01% or 1 per 10,000 consultations for heavy menstrual bleeding in primary care, risk increases in the presence of risk factors like obesity and chronic anovulation.[3]
3. Special hematological investigations when indicated are:

- Bone marrow aspiration
- vWD antigen assay
- vWD ristocetin cofactor activity
- FVIII coagulant activity
- Factor assay (VIII and IX)
- Platelet function study

Q.3. What is your provisional diagnosis in this patient?

Ans: Anovulatory dysfunctional uterine bleeding, as the urine pregnancy test is negative, uterus is normal sized, investigations for coagulation disorders, tuberculosis and thyroid function are normal.

Q.4. What are the important causes of puberty menorrhagia?

Ans: The important causes are:

1. **Dysfunctional Uterine Bleeding** – could be ovulatory or anovulatory DUB.
   - **Anovulatory DUB** is the most common cause due to immaturity of the hypothalamo-pituitary-ovarian axis. Unopposed estrogen causes endometrial proliferation and hyperplasia to abnormal heights when it becomes fragile. Without the growth limiting and organizing effects of progesterone, the endometrium lacks the stromal support structure to maintain stability. Focal areas breakdown and bleed, as these areas later heal under the influence of continued estrogen stimulation, others break down and bleed, resulting in irregular shedding of the endometrium leading to heavy, prolonged and continuous bleeding.[4] It is also part of the syndrome of polycystic ovarian disease.
   - **Ovulatory DUB** is cyclic with a predictable pattern. The cause is not well defined, however, some theories suggest a change in endometrial hemostasis, and alterations in the synthesis and release of prostaglandins as key etiological factors. A change in the ratio of endometrial vasoconstrictor (PGF2α) to endometrial vasodilator (PGE2) and increase in total endometrial prostaglandins have been seen in patients with ovulatory DUB.[1]
2. **Tuberculosis**
   Menorrhagia is seen in 19% of patients with genital tuberculosis. Symptoms of fever/cough/night sweat/chest pain and family history of tuberculosis are suggestive.
3. **Coagulation abnormalities**
   Coagulation abnormalities are responsible for 30% of cases of puberty menorrhagia.[1] The commonest disorder is vWD in 5 to 15% of cases, other disorders which can present in this age group are ITP, platelet function disorder, factor XI deficiency and hemophilia.[5] Coagulation abnormalities are suspected when there is a family history of bleeding diatheses, when the patient gives a history of frequent epistaxis, bleeding from the mucous membranes (e.g. with the toothbrush), and excessive bleeding following minor surgery like tooth extraction.
4. **Hypothyroidism**
   Hypothyroidism should be suspected in patients presenting with associated symptoms like fatigue, weakness, pedal edema, weight gain, constipation, excessive sleepiness, mental slowing.
5. **Systemic illness** leukemia, anticoagulant therapy and injudicious use of hormones could be a cause.

Q.5. How will you treat a patient of pubertal DUB?

Ans: The following treatment is to be initiated only if all other causes are ruled out.

A Patient can be divided into three categories on the basis of severity of anemia.[6]

1. **Mild anemia** (Hb 9-10.5 gm)
   - Reassurance.
   - Menstrual charting.

- Perimenstrual nonsteroidal anti-inflammatory drugs.
- Iron and vitamin supplementation.
- Cyclical oral contraceptive pill for 3-6 months if symptoms persist.

2. **Moderate anemia** (7-9 gm)
   - Oral or parenteral iron with other hematinics
   - Non-hormonal – NSAIDS like mefenamic acid 500 mg bd to tds.
   - Tranexamic acid 1 to 3 gm daily during menstruation.
   - Hormonal treatment – cyclical progesterone treatment (medroxy progesterone acetate 10 mg/day for 14 days every 3 months).
   - Oral contraceptives (continuous or cyclical).
3. **Severe anemia** (< 7 gm)
   - Hospitalization.
   - If in hypovolemic shock – resuscitate with IV fuids (crystalloid) and blood transfusion.
   - Blood products will be required if coagulation profile is deranged, such patient should be managed in liaison with hematologist.
   - Hormonal therapy
     – IV conjugated equine estrogen (25 mg every 4 hours) as indicated till bleeding stops or diminishes significantly followed by oral progesterone or oral contraceptive pills.
     – Oral progestin norethisterone acetate can be given in a dose 10-20 mg 8 hourly till bleeding stops followed by gradual tapering.
     – Oral combined contraceptive 3-4 tablets per day till bleeding stops followed by tapering to 1 tablet/day over 3-4 weeks.
   - If bleeding is does not repond to above measures than surgical intervention with D and C or balloon tamponade may be necessary.

Maintenance therapy

- Hormones: Cyclic progesterones; usually medroxyprogesterone (lesser side effects and more effective in reverting hyperplasia) in a dose of 10 mg/day in a divided doses, typically, for 10-14 days each month starting from day 15 to day 26 of menstrual cycle for 3-4 cycles.
- Oral contraceptive can also be prescribed in a dose of 1 tablet/day for 21 days for 3-4 cycles.
- Oral hematinics to correct anemia.
- Exercise and dietary advise to reduce weight if obese.
- Menstrual charting.
- Follow-up after every cycle to see improvement, check compliance.
- Treatment can be stopped after 3-4 months or can be continued longer if patient desires. On stopping treatment patient should be evaluated to ascertain if cycles are regular with normal flow.

The treatment of systemic diseases causing menorrhagia is outside the scope of this chapter.

CASE 2

History

A 30-year primiparous women presented to the gyne OPD with complaints of heavy bleeding during periods for the last six months.

Examination findings

- *No pallor*
- *Abdomen soft*
- *Speculum exam – cervix and vagina healthy*
- *Vaginal examination – uterus normal sized, firm, smooth, nontender, no adnexal mass.*

What are the relevant points to be included in the history of this patient?

History

1. Menstrual history like amount, duration of bleeding and cycle length.

2. History of postcoital bleeding suggest cervical pathology like polyps, fibroid, ectropian and cancer of the cervix.
3. History of intermenstrual bleeding could be due to endometrial polyp or submucous fibroid.
4. History of pain abdomen and discharge per vaginum suggests pelvic inflammatory disease.
5. History of weight gain/lethargy/sleepiness/constipation suggests hypothyroidism.
6. History of dysmenorrheal/dyspareunia/dyschezia/dysuria/infertility is suggestive of endometriosis.
7. History of usage of intrauterine contraceptive device.
8. History of hormonal drug intake or herbal remedies which may contain estrogen.
9. History suggestive of bleeding disorder (as described in problem A).

Q.6. List the causes of menorrhagia in the reproductive age group.

Ans: Menorrhagia – is cyclical bleeding at regular intervals which is excessive in amount (> 80 mL) or duration (longer than 7 days) or both. It is generally caused by conditions affecting the uterus and its vascular apparatus.

Causes of menorrhagia could be:

1. **Anatomical**
   a. Submucous fibroid
   b. Adenomyosis
   c. Endometriosis
   d. Pelvic inflammatory disease
   e. Tubercular endometritis (early)
   f. Intrauterine contraceptive device
   g. Functioning ovarian tumors
   h. Uterine A-V malformation.
2. **Hormonal**
   a. Hypothyroidism
   b. Dysfunctional uterine bleeding.
3. **Systemic** – thrombocytopenia, leukemia.
4. **Drug related** – anticoagulant like warfarin, heparin, antiplatelet like aspirin, some herbal remedies rich in estrogen.

Q.7. What are the important differential diagnosis in this patient?

Ans:

1. Dysfunctional uterine bleeding
2. Pelvic inflammatory disease
3. Adenomyosis
4. Hypothyroidism.

Q.8. List examination finding for and against the differential diagnosis of dysfunctional uterine bleeding in this patient?

Ans: Table 22.1 would help in the differential diagnosis**:**

Q.9. What is your provisional diagnosis in this patient ? Will you order imaging for this patient?

Ans: The above patient is case of ovulatory DUB, as on history there are no sign and symptom suggestive of any systemic disease, the cycles are regular and on examination uterus is normal in size and nontender.

In this patient imaging is not indicated as it is required only if:

1. The uterus is palpable per abdomen
2. Vaginal examination has revealed mass of uncertain origin
3. Pharmacological treatment has failed.

Transvaginal ultrasound (TVS) should be the first line modality to assess the pelvis for structural abnormality. TVS is done to assess the endometrial lining, its thickness, detect any endometrial polyp, fibroid and adenomyosis, adnexal pathologies such as tubo-ovarian masses, endometriomas, etc. The detection of focal pathology within the uterine cavity (e.g. polyp and fibroid) can be enhanced by performing the scan immediately postmenstrual or with the use of saline as a contrast agent (sono-salpingography).

Q.10. How will you manage this patient?

Ans: This patient will be managed medically

- Menstrual charting
- Tab Tranexamic acid (500 mg) 8 hourly during periods.
- Follow-up after 3 months for response.

Table 22.1: Differential diagnosis of dysfunctional uterine bleeding

Symptoms and signs	*DUB*	*PID*	*Adenomyosis*	*Hypothyroidism*
Menorrhagia	+	+	+	+
Discharge foul smelling P/V	–	+	–	–
Dysmenorrhea	+/–	+	++	–
Dyspareunia	–	+	++	–
Dyschezia	–	–	++	–
On Examination				
Perspeculum	*DUB*	*PID*	*Adenomyosis*	*Hypothyroid*
Vagina	Normal	Discharge	Red, blue, brown deposits of endometriosis may be present	Normal
Cervix	Normal	Discharge seen	do	Normal
Pervaginum				
Cervix	Normal	Tender +	Tender +	Normal
Uterus-Size, shape	Normal	Normal	Normal	Normal
Mobility	Mobile	Restricted mobility if chronic PID	Restricted if associated with endometriosis	Normal
Tenderness	Nontender	Tenderness +	Tenderness +	Normal
Fornix	Free	One or both fornices may be thickened, tender or tender adnexal masses may be present	Adnexal tenderness and thickening is seen if associated with endometriosis	Normal

Q.11. What is definition of dysfunctional uterine bleeding? What are the different types of endometrial histology obtained in patients of DUB?

Ans: Dysfunctional uterine bleeding is defined as abnormal uterine bleeding that occurs in the absence of systemic or organic pathology of the genital tract. DUB is classified into Anovulatory and ovulatory bleeding.

Ovulatory DUB: The endometrial histology reveals various types of secretory endometrium.

a. *Irregular shedding of endometrium (Halban's disease):* It is due persistent corpus luteum. The menstruation comes on time, but is prolonged and not heavy. Histopathology reveals mixed picture of secretory and proliferative endometrium even on day 5-6 of menstruation. Treatment is NSAIDs up to 6 months. It is a self-limiting process.
b. *Irregular ripening*: In this condition, the endometrium receives inadequate support of progesterone due to deficient corpus luteal function and so breakthrough bleeding occurs before the actual menstruation in the form of spotting or brownish discharge. The endometrium reveals incomplete secretory changes. Treatment is to administer progesterone in the premenstrual phase.

Anovulatory DUB: The endometrial histology could be of the following types, the percentage of patients with abnormal histology in DUB is as shown in Table 22.2

a. Proliferative endometrium
b. Simple hyperplasia without atypia
c. Complex hyperplasia without atypia
d. Simple hyperplasia with atypia
e. Complex hyperplasia with atypia.

Table 22.2: Endometrial histology in DUB[7]

	Type of endometrial histology	*Percentage (%)*
1	Normal endometrium	50%
2	Endometrial hyperplasia	31.7%
3	Irregular shedding	6.9%
4	Irregular ripening	3.6%
5	Atrophic endometrium	3.6%
6	Chronic endometritis	1.4%

- **Simple hyperplasias** have endometrial glands with predominately simple (tubular or cystic) shapes, lack gland crowding, and have a low gland-to-stroma ratio.[8]
- **Complex hyperplasias** show gland crowding with an increased ratio of glands relative to the stroma. Complex glands have irregular shapes with branching and infoldings.[8]
- **Cytologic atypia** is defined when epithelial cells or nuclei lose their normally polarized columnar shape (i.e. loss of polarity), and when nuclear enlargement or variation in size and shape are present or abnormal nuclear staining quality with chromatin clumping or clearing.[8]

Q.12. What is a pictorial blood assessment chart? List other method of evaluation of amount of blood loss?

Ans: ***Pictorial blood assessment chart (PBAC)*** (Fig. 22.1 and Table 22.3) is a simple nonlaboratory method for semiobjective diagnosis of menorrhagia, using scores recorded by women themselves. It was first described by Higham et al. The scoring was based on the number of sanitary towels and tampons used each day and their degree of soiling. A score of 100 was used to define menorrhagia in its originally described form. The number and size of any clots passed were also taken into account and scored. Although the validity of this chart has been debated as it is very subjective, it is simple to use and is at present the best practical tool available for the assessment of menstrual blood loss. The method has been reported to have a sensitivity of 86% and a specificity of 89%.[9]

The ***alkaline hematin method*** is highly precise method of measuring blood loss. However, it is cumbersome and an impractical method in routine practice.

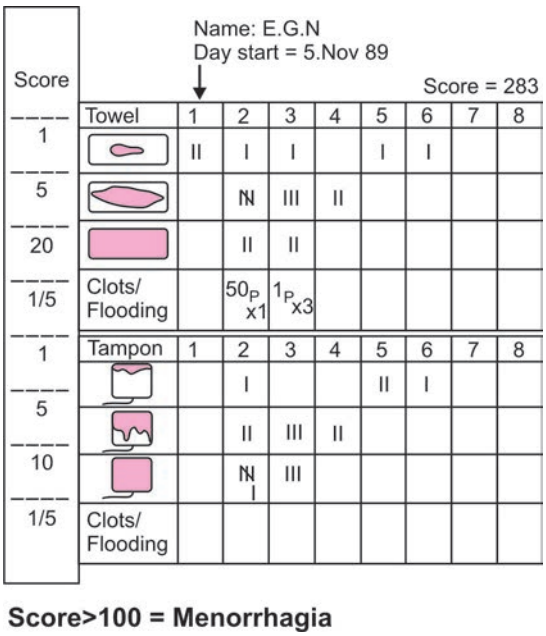


Fig. 22.1: Assessment of menstrual blood loss using a pictorial chart, British Journal of Obstetrics and Gynaecology, 97, 734-39. Source-Higham et al, (1990).

Table 22.3: Nonlaboratory menstrual blood assessment methods

Methods	*Points*	*Degree of staining*
Towels	1	Lightly stained
	5	Moderately soiled towel
	20	Completely saturated with blood
Tampon	1	Lightly stained
	5	Moderately soiled towel
	20	Completely saturated with blood
Clots	1	Small clot
	5	Large clot

Other tests used to quantify menorrhagia are hemoglobin, serum iron and serum ferritin. Measuring menstrual blood loss either directly (alkaline hematin) or indirectly ('pictorial blood loss assessment chart') is not routinely recommended for HMB. Whether menstrual blood loss is a problem, it should be determined not by measuring blood loss but by the woman herself.[9]

Q.13. What are the causes of menorrhagia in patients using intrauterine copper T device as a contraceptive?

Ans: The exact cause of increased blood loss is not known; the postulated mechanisms are:[10]

- Increased production of plasminogen activating enzymes leading to lysis of fibrin of blood clot.
- Increased vascularity of the endometrium.
- Hormonal asynchronization, because menstruation is advanced by about 2 days before the end of the luteal phase when the level of progesterone still remains relatively high. The bleeding is more related to surface contact and as such is greater with the lippes loop than copper T.

Q.14. What are the indications of endometrial sampling in AUB?

Ans: The recommendations for endometrial biopsy are:

1. All women with AUB > 45 years of age as incidence of endometrial cancer increases with age (Table 22.4).
2. Women who do not respond to medical therapy.
3. Persistent intermenstrual bleeding.
4. Those who have other risk factors for endometrial cancer.
5. Even in adolescents after 2 to 3 years of anovulatory bleeding, particularly in obese girls.

Endometrial biopsy should also be done if on ultrasonography endometrial morphology is abnormal or increased endometrial thickness on ultrasound (ET > 12 mm)[11] in premenopausal women.

Q.15. List different methods of endometrial sampling?

Ans:

1. **Dilatation and curettage** was used earlier for evaluation of endometrium, the disadvantages are that it requires dilatation and secondly, that it is a blind procedure which may miss focal lesion. In a study by Leather et al 60% of patients were found to have less than half of uterine cavity curetted and less than quarter in another in 16%.[12] In another study, D and C failed to detect 62.5% of intrauterine disorders subsequently found at hysterectomy.[13]
2. **Office endometrial aspiration biopsy** is also a blind sampling technique like D and C. But it is less painful as it does not require dilatation and chances of perforation are also very less. Endometrial aspiration showed a sensitivity of 89.6% and specificity of 100% in diagnosis of abnormal uterine bleeding.[14] Endometrial sampling can be done by Karman cannula, Pipelle device and Vabra aspirator.
3. **Hysteroscopic directed biopsy** is the gold standard for evaluation of endometrial pathology because it allows for direct visualization of endometrium and taking targeted biopsies. Hysteroscopy has shown to have a high sensitivity of 90-97% and specificity of 62-97%.[15] Office hysteroscopy is not used as routine screening method for evaluation of menorrhagia because it is invasive, expensive, requires specialized training to perform and

Table 22.4: Likely rates of endometrial cancer per 10,000 consultations for HMB in primary care[9]

Age range (years)	30	35	40	45	50	55	60	65	70
% risk of endometrial cancer	0.01	0.03	0.06	0.13	0.25	0.45	0.76	1.14	1.52

interpret. Its main role has been to verify the intrauterine status visually and take a directed biopsy when less invasive measures such as endometrial blind biopsy, sonography are in conclusive.

Q.16. List the investigations done under special circumstances?

Ans: *Laboratory tests (NICE guideline)*[9]

=• Testing for coagulation disorders (for example, von Willebrand disease) should be considered in women who have had HMB since menarche and have personal or family history suggestive of a coagulation disorder.

• Thyroid testing should only be carried out when other signs and symptoms of thyroid disease are present.

Q.17. What is the role of dilatation and curettage in management of patient of menorrhagia?

Ans: Dilatation and curettage was traditionally used earlier for both diagnosis and as a therapeutics procedure. It has been replaced by less traumatic, less painful and equally efficacious, outpatient procedure of endometrial aspiration biopsy in which dilatation is not required as the cannula is only of 4 mm hence less painful. The therapeutic effect of dilatation and curettage is limited to the current menstrual cycle, therefore, its use is justified only in patient with heavy bleeding not responding to medical management, or patients presenting with shock due to heavy bleeding.[16]

Q.18. What is the medical management of DUB?

Ans: The medical management consists of:

Nonhormonal methods are the first line drugs:

1. ***NSAIDs*** reduce menstrual blood loss by 20-50% as they inhibit cyclo-oxygenase thus reducing prostaglandin levels (increased levels found in patients with menorrhagia). Mefenamic acid is prescribed in a dose of 500 mg three times per day during the menstrual cycle.[17]
2. ***Tranexamic acid*** reduces menstrual loss by inhibiting the action of plasminogen activators, which activate lysis of blood clots. If given in a dose of 1 gm three to four times per day during menstruation it reduces blood loss by 50%.

Hormonal therapy

1. ***Progesterone*** – progestins halt endometrium growth and allow for an organized sloughing of the endometrium. They increase the PGF-2/PGE ratio stimulating arachidonic acid formation in the endometrium.[1]
   - ***Cyclic progesterone therapy*** – are typically efficacious for anovulatory bleeding in pubertal and perimenopausal women as the goal of treatment for is to restore the natural cycle of orderly endometrial growth and shedding. Medroxyprogesterone acetate 5 to10 mg daily for 2 weeks every month for 3-4 cycles is sufficient for anovulatory cycle.[11] Cyclic progesterone for 21 days starting from day 5 to 26 every month for 3-6 cycles is advocated for endometrial hyperplasia.
   - ***Continuous progesterone*** can also be given in those patients who cannot tolerate heavy withdrawal bleeding and are anemic.[18] Ovulatory DUB does not respond to luteal phase progesterone, hence treatment with progesterone (norethisterone or medroxyprogesterone) for 21 days is effective.[1]
   - ***Intrauterine progesterone*** – the levonorgestrel IUD (Mirena) contains 52 mg of levonorgestrel, which is released at daily dose of 20 μg over 5 years. The daily dose of progesterone causes decidualization of the endometrium stroma and atrophy of the endometrium glands. The LNG-IUS is effective in both ovulatory and anovulatory bleeding. It has been demonstrated to reduce menstrual blood loss by 94% after 3 months and is well tolerated by majority of women.
   - ***Depot medroxyprogesterone(depoprovera)*** 150 mg every 3 month is also given in anovulatory DUB. The progestin causes

endometrial thinning to atrophic levels, which causes amenorrhea with intermittent spotting hence is not a very popular therapy.

2. ***Combined estrogen and progesterone:*** Oral contraceptives are among the best treatment options in women who present with episodes of heavy bleeding. They are also effective in ovulatory DUB. To stop or slow a heavy period, a " taper" can be performed with any of the low-dose monophasic pill. The treatment begins with 3-4 tablets per day till bleeding stops, and then gradual tapering to 2 tablets per day for the next three days, and then one pill per day until pack is finished and withdrawal bleeding begins. The patient can be started on one tablet per day of OCP for next 3-4 cycles or can be started on cyclic progestin therapy if estrogens are contraindicated.[11]
3. ***Estrogen:*** High dose estrogen therapy is useful in controlling acute bleeding episodes as because it promotes rapid endometrial growth to cover denuded endometrial surfaces. Estrogen is usually used in the intravenous or oral form for acute heavy bleeding. It is very effective method but not used commonly at present but could be given if one method fails to control acute heavy bleeding.
   - **Intravenous estrogen** (25 mg conjugated equine estrogens every 4 hours for 24 hours or until bleeding diminishes significantly) is the usual regimen and has been shown to be successful in most of the cases.
   - **Oral estrogen** – when bleeding is heavy and does not require inpatient treatment, high doses oral estrogen can be used as an alternative (1.25 mg conjugated estrogen or 2.0 mg micronized estradiol every 4-6 hours for 24 hours), the dose is then taperd down to one dose per day for 7 to 10 days after the bleeding is controlled.

     All of these initial estrogen treatments should be followed by progestin treatment or combi-nation contraceptives to stabilize the estrogen stimulated endometrial growth.[11]
4. ***Gonadotropin Releasing Hormones Agonist (GnRHa):*** Gonadotropin releasing hormones agonist-like goserein acetate, leuprolide acetate can achieve short-term relief of bleeding and are often used prior to surgical treatment such as ablation, myomectomy, and hysterectomy.
   When administered continuously, GnRH agonists reversibly suppress pituitary secretion of gonadotropins and create a hypoestrogenic state.[1] The amenorrhea thus achieved by use of GnRHa provides relief of bleeding, which allow the hemoglobin to rise and decrease the risk of transfusion in subsequent surgery. The role of GnRHa in DUB is limited because of the high cost, effect on bone density, and other side effects from the estrogen deficiency (e.g. hot flushes and night sweat), as long-term use (more than 6 months) is generally not recommended.

Q.19. What are the surgical management options in of DUB?

Ans: The options are endometrial ablation, endometrial resection and hysterectomy.

Endometrial ablation

Endometrial ablation is an option in women in whom medical management has failed, who not desirious of future fertility, who wish to avoid a hysterectomy and who are not candidates for major surgery. Endometrial resection involves destruction of the entire endometrial thickness with superficial myometrium while leaving the rest of uterus intact.

Exclusion criteria[1]

- Uterine size >12 weeks
- Premalignant or malignant lesion of the cervix and endometrium
- Acute pelvic inflammatory lesion
- Bleeding disorder
- Submucous and intramural fibroids
- Septate uterus
- Previous failed endometrial ablation procedure

- Incidental pregnancy
- Desire for future fertility
- History of gynecological malignancy within the last 5 years.

Pretreatment with an agent such as GnRHa, medroxyprogesterone acetate, or danazol is essential to make the endometrium thin for better results.

Endometrial Ablation Techniques (Table 22.5)

The **first generation** procedures (endometrial resection and roller ball or laser ablation) are performed through a hysteroscope after uterine infusion of a distention media to improve visualization. They are more time consuming, require regional or general anesthesia, and are technically more difficult than the second gene-ration methods.

The **second generation** methods are performed "blind" (without hysteroscope), usually in the outpatient setting under local anesthesia, require less operative time and minimum cervical dilatation. These methods include cryoablation, thermal balloon ablation, radiofrequency ablation, microwave, and diode laser thermotherapy. However there is no difference in patient outcome, rate of amenorrhea and patient satisfaction rate with any method.

Q.20. When should hysterectomy be done in patient of DUB.?

Ans: Hysterectomy should not be used as a first-line treatment solely for HMB. Hysterectomy should be considered only when:[9]

- Other treatment options have failed, are contraindicated or are declined by the woman
- The woman no longer wishes to retain her uterus and fertility.

Q.21. How would you counsel a woman wanting a hysterectomy?

Ans: Counseling will include explaining the major, minor risks and extra procedures that might be required during surgery.[19]

Table 22.5: Endometrial ablation techniques

First generation techniques	*Second generation techniques (Global endometrial ablation)*
• Hysteroscopic laser ablation (HLA)	• Fluid balloon: *cavaterm, thermachoice, menotreat*
• Transcervical resection of endometrium (TCRE)	• Microwave*: MEA*
• Rollerball endometrial ablation	• Cryotherapy: *Cryogen, Herchoice* • Electrode-Mesh: *Vesta* Balloon: *Novasure* • Interstitial laser: *ELITT* • Photodynamic therapy • Hydrothermal ablation

Major risks

- Injury to the bladder and/or the ureter (seven women in every 1000) and/or long-term disturbance to the bladder function (uncommon).
- Injury to the bowel: Four women in every 10,000 (rare).
- Hemorrhage requiring blood transfusion, 23 women in every 1,000 (common).
- Return to theater because of bleeding/wound dehiscence, and so on – seven women in every 1,000 (uncommon).
- Pelvic abscess/infection: Two women in every 1,000 (uncommon).
- Venous thrombosis or pulmonary embolism, four women in every 1,000 (uncommon).
- Risk of death within 6 weeks, 32 women in every 100,000 (rare). The main causes of death are pulmonary embolism and cardiac disease.

Frequent risks

- Wound infection, pain, bruising, delayed wound healing or keloid formation.
- Numbness, tingling or burning sensation around the scar (the woman should be reassured that this is usually self-limiting but warned that it could take weeks or months to resolve).

- Frequency of micturition and urinary tract infection.
- Ovarian failure.

Any extra procedures which may become necessary during the procedure

- Blood transfusion.
- Repair to bladder, bowel or major blood vessel.
- Oophorectomy for unsuspected disease. Oophorectomy for unexpected disease found at hysterectomy should not be performed without consent. All women undergoing hysterectomy should be informed that unexpected disease may be found in one or both ovaries and their wishes (to remove this or leave alone) should be documented.

Q.22. What are types of hysterectomy done in patients of DUB refractory to medical management?

Ans: Three types of hysterectomies are performed based on the route of removal of the uterus[9]

1. Abdominal hysterectomy (AH)
2. Vaginal hysterectomy (VH)
3. Laparoscopic hysterectomy (LH) LH has three subdivisions:
   a. Laparoscopically assisted vaginal hysterectomy (LAVH), where a vaginal hysterectomy is assisted by laparoscopic procedures that do not include uterine artery ligation.
   b. Laparoscopic hysterectomy [LH(a)], where the laparoscopic procedures include uterine artery ligation.
   c. Total laparoscopic hysterectomy (TLH), where there is no vaginal component and the vaginal vault is sutured laparoscopically.

Individual assessment is essential when deciding the route of hysterectomy. The following factors need to be taken into account:

- Presence of other gynecological conditions or disease
- Uterine size
- Presence and size of uterine fibroids
- Mobility and descent of the uterus
- Laxity of the vagina
- Previous surgery
- Expertise of the operating surgeon.

CASE 3

History

A 42 year-old P3L3 presented to the gyne OPD with complaints of the menorrhagia with severe dysmenorrhea, dyspareunia with increased frequency of urine for 2 years. There is no family or personal history of any cancer.

Examination

- Obesity +
- Pallor +
- No Lymph nodes, thyroid and breast normal
- Per abdomen – uterus is just palpable
- Per speculum examination – cervix and vagina healthy.
- Per vaginum examination – uterus is 12 weeks, midposition, firm, restricted mobility, both fornices free and nontender.

Q.23. What is the differential diagnosis in this patient?

Ans:

1. Uterine fibroid (discussed in a separate chapter)
2. Adenomyosis
3. Uterine malignancy (endometrial cancer, sarcomas) (see chapter on post-menopausal bleeding).

Q.24. What is adenomyosis?

Ans: Adenomyosis is a condition whereby endometrial glands and stroma deep in the myometrium are associated with surrounding myometrial hypertrophy. It is thought to affect 1% of women. The average age of symptomatic women is usually older than 40 years, but it can be present in younger women.[20]

Q.25. How does it present?

Ans: Adenomyosis is often asymptomatic.

The common symptoms associated with adenomyosis are:[20]

- Menorrhagia (23-82%)
- Dysmenorrhea (up to 50%)
- Dyspareunia and chronic, erratic or constant pelvic pain (less commonly reported)
- Pressure symptoms on bladder and bowel from bulky uterus (uncommon).

Signs

- The uterus is diffusely enlarged (usually less than 14 weeks size), and it is soft and tender, particularly at the time of menses.[21]
- Mobility of uterus is not restricted, if there is no associated adnexal pathology. However, it commonly coexists with a number of other pelvic pathologies like endometriosis and fibroid which can cause restricted mobility.

Q.26. What are the ultrasound feature of adenomyosis? What is the sensitivity and specificity of ultrasound for diagnosing adenomyosis?

Ans: Ultrasound features of adenomyosis include:[22]

- Rainy pattern of acoustic shadowing, normal vessels, enlarged uterus.
- Myometrial cysts characterized by cystic spaces ranging from 2-7 mm in diameter located within the myometrium (52% of uteri). Presence of myometrial cysts for diagnosing adenomyosis has a sensitivity of 45%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 82%.
- Some other diagnostic features are diffuse heterogeneous echo-texture of myometrium, asymmetric thickening of either the anterior or posterior wall of the uterus, subendometrial myometrial cysts which cause the endometrial - myometrial junction to be poorly defined.

However, there are no pathognomonic sonographic characteristics that correlate completely with the histology, hence tissue diagnosis is essential.

Q.27. What is the role of conservative management in adenomyosis?

Ans: The definitive treatment is hysterectomy. However, there are some reports suggesting that conservative options may be effective. Like endometriosis and uterine myomas, adenomyosis presents the typical characteristics of estrogen-dependent diseases. The medical treatment of adenomyosis is based on the hormonal dependency of the disease and its similarities with endometriosis. that targets the ectopic endometrium directly. Gonadotropin-releasing hormone agonists, danazol and intrauterine levonorgestrel, or danazol-releasing devices have been used in the treatment of adenomyosis. There are reports suggesting that medicated intrauterine device, uterine artery artery embolization and MRI guided focused ultrasound urgery may be effective.[23,24] Despite the evidence of benefit with hormonal treatment, few studies have been performed on medical therapy for adenomyosis.

CASE 4

History

A 48-year-old multiparous lady with history of irre-gular and heavy bleeding: 12 months.

Examination

- Per speculum – cervix and vagina healthy
- Per vaginum – uterus 8 weeks, firm, smooth, mobile, nontender.

Q.28. What are possible differential diagnosis in this patient?

Ans: The possible differential diagnosis are:

1. Perimenopausal DUB
2. Fibroid polyp
3. Endometrial carcinoma

The above conditions have been discussed in various sections.

CASE 5

History

- A 36 year-old P2
- Irregular uterine bleeding not associated with period of amenorrhea.

Examination

- Abdominal examination – normal.
- Per speculam – 4 × 4 cm polyp coming out of cervix, surface inflamed but smooth, vagina healthy.
- Per-vaginum- cervical rim felt all around the polyp, seems to be originating from the uterine cavity, firm in consistency with a smooth surface. Uterus 8 weeks in size, mobile, ante-verted, firm, nontender, no adnexal mass.

Q.29. What are the salient points to be taken in the history?

Ans:

- Age – as the age advances, risk of endometrial cancer increases.
- Parity – high parity is a risk factor for cervical cancer and low parity is a risk factor for endometrial cancer.
- Menstrual complain like amount, duration, cycle length, period of amenorrhea prior to heavy bleeding.
- History of postcoital bleeding indicates cervical pathology like polyps, fibroid, ectropian and cancer.
- History of intermenstrual bleeding can be due to endometrial polyp or submucous fibroid.
- History of pain abdomen, discharge per vagi-num, backache to rule out pelvic inflammatory disease.
- History of intrauterine contraceptive device insertion.
- History of bowel or bladder complaints.
- History of hormonal drug intake.
- History of onset of symptom following D & C (retained POCs or endometritis can cause irregular bleeding).
- Personal and family history of any cancers.

Q.30. What is the differential diagnosis? How will you differentiate between two?

Ans:

A. Uterine fibroid polyp.
B. Chronic uterine inversion (Table 22.6)

Q.31. How will you do a polypectomy in this case?

Ans: Vaginal polypectomy will be planned with a consent for hysterectomy in case of uncontrolled vaginal bleeding. Under anesthesia traction is given on the pedicle of the polyp to locate its origin. Clamps are then applied on the pedicle as high as possible, the pedicle is cut distal to the clamp and transfixed.

If the pedicle is broad and cannot be reached, the myoma is initially removed by incising the psuedocapsule (enucleatation as done in an abdominal myomectomy) followed by transfixation suture on the pedicle and removal of the redundant pedicle distal to the ligature.

A polyp can harbor malignancy both in the pedicle and in core of the tumor and should be sent for histopathology.

Q.32. What are the different types of polyp and management for each type?

Ans: Polyps can be of different types:

1. **Endometrial polyp** – these are single or multiple and pedunculated, they are usually larger than 1 cm, arise from the endometrium and are soft in consistency.

Table 22.6: Differential diagnosis of fibroid polyp and chronic uterine inversion

	Fibroid polyp	*Chronic uterine inversion*
History	No relation to vaginal delivery	Onset of symptom following vaginal delivery usually
Per speculum	Cervical rim is seen all around polyp Surface is smooth	Cervical rim is high up in incomplete uterine version but not seen in complete uterine inversion Surface has shaggy appearance
Per vaginum	Uterus is in normal position	Uterus is not felt or cup shaped depression is felt at fundus
Per rectal examination – is more informative to note fundal depression or displacement of the uterus.		
Uterine sound test	Uterine sound can be passed into the uterine cavity	Uterine sound can be passed only for short distance in incomplete uterine inversion and cannot be passed at all in complete uterine inversion
USG pelvis	Associated fibroid can be diagnosed	Absence of endometrial cavity is diagnostic

2. **Fibroid polyp** – is almost always due to extrusion of a submucous fibroid into the uterine cavity, the overlying surface is lined by endometrium. The uterus contracts to expel the polyp out through the cervix. There is usually necrosis, infection and hemorrhage at the surface. The pedicle is broad. There could be associated uterine fibroids.
3. **Placental polyp** – a placental polyp is an intrauterine, polypoid or pedunculated mass of placental tissue retained after an incomplete abortion or term pregnancy. A retained bit of placental tissue when adherent to the uterine wall gets organized with the surrounding blood clots.

Management options for polyps

1. **Dilatation and curettage** – endometrial polyps can be curetted out, however, the chances of recurrence are higher due to incomplete removal as it is a blind procedure and can miss 60% of focal lesions in the uterine cavity.
2. **Operative hysteroscopy** – hysteroscopic removal of endometrial polyp, fibroid polyp (intrauterine) and placental polyp has a higher success rate, as it is visually directed procedure.
3. **Polypectomy** – vaginal approach for removing polyp lying in the vagina is discussed above. If the pedicle of polyp is thin which can be removed by simply twisting it after holding it with sponge holder.
4. **Hysterectomy** can be done under following circumstances
   - If woman does not desire to preserve the uterus
   - Coexistent uterine or adnexal pathology
   - Recurrent symptomatic polyp
   - High suspicion of malignancy.

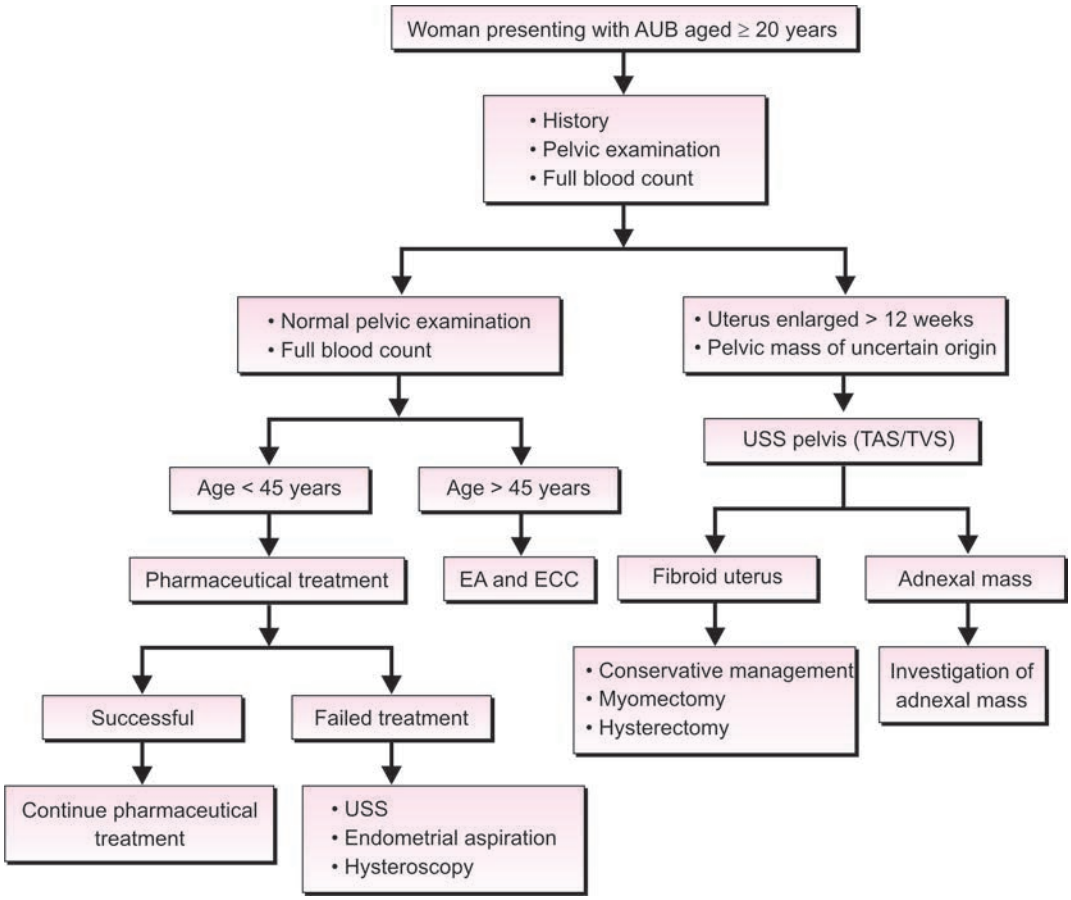
Q.33. What are the other potential structural cause of irregular uterine bleeding?

Ans:

- Endometrial hyperplasia
- Endometrial carcinoma
- Uterine cancers
- Infections – endometritis, PID, tuberculosis
- Foreign objects (intrauterine device) due to chronic inflammatory response
- Vascular (arteriovenous malformations).

Q.34. What is the treatment for chronic endometritis causing irregular uterine bleeding?

Flow Chart 22.1: Management of a woman ≥ 20 years with AUB



Ans: Endometritis may be caused by several processes, including infections, intrauterine foreign bodies or growths, and radiation therapy; however, a significant number of patients have no obvious cause. Inflammatory cells in this condition produce proteolytic enzymes that delay normal healing and damage the endometrium, which makes it fragile and prone to erosions. The inflammatory cells also can release prostaglandins and platelet-activating factors, which are potent vasodilators. Chronic endometritis may be one of the causes of abnormal bleeding in women with leiomyomas or polyps. The treatment consists of antibiotics, such as doxycycline, 100 mg, twice a day for 10-14 days.

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23 Approach to a Case of Adnexal Mass in a Young Patient

INTRODUCTION

Adnexal masses present a diagnostic dilemma; the differential diagnosis is extensive, with most masses representing benign processes. However, without histopathologic tissue diagnosis, a definitive diagnosis is generally precluded. Physicians must evaluate the likelihood of a pathologic process using clinical and radiologic information and balance the risk of surgical intervention for a benign versus malignant process.

The term adnexa is derived from the pleural form of the Latin word meaning "appendage." The adnexa of the uterus include the ovaries, fallopian tubes, and structures of the broad ligament. Most frequently, adnexal masses refer to *ovarian masses or cysts*; however, paratubal cysts, hydrosalpinx, and other non-ovarian masses are also included within the broader definition of adnexal masses.

Frequency

Determining the true frequency of adnexal masses is impossible because most adnexal cysts develop and resolve without clinical detection. When assessing the clinical significance of an adnexal mass, considering several age groups is important.

- In girls younger than 9 years, 80% of ovarian masses are malignant and are generally germ cell tumors. During adolescence, 50% of adnexal neoplasms are adult cystic teratomas. Women with gonads that contain a Y chromosome have a 25% chance of developing a malignant neoplasm. Endometriosis is uncommon in adolescent women but may be present in as many as 50% of those who present with a painful mass.[1] In sexually active adolescents, one must always consider a tubo-ovarian abscess as the cause of an adnexal mass.
- In women of reproductive age who have had adnexal masses removed surgically, most are benign cysts or masses. Ten percent of masses are malignant, many tumors in patients younger than 30 years are of low malignant potential. Thirty-three percent are adult cystic teratomas, and 25% are endometriomas.[2] The rest are serous or mucinous cystadenomas or functional cysts.

CASE 1

A 25-year-old lady, Mrs A presented with pain lower abdomen since 2 months. On examination a 5 × 5 cm firm to cystic mass, slightly tender with restricted side to side mobility is felt in the left adnexa.

To arrive at a diagnosis, following **history** should be taken

1. Amenorrhea
2. Chronic pelvic pain
3. Infertility
4. Dyspareunia
5. Backache

6. Discharge per vaginum
7. Urinary complaints
8. Bowel complaints

1. Amenorrhea

Important in cases of ectopic pregnancy and may be present in later stages of genital kochs

2. Chronic pelvic pain

May be seen in cases of chronic pelvic inflammatory disease (PID) due to hydrosalpinx. The pain can also be related to adhesions surrounding the ovary and fallopian tube.

Also seen in endometriosis due to secretion of inflammatory substances such as prostaglandins, cytokines and growth factors that initiate the sequences of events resulting in development of pain. The extravasated debris and blood from endometriotic implants may stimulate an inflammatory reaction in peritoneal Cavity with production of the above mentioned substances.[3]

3. Infertility

- In chronic PID, it occurs due to peritubular and periovarian adhesions which may interfere with ovum pick up or due to complete obstruction of tube and disturbance of tubo-ovarian relationship.
- In endometriosis, possible mechanisms for infertility include pelvic adhesions, chronic salpingitis, altered tubal mobility, distorsion of tubo-ovarian relation and impaired oocyte pick up. Other mechanisms proposed include, altered immune system response, implantation failure etc.[3]
- It is also commonly seen in genital tuberculosis. Possible mechanisms include destruction of endometrium, tubal obstruction, peritubal adhesions, etc.

4. Dyspareunia

Seen in endometriosis due to stimulation of pain fibers by stretching of scarred, inelastic tissue or by direct pressure on nodules and endometriosis embedded in fibrous tissue.

5. Dysmenorrhea

Congestive dysmenorrhea seen in cases of PID, endometriosis. In endometriosis, dysmenorrhea is usually progressive and is not relieved by NSAIDs/oral contraceptive pills.

6. Urinary complaints

- Dysuria may be seen in cases of PID due to associated urethritis.
- Urinary complaints like flank pain, urgency, frequency and hematuria may be seen in cases of involvement of urinary system by endometriotic implants.
- Urinary difficulty may be seen in large ovarian tumors due to compression.

7. Bowel complaints

- Constipation is seen in cases of ovarian tumors due to compression and or gut involvement.
- Also, complaints like diarrhea, hematochezia, dyschezia, tenesmus, etc. may be seen in cases of bowel involvement by endometriotic implants.[3]

8. Backache

Seen in endometriosis due to involvement of rectovaginal septum or uterosacral region as there is premenstrual swelling of ectopic implants.

9. Mentrual irregularities

- Menorrhagia may be seen in initial stages of genital tuberculosis.[4]
- Irregular uterine bleeding/spotting preceded by amenorrhea in ectopic pregnancy.
- Metrorrhagia/menometrorrhagia in cases of granulosa cell tumors.

10. History of low grade fever with evening rise of temperature, night sweats, anorexia, weight loss, cough with sputum, hemoptysis to rule out tuberculosis.
11. History of prior medication/any procedure if she underwent in the past.

Menstrual history

- Bleeding duration, regularity, amount of blood loss (Clots+/-)
- Associated dysmenorrhea
- If present –(spasmodic/congestive)
- History of relief in symptoms and if so, with which drug.
- Any irregularity in menses

Obstetric history H/o surgical MTPs, if repeated predisposes to PID

Past history

Any chronic medical/surgical illness

On examination

General examination:

- General condition
- Vitals
- Pallor
- Cervical/axillary lymphadenopathy

Per abdomen:

- Description of mass if present, e.g. mass arising from the lower abdomen, its consistency, surface, any vascularity over the surface, side to side mobility, whether lower limit could be reached or not, tenderness present/absent.
- Associated free fluid.
- Any other associated organomegaly

Per speculum examination:

- Condition of cervix and vagina. Any associated discharge.

Per vaginal examination (P/V):

- Size of uterus –Anteverted (A/V) retroverted (R/V). If any mass felt –description of the mass, its consistency, side to side mobility, tender/non tender, relationship with uterus, mobility associated with cervical motion.

Per rectal examination (P/R):

- For confirmation of P/V findings
- To feel for any nodularity on uterosacrals.

Laboratory studies

- A complete blood count (CBC) helps evaluate for presence of inflammation and anemia.
  - An infected mass such as a tubo-ovarian abscess results in an increased WBC count with an associated left shift.[5]
  - Adnexal masses rarely cause anemia, but because they often require surgical removal, this information should be known.
- Chest X-ray, Mantoux test – these are done to rule out tuberculosis
- Urine or serum beta human chorionic gonadotropin (β-hCG) should be obtained in women of reproductive age to rule out pregnancy and pregnancy-related etiologies of adnexal masses.
- CA-125 is a marker that is elevated in approximately 80% of women with epithelial ovarian cancer with sensitivities of 50% in women with stage I disease and 90% in patients with advanced disease.[6] However, it can be elevated in many other conditions, including gynecologic etiologies such as endometriosis, uterine fibroids, pregnancy, and nongynecologic conditions such as gastroenteritis, pancreatitis, cirrhosis, and congestive heart failure. As such, the specificity of CA-125 is limited and is not recommended for routine screening purposes in the general population.
- Other serum markers such as AFP and LDH can be helpful when a germ cell tumor is suspected.
- Urine analysis (U/A) results are generally normal in the presence of an adnexal mass.
  - Bladder pathology may present with symptoms of an adnexal mass and may be discovered based on U/A results.
  - Appendicitis can present similar to an adnexal mass but is often associated with WBCs in the U/A findings.
- Results from testing stool for blood should be negative for adnexal masses but may be positive in those women with colonic pathology.
- Serum electrolytes should not be altered by an adnexal mass; however, symptoms associated

with masses, such as nausea and vomiting, can cause alterations that must be known before anesthesia and surgery is considered.

- Measuring other hormone levels is generally of limited value in the evaluation of adnexal masses. Obtaining estrogen and progesterone levels may be helpful in women suggested to have functional tumors, such as germ cell tumors, or if a girl younger than 12 years is being evaluated.

Imaging studies

- The most commonly performed test to evaluate an adnexal mass is transabdominal or transvaginal ultrasonography.
  - This test helps to demonstrate the presence of the mass and organ of orign (e.g., ovarian, uterine, bowel). It also provides the mass size, consistency, and internal architecture. Scoring systems, such as that suggested by DePriest[7] and associates, can then be used to determine the likelihood of a malignant component.
  - Hysterosonography (ultrasonography with the presence of fluid in the uterine cavity) may be used to help distinguish a uterine mass. However, active tuberculosis is a contra indication.
  - Color Doppler ultrasonography can be used to evaluate the resistive index of the mass vessels, which, when low, has been indicative of a malignancy because of rapid vascularization.[7]
- Pelvic radiographs are generally not helpful in the evaluation of adnexal masses. A dermoid cyst generally contains areas of calcification that may be picked up on a plain radiograph.
- CT scans are most useful for assessing the remainder of the abdomen and pelvis when metastatic disease is suspected. Incidental adnexal masses are sometimes found when CT is performed for evaluation of other conditions. As with ultrasonography, CT scan can help identify the size, location, and relationship to other organs. CT scan is less effective than ultrasonography for determining the internal architecture of these masses.
- MRI scans can help characterize adnexal mass characteristics in select cases when ultrasonographic findings are limited.

In the above case of Mrs A, following differential diagnosis should be considered:

1. Ectopic pregnancy
2. Ovarian tumour (benign/malignant)
3. Endometrioma
4. Genital tuberculosis
5. Pelvic inflammatory disease (Tubo-ovarian mass)
6. Broad ligament/pedunculated fibroid
7. Ovarian torsion
8. Folicular cysts
9. Corpus luteum
10. Follicular cysts
11. Hydrosalpinx
12. Non-gynecological causes like appendicitis, diverticular disease.

Management

If the final diagnosis is ectopic pregnancy, the various options available are:

1. Expectant management, which may not be possible in this patient in view of big tender mass.
2. Conservative (medical management)

Q.1. What are the criteria for medical management?

Ans:

a. gestational sac <3.5 cm
b. βHCG <15000 mIU/ml
c. hemodynamically stable[8,9]

This patient has mass 5 × 5 cm and beta hCG was 20,000 mIU/ml, so she was not a fit patient for medical management.

Q.2. What are the criteria for the expectant management in ectopic pregnancy?

Ans:

a. Gestational sac <2 cm
b. βHCG < 1000 U/ml
c. Hemodynamically stable patient

Q.3. What are the various options in medical management of ectopic pregnancy?

Ans:

a. Single dose methotrexate in the dose of 50 mg/sq.m IM, measure β-hCG on day 4 and 7
   If difference >15 percent, repeat weekly until undetectable
   If difference <15 percent repeat methotrexate and begin as new day 1
b. Variable dose regime: Methotrexate 1 mg/kg IM days 1,3,5,7
   Leukovorin 0.1 mg/kg IM days 2,4,6,8[10-12]
   Measure weekly β-hCG till undetectable.

Q.4. What are the common side effects of methotrexate therapy?

Ans: Liver involvement (12%), stomatitis (6%) and gastroenteritis (1%).[13] Rarely bone marrow depression may be seen.

Q.5. What are the various surgical management procedures?

Ans: Options—salpingectomy (laproscopic or on laprotomy)

- Salpingotomy
- Salpingostomy

Q.6. In which cases segmental resection and anastamosis is done?

Ans: Resection of tubal mass and reanastomosis is sometimes used for unruptured isthmic pregnancy because salpingostomy may cause scarring and subsequent narrowing of small isthmic lumen.

Q.7. What are the risk factors for persistent ectopic pregnancy?

Ans:

1. Small pregnancies viz. less than 2 cm
2. Early therapy viz. before 42 days
3. β-hCG levels>3000 u/ml
4. Implantation medial to the salpingostomy site

CASE 2

A 32-year-old Mrs B, P3 with history of pain in lower abdomen. On examination mass about 4 × 4 cm felt in left fornix, nodularity on uterosacrals. β-hCG negative,USG (right ovary normal, left ovary 4.3 × 3.8 cm cystic lesion with internal echoes). CA-125 78 mIU/ml. Provisional diagnosis of ovarian endometrioma.

Q.8. What are the various options in medical therapy?

Ans:

1. High dose estrogen/progesterone combination: act by causing decidualization followed by involution and necrosis. However, this regime has side effects like mastalgia, weight gain, nausea, headache, irregular bleeding.
2. Progesterogen only regimens: Because of the side effect of the above mentioned regimen these have become more popular. These act by inhibiting LH release and thereby suppressing ovarian steroidogenesis and promoting decidualization of the endometrium.
3. GnRH analoges: Act by down regulation of pituitary ovarian axis leading to fall in the estrogen levels.
4. Danazol: It is a 17 α-ethinyl testosterone. It acts by inhibiting GnRH secretion, thereby inhibiting ovarian steroidogenesis. Also, it displaces the androgens from sex binding globulin and increases the clearance of estradiol. Dose: 400-800 mg/day for 6 months.

Q.9. What is add back therapy?

Ans: Estrogen replacement "add back therapy" is given to reduce unwanted side effects of hypoestrogenism in cases of long-term GnRH agonist regimens, without reducing the efficacy of treatment. The rationale for this approach is "estrogen threshold hypothesis" which states that certain threshold level of estrogen is low enough to suppress endometriosis but is enough to relieve symptoms and minimize bone loss. The various combination "add back therapy" used are – conjugated equine estrogens 0.3 mg, 0.625 mg + medroxy progesterone acetate 2.5 mg daily. Estradiol patches 25 pgm/day and 50 pgm/day.Norethisterone acetate 5-10 mg/day also has some beneficial effect on menopausal therapy.

Q.10. What are the side effects of danazol therapy?

Ans: These include acne, hirsutism, dyslipidemia, vasomotor symptoms, weight gain, muscle cramps, etc.

Q.11. What are the other options in the management of endometriosis?[13]

Ans: Conservative surgery may be done which include

a. Incision and drainage of the cyst contents followed by fulguration of the cyst lining in case of small cysts (< 3 cm).
b. Cyst excision (laparoscopic/laparotomy): if cyst size > 3 cm.

Q.12. What is the role of postoperative medical treatment?

Ans: Initiation of this therapy may inhibit the activity of any residual disease, suppress ovulation and decrease the activity of adverse effects of peritoneal spillage during resection. However, it is to be avoided in patients who are trying to conceive as best chance for postsurgical conception is during the initial 6 months.[14]

Q.13. What is the role of assisted reproductive techniques in patients with associated infertility?

Ans: It is indicated when spontaneous conception is not achieved within 3 years of surgical resection or within one year of repair of tubal obstruction associated with endometriosis or when there is associated male factor infertility.[15]

CASE 3

A 24 years P 1, with secondary infertility and back ache. On examination 6 × 6 cm mass variegated feel in right fornix.Ultrasonography showed 7 cm complex mass in right adnexa. CA-125 was 50 mIU/ml, ESR raised, tuberculin test positive, X-ray chest negative. Endometrial biopsy showed few granulomas, but no acid-fast bacilli.

With all this background diagnosis of genital tuberculosis was made.

Q. 14. How do you manage genital tuberculosis?
The mainstay of treatment is medical though surgery may be required in some cases Treatment is given under category I under DOTS strategy. The principle is to give four drugs (H, R, Z, E) for initial 2 months followed by 2 drugs for remaining 4 months (H,R) in the continuation phase.[16] DOTS is the strategy to ensure cure by providing the most effective medicine and confirming that it is taken.

Recommended adult dosages of anti-tubercular drugs:

Drug	*Daily dosages*
Isoniazid	5-10 mg/kg
Rifampicin	10 mg/kg
Pyrizinamide	20-40 mg/kg
Ethambutol	15-25 mg/kg
Streptomycin	15 mg/kg

Q.15. What are the various side effects of antitubercular drugs?

Ans:

1. Isoniazid—Hepatitis, rash, peripheral neuropathy, neurological disturbances.
2. Rifampicin—Gastrointestinal side effects, rash, hepatotoxicity, thrombocytopenia.

3. Pyrizinamide—Hepatitis, rash, hyperuricemia, arthralgia, gout
4. Ethambutol—Retrobulbar neuritis
5. Streptomycin—Ototoxicity, nephrotoxicity[16]

Q.16. Treatment options in cases of tuberculosis resistant to first line therapy?

Ans: These patients are treated with second line drugs including kanamycin, amikacin, capreomycin, ethionamide, cycloserine, paraaminosalicylic acid, ofloxacin, clofazimine, thiocetazone. These have lower efficacy and higher toxicity.

Q.17. What is the role of surgical treatment in such cases?

Ans: Indications of surgery are as follows:[17]

1. Progression or persistence of active disease in spite of adequate medical therapy.
2. Presence of large inflammatory masses, pyosalpinx, ovarian abscess.
3. Recurrence after 6 months of chemotherapy.

Contraindications

1. Active disease elsewhere in the body.
2. Presence of dense adhesions around pelvic organs.

CASE 4

A 28-year-P 2 with severe pelvic pain for two days. On examination 8 × 8 cm tender cystic mass felt in right fornix. TLC 20,000, temperature 101 degree F, hCG negative, CA-125, 67 mIu/ml, USG: 8 cm complex mass with free fluid.

Provisional diagnosis of PID with tubo-ovarian abscess made.

Q. 18. How do you manage pelvic inflammatory disease?

Treatment options

1. Oral antibiotics
2. Parental antibiotics
3. Surgical treatment

Q.19. What are the various oral regimens available?

Ans: Regimen A

Ofloxacin 400 mg orally once a day daily for 14 days

Or

Levofloxacin 500 mg orally once daily for 14 days
With or without
Metronidazole 500 mg orally twice a day for 14 days.[18]

Regimen B

Ceftriaxone 250 mg I/M in a single dose or cefoxitin 2 gm IM in a single dose and probenecid, 1g orally.

Plus

Doxycycline 100 mg twice a day for 14 days
With or without
Metronidazole 500 mg orally twice a day for 14 days[18]

Q.20. What are the indications of hospitalization in PID?

Ans:

1. Severe illness, high grade fever with nausea, vomiting
2. Tubo-ovarian abscess
3. Lack of response to oral therapy
4. Adolescents
5. Intolerance to oral therapy
6. Diagnosis is unclear and surgical emergency cannot be excluded.

Q.21. Indications for parenteral therapy

Ans: It is indicated in patients who are intolerant or non responsive to oral therapy or in severe cases
Various options are as follows:

Parenteral regimen A

Cefototan 2gm IV 12 hourly

Or

Cefoxitin 2 gm IV 6 hourly

Plus

Doxycycline 100 mg orally or IV 12 hourly

Parenteral regimen B

Clindamycin 900 mg IV 8 hourly

Plus

Gentamycin loading dose IV or IM(2 mg/kg) followed by a maintenance dose (1.5 mg/kg) 8 hourly.

Patient is switched over to oral therapy after 24 hours of clinical improvement.[18]

Q.22. What is the role of surgical intervention?

Ans: It is required in severe cases or in cases of pelvic abscess or tubo-ovarian abscess. Dramatic improvement is seen in patient's condition after the drainage of pus. It is also indicated in patients who are not responding to treatment.

CASE 5

A 35-year-old female P 2 with mild menorrhagia, off and on pain lower abdomen was detected to have left adnexal mass 6 × 6 cm on examination. hCG negative, CA-125: 25 mIU/ml, USG: bulky uterus with subserous fibroid 8 × 8 cm.

Provisional diagnosis of pedunculated fibroid was made.

Planned for myomectomy.

Management of broad ligament fibroid and pedunculated fibroid:

Small and aymptomatic fibroid do not require any treatment. Surgical removal is done in case of large and symptomatic fibroid.

Q.23. What complications can occur while operating on broad ligament fibroid?

Ans: As in such cases, anatomy of ureter gets distorted, ureteric injuries can occur. To avoid that one should remain within the capsule of fibroid.

In case this patient was diagnosed to have ovarian cyst

Q.24. How do you manage benign ovarian tumors/ovarian cysts?

Ans: Expectant management if

- Mass is cystic
- Size is less than 6 cm
- There is no doubt of malignancy on clinical findings and investigations.
- Ultrasound is to be repeated in such cases after 6 weeks/suppression with birth control pills can be done
- If mass >6 cm or is a complex/solid mass, surgical removal is preferred.

Q.25. Which is the most common tumor in the reproductive age group women?

Ans: Dermoid cysts. It constitutes 25% of all ovarian neoplasms. Mostly these are aymptomatic (i.e. in about 50% of the cases). About 15% of dermoid cysts are bilateral. Malignant change is seen in 1-2% of such cases. Treatment of choice is ovarian cystectomy or oophorectomy.

Q.26. What are the complications of benign cystic teratoma?

Ans: These include rupture, torsion, infection, hemorrhage, malignant transformation, thyrotoxicosis.

Q.27. What are the non-gynecological causes of adnexal mass?

Ans:

1. Appendicitis – Managed by surgical removal.
2. Diverticular disease – Managed by antibiotics for acute attacks, dietary changes. Surgery is done if needed.

Q.28. Describe management of hemorrhagic cyst?

Ans: These are usually managed with narcotic analgesics as these are usually self limiting. Occasionally surgical intervention is required. Suppression with birth control pills is also acceptable.

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Reva Tripathi, Nilanchali Singh

24 Lump in Abdomen

An abdominopelvic lump in a female is a clinical finding which may have varied causes which could be either gynecological or non-gynecological. Causes of lump in the lower abdomen will also differ depending on the age at presentation. Detailed history and physical examination along with various ancillary aids will be required to arrive at the diagnosis.

CASE

A 60-year-old postmenopausal woman presented to gynae OPD with complaints of progressive distension of the abdomen for three months, loss of appetite and weight. A 24 weeks size ill defined, firm, non-tender mass was found arising from the pelvis. How is this case to be managed?

After taking history and doing clinical examination, work up of the patient should be done to identify the cause. On the basis of her symptomatology, age group and clinical finding, ovarian malignancy appears to be a likely possibility.

Q.1. What are the points to be especially sought for in history?

Ans:

- Age of the patient is very important. The causes of abdominopelvic lump vary with the age of the patient. Ovarian malignancies are common in old age. More than 80% epithelial ovarian cancers are found in postmenopausal women. The peak incidence of invasive epithelial ovarian cancer is 56 to 60 years. About 30% of ovarian neoplasms in postmenopausal woman are malignant, whereas only 7% of ovarian epithelial tumors in premenopausal women are frankly malignant. For Breast Related Cancer Antigen (BRCA)-associated ovarian cancer, the average age at diagnosis is about 50 years, and for HNPCC (Hereditary Non-Polyposis Colorectal Cancer), it is 40 years.
- Symptoms of the patient give a clue to the origin of pathology. Vague symptoms, non-specific lower abdominal pain and discomfort, distension and pressure can be present in lump of any origin but are frequently present in case of ovarian malignancy.
- Gastrointestinal problems like flatulence, eructations and bloating after meals, constipation, diarrhea or bleeding per rectum may point towards gastrointestinal pathology like inflammatory bowel disease, diverticular disease or colonic or rectal tumors.
- Predominance of urinary complaints may point towards urinary tract disorders.
- Loss of appetite and weight loss are non-specific symptoms which may indicate malignancy at any site. Patients with ovarian malignancy may present with respiratory distress due to

associated ascites and pleural effusion. Apart from the lump the presence of ascites will further contribute to the distension.

- Acute symptoms like pain which may be secondary to rupture or torsion of ovarian tumor are unusual.
- History of any discharge per vaginum or post-coital bleeding should also be enquired as they may be due to carcinoma cervix which could lead to pyometra presenting as lump in abdomen.
- **Menstrual history:** Menstrual history is likely to be of little relevance in these patients. However, early menarche and late menopause may increase the risk of ovarian cancer and postmenopausal bleeding may be present in granulosa cell tumor. Irregular menses may be present in few cases of ovarian tumor in perimenopausal woman.
- **Obstetric history:** Obstetric history is also important. Ovarian malignancy has been associated with low parity and infertility. Having at least one child is protective of the disease with a risk reduction of 0.3 to 0.4.[1] The risk gets even lower with each pregnancy. Breast-feeding may lower the risk even further. However, most patients we see in India are multiparous who have lactated their children.
- **Contraceptive history:** History of oral contraceptive usage during the reproductive years needs to be taken. Oral contraceptive pills are the only documented method of chemoprevention for ovarian cancer.[2,3]
- **Past history:** History of any previous gynecological surgery is also relevant. Tubal ligation may reduce the chance of developing ovarian cancer by up to 67%.[4] A hysterectomy (without oophorectomy) also seems to reduce the risk of getting ovarian cancer by about one-third.[4] It also rules out any uterine cause of the lump.
- **Family history:** It is important in some cases of ovarian cancer. Any family history of ovarian, breast, colorectal, pancreatic, stomach, small bowel, urinary tract, and biliary tract cancer needs to be enquired for. Familial or hereditary ovarian cancers account for 5 to 10% of ovarian malignancies. Most hereditary ovarian cancers are associated with BRCA I (Chromosome 17), BRCA II (Chromosome 13) and Lynch II (Hereditary non-polyposis colorectal cancer syndrome). The risk of familial ovarian cancer decreases with age. The proportion of ovarian cancers in the general population attributable to BRCA I gene is estimated to be 5.9% for women in the third decade or younger, and steadily declines with increasing age, dropping to 1.8% in the seventh decade.[5,6] This cause is to be sought for in case of malignancy presenting at a younger age and must not be confused with coincidental occurrence of malignancy in family members.

Q.2. How should such a patient be examined?

Ans:

- **General examination:** As in any other case general examination is important for this patient. A patient of ovarian malignancy may reveal cachexia and pallor of varying degrees, jaundice, left supraclavicular lymph node (Virchow's), edema of leg and vulva and varicose veins. Women who are obese (Body mass index 30) do have a higher risk of developing ovarian cancer. Systemic examination including heart and lung examination to exclude co-existing medical disorders or distant metastasis must also be performed.
- **Per abdominal examination** is the next important step. Any organomegaly needs to be detected if present. The presence of hepatomegaly, indicated by the presence of an

enlarged, firm, and nodular liver may be indicative of hepatic metastasis. A mass may be felt in the hypogastrium arising from the pelvis. The features of the mass are to be noted with special reference to the following:

- Consistency needs to be noted whether it is soft, firm, cystic or hard. In ovarian malignancy it may be of solid or heterogeneous consistency.
- Mobility is also important as restricted mobility points towards malignancy or may be an indirect evidence of local spread though it is difficult to comment in presence of large tumors.
- Tenderness may or may not be present.
- Surface may be smooth or irregular. Irregular surface points towards malignancy.
- Margins may or may not be well-defined. The lower pole is usually not reached in pelvic lump.
- Abdominal examination is incomplete without testing for percussion note. On percussion, there is usually dullness over the tumor though there may be resonance due to overlying intestinal adhesions. Shifting dullness may be present in case of ascites.

- **Local examination:** Any growth, ulceration, abnormal pigmentation should be noted on vulva, perineum, urethra, suburethral region and anus.
- **Per speculum:** Cervix and vagina should be inspected. Any discharge, ulcer, growth, white patches, warts, varicosities, atrophic changes should be looked for as in any gyne case.
- **Per vaginum:** Check uterine size and mobility, feel for presence of an adnexal mass and for nodularity in pouch of Douglas. The most important sign of ovarian malignancy is presence of solid or solid/cystic, irregular and fixed mass felt per vaginum. Uterus may or may not be separated from the mass felt per abdomen. There may be nodularity in posterior fornix. It is not unusual to detect another small pelvic mass on the contralateral side of the abdominal mass. This would then make the patient a case of bilateral ovarian tumor which is more likely to be malignant.
- **P/V/R:** Examination is incomplete without this procedure. It is done to confirm findings of vaginal examination and check for presence of mass or nodularity in the pouch of Douglas, parametrial thickening and whether rectal mucosa is free or not. In ovarian malignancy, P/V/R may reveal nodularity in the pouch of Douglas and involvement of the rectal mucosa in advanced stages. In some cases where the uterus is not identifiable on vaginal examination it may be felt as a small structure during per rectal examination.

Q.3. How should such a patient be investigated?

Ans: Investigations in these patients aim at:

- Confirming site of origin of tumor and presence of malignancy.
- Identifying extent of lesion
- Identifying primary if any.

Investigations for preoperative evaluation like hematocrit, complete blood count, kidney and liver function tests, urinalysis and ECG are routinely done in all patients. Two important investigations which are done for all the patients in whom ovarian malignancy is suspected are ultrasonography and estimation of CA-125.

- **Ultrasonography:** It may identify the site of origin or other associated pathologies. It may also aid in differentiating malignant from benign ovarian tumors. The sonographic findings suggestive of malignancy are multilocularity, bilaterality, presence of solid areas, metastasis and ascitis. Increased neoangiogenesis as shown in Doppler study increases the risk of malignancy. Thin wall, smooth inner wall structure and anechogenicity or low echogenicity of the lesions are important

features of benign tumors. Complex mass without demonstrable wall, indistinct inner wall structure and highly echogenic lesion with solid component are predictors of malignancy. Ovarian tumor may be cystic or solid and can be benign or malignant.[7] Cystic ovarian masses have a smooth wall, no internal echoes, and demonstrate enhanced through transmission. But cystic masses often contain low-level echoes representing blood, pus, or cellular debris.[8] Solid tumors are highly, but irregularly, echogenic masses. Solid ovarian tumors are relatively uncommon, forming 7.8% of all the ovarian tumors, but tend to be more often malignant (51.7%). They could present with varied pictures of solid-cystic areas, complex masses or truly solid tumors. If more than 80% of the tumor mass has solid areas, they will be classified as solid and carry a risk of malignancy which can be 40% or more.[9,10]

Tumor markers: CA-125 is a glycoprotein used for screening and diagnosis of epithelial cancers of ovary. Value more than 35 U/ml is significant. It is also used for monitoring of patients on chemotherapy and for follow-up. It may be raised in several other malignancies like carcinoma breast, lung, colon and endometrium and also in some benign conditions viz. endometriosis, pelvic inflammatory disease, peritonitis and in 1% of normal women. However, a number of factors are known to influence serum CA-125 levels in healthy women like age (pre-menopausal women have higher serum CA-125 levels than postmenopausal women); menstrual cycle (some women have fluctuating serum CA-125 levels throughout the menstrual cycle); pregnancy (CA-125 levels increase during pregnancy) and race (significantly higher CA-125 levels are found in healthy Caucasian women compared to Asian or African women). These factors should be taken into account when interpreting CA-125 test results.

Others tumor markers are Macrophage Colony Stimulating Factor (M-CSF), OVXI, HER-2/neu and inhibin but are rarely done except when specifically indicated or in research settings.

- **Abdominal and pelvic CT scan and MRI:** Either CT scan or MRI can be done to identify the extent of disease and detect presence of enlarged lymph nodes. Although MRI is not widely used in the staging and subsequent follow-up of ovarian cancer patients, this technology may have a role in the diagnosis of recurrent disease. It is currently not considered superior to CT scan, although no comparative studies have been performed.
- **Cytologic examination:** Malignant cells can be detected from the fluid collected by abdominal paracentesis or culdocentesis. Fine needle aspiration cytology can be done from the ovarian mass to detect malignant cells. Ovarian masses are easily accessible for cytological evaluation by fine needle aspiration during laparoscopy or sonography. Aspiration cytology can provide particularly useful information in young women with functional ovarian cysts, preventing unnecessary operations. Acellular cystic fluids should not be considered non-diagnostic because they represent benign cysts in the majority of cases.
- **Chest X-ray:** This is done to exclude pleural effusion and chest metastasis.

Once ovarian malignancy has been diagnosed, few investigations which aid in differentiating between primary and secondary malignancy may be done, as mentioned below:

- **Barium enema/colonoscopy:** These investigations help to rule out large bowel malignancy.
- **Upper GI series/gastroscopy:** This is done if there are any signs and symptoms of upper gastrointestinal tract involvement.

- **Intravenous Pyelography:** This is helpful in detecting ureteral obstruction and deviation
- **Other possible modalities of evaluation are Positron Emission tomography (PET), cystoscopy, laparoscopy and mammography**.

Q.4. What is the differential diagnosis of lump arising from pelvis in a postmenopausal woman?

Ans: The causes of an abdominopelvic lump can be divided into gynecologic and non-gynecologic causes.

Gynecological causes:

- Benign neoplasm of ovary
- Malignant ovarian tumor
- Pyometra
- Sarcoma uterus
- Tubo-ovarian abscess
- Uterine leiomyoma (Pedunculated/non-pedunculated)

Non-gynecological causes:

- Inflammatory bowel disease
- Colonic neoplasms
- Pelvic kidney
- Diverticular mass
- Mesenteric cyst
- Retroperitoneal tumors
- Enlarged lymph nodes

Q.5. What is risk of malignancy index (RMI)?

Ans: This index is used to differentiate between malignant and benign ovarian lesion. The risk of malignancy index[11] is calculated as follows:

RMI = U × M × CA-125

U = Ultrasound score (one point each for: multilocular cyst; solid areas; metastasis; ascitis; bilateral lesion)

M =3 (postmenopausal women)

CA-125 in U/ml

The above mentioned values could be combined in a risk of malignancy index (RMI) which is simply calculated using the product of the serum CA-125 level (U/ml), the ultrasound scan result (expressed as a score of 0, 1 or 3) and the menopausal status (1 if premenopausal and 3 if postmenopausal). Using an RMI cut-off level of 200, the sensitivity was 85% and the specificity was 97%. Patients with an RMI score of greater than 200 had, on average, 42 times the background risk of cancer and those with a lower value 0.15 times the background risk as shown in a study. The risk of cancer is 75% when the RMI value is >250.

Q.6. How should such a patient be managed?

Ans: Surgery is the mainstay of treatment. These patients require staging laparotomy and debulking followed by chemotherapy in most cases.

Q.7. How is the surgical staging done for these patients?

Ans: The staging laparotomy is done as follows:

- Liberal vertical incision should be given as it minimizes chances of tumor rupture and facilitates better exploration of peritoneal cavity.
- The character of ascitic fluid is noted and collected for cytology. If fluid is absent or not sufficient then a sample of peritoneal washing is taken from the paracolic gutters, the pouch of Douglas and the under surface of diaphragm by instilling 10-20 ml of normal saline or distilled water.
- A systematic visual and manual inspection is done- palpation of liver, GIT, subdiphragmatic area, omentum and para-aortic lymph nodes. The palpation of gastrointestinal tract is done in clockwise manner starting from cecum.
- Pelvic exploration is done and gross physical characteristic of tumor should be noted along with extent of adhesions, condition of the contralateral ovary, uterus and tubes. Palpation of the pelvic lymph nodes and rectovaginal area is also done.
- Any suspicious metastatic deposit on the peritoneal surface and the under surface of diaphragm should be biopsied.

- Pelvic and para-aortic lymph node sampling should be done.
- Multiple peritoneal biopsies should be taken even in absence of any obvious metastatic disease.
- The type of surgery depends upon the stage of tumor. The surgeon may perform unilateral oophorectomy or bilateral oophorectomy along with salpingectomy and hysterectomy. For early tumors (stage 1, low grade or low-risk disease), only unilateral salpingo-oophorectomy can be done, especially in young females who wish to preserve their fertility. In advanced malignancy, where complete resection is not feasible, as much tumor as possible is removed (debulking surgery). In cases where this type of surgery is successful (i.e. < 1 cm in diameter of tumor is left behind known as optimal debulking), the prognosis is improved compared to patients where large tumor masses (> 1 cm in diameter) are left behind.

Q.8. How are ovarian malignancies staged?

Ans: Ovarian cancer staging usually is described in terms of the FIGO system (staging scheme developed by the International Federation of Gynecology and Obstetrics). In general, the lower the stage, the more favorable is the prognosis.

Stage1: Tumor is limited to one or both ovaries.

1a: Tumor is limited to one ovary. The capsule, or outer wall of the tumor, is intact, there is no tumor on the external ovarian surface, and there are no cancer cells in ascites (abdominal fluid build-up) or peritoneal lavage ("washings" from the abdominal cavity).

1b: Tumor is limited to both ovaries. The capsule is intact, there is no tumor on the ovarian surface, and there are no cancer cells in ascites or peritoneal lavage.

1c: Tumor is limited to one or both ovaries with any of the following: ruptured capsule (burst outer wall of the tumor), tumor on ovarian surface, or cancer cells in the ascites or peritoneal lavage.

Stage2: Tumor involves one or both ovaries with spread into the pelvis.

2a: Tumor has spread and/or attaches to the uterus and/or fallopian tubes. There are no cancer cells in ascites or peritoneal lavage.

2b: Tumor has spread to other pelvic tissues. There are no cancer cells in ascites or peritoneal lavage.

2c: Tumor has spread to pelvic tissues, with cancer cells in ascites or peritoneal lavage.

Stage3: Tumor involves one or both ovaries, with microscopically confirmed peritoneal metastasis outside the pelvis and/or metastasis to regional (nearby) lymph node(s).

3a: Microscopic peritoneal metastasis beyond the pelvis.

3b: Macroscopic (visible to the naked eye) peritoneal metastasis beyond the pelvis, 2 cm or less in greatest dimension.

3c: Peritoneal metastasis beyond the pelvis, more than 2 cm in greatest dimension.

Stage4: Distant metastases are present. Pleural effusion if present is included in stage IV if malignant cells are present. Parenchymal liver disease is also included in stage IV.

Q.9. What are the risk factors for epithelial ovarian cancer?

Ans:

- **Age:** The risk of developing ovarian cancer gets higher with age. Ovarian cancer is rare in women younger than 40. Most ovarian cancers develop after menopause. Half of all ovarian cancers are found in women over the age of 65.
- **Obesity:** Various studies have looked at the relationship of obesity and ovarian cancer. Overall, it does seem that obese women (those with a body mass index of at least 30) do have a higher risk of developing ovarian cancer. A study from the American Cancer Society also

found a higher rate of death from ovarian cancer in obese women.[12]

- **Reproductive history:** A woman who has had children has a lower risk of ovarian cancer than women who have no children. The risk gets even lower with each pregnancy. Breastfeeding may lower the risk even further. Using oral contraceptives also lowers the risk of ovarian cancer.
- **Gynecologic surgery:** Tubal ligation may reduce the chance of developing ovarian cancer by up to 67%.[4] Hysterectomy (removal of the uterus without removing the ovaries) also seems to reduce the risk of getting ovarian cancer by about one-third.[4]
- **Fertility drugs:** In some studies, researchers have found that using clomiphene citrate for longer than one year may increase the risk for developing ovarian tumors. The risk seemed to be highest in women who did not get pregnant while on this drug. However, women who are infertile may be at higher risk than fertile women even if they do not use fertility enhancing drugs so the extent of the contribution of the drugs to the development of malignancy is difficult to quantify.
- **Androgens:** Women who took androgens were found to have a higher risk of ovarian cancer. Further studies of the role of androgens in ovarian cancer are required.
- **Estrogen therapy:** Some recent studies suggest women using estrogens for hormone replacement therapy have an increased risk of developing ovarian cancer. The risk seems to be higher in women taking estrogen alone (without progesterone) for many years (at least 5 or 10). The increased risk is less certain for women taking both estrogen and progesterone.
- **Family history of ovarian cancer, breast cancer, or colorectal cancer:** Many cases of familial epithelial ovarian cancer are caused by inherited gene mutations that can be identified by genetic testing.
- **Personal history of breast cancer:** The risk of ovarian cancer after breast cancer is highest in those women with a family history of breast cancer. A strong family history of breast cancer may be caused by an inherited mutation in the BRCA1 or BRCA2 genes. These mutations can also cause ovarian cancer.
- **Others:** Many other causes or protective agents have been mentioned in literature. Some of the common ones are enumerated below. **Talcum powder** applied directly to the genital area or on sanitary napkins may be carcinogenic (cancer-causing) to the ovaries. Some, studies suggest a very slight increase in risk of ovarian cancer in women who used talc on the genital area.[13] Some studies have shown a reduced rate of ovarian cancer in women who ate a diet high in vegetables, but other studies disagree. In some studies, both **aspirin** and **acetaminophen** have been shown to reduce the risk of ovarian cancer. However, the information is not consistent. **Smoking and alcohol use** do not increase the risk for most ovarian cancers, but some studies have found they increase the risk for the mucinous type.

Q.10. What are familial ovarian cancers?

Ans: While approximately 90% of ovarian cancers occur sporadically, 10% of women with ovarian cancer have inherited genetic changes that predisposed them to ovarian cancer.[14] There are three hereditary syndromes that predispose to ovarian cancer:

- Hereditary breast-ovarian cancer syndrome due to mutations in the tumor suppressor genes BRCA1 and BRCA2
- Hereditary non-polyposis colorectal cancer (Lynch syndrome)
- Hereditary site-specific ovarian cancer.

Hereditary Breast Ovarian Cancer Syndrome

Approximately 10% of women with ovarian cancer are carriers of a breast/ovarian cancer susceptibility gene. The proportion of cases of ovarian cancer due to such a gene decreases with age and is estimated to be 14% for women diagnosed in the fourth decade, dropping to 7% for women diagnosed in the sixth decade.[15,16] Gene carriers have a greater than fifteen-fold risk of ovarian cancer compared to non-carriers. The lifetime risk for ovarian cancer in the general population is 1.3%, while estimates for gene carriers range from 10 to 60%.[17] BRCA1 and BRCA2 together have been estimated to account for 85% of breast ovarian cancer families. Both BRCA1 and BRCA2 are transmitted in an autosomal dominant fashion. Certain ethnic groups, such as Ashkenazi Jews, have high rates of specific mutations of these genes. The large number of mutations described makes genetic testing and patient counseling complex, and illustrates the need for genetic counseling by a qualified health care provider.

BRCA1: BRCA1 is a gene associated with increased risk for breast and ovarian cancer. The lifetime risk of breast cancer is estimated to be 55-85%, while the lifetime risk of ovarian cancer is 20-40%, with some studies suggesting as high at 60%. The proportion of ovarian cancers in the general population attributable to this gene is estimated to be 5.9% for women in the third decade or younger, and steadily declines with increasing age, dropping to 1.8% in the seventh decade. Features suggestive of a BRCA1 mutation include a family history of:

- Two or more cases of ovarian cancer
- Breast and ovarian cancer in the same woman
- One or more cases of premenopausal breast cancer with or without a case of ovarian cancer diagnosed at any age
- Two or more cases of postmenopausal breast cancer and one or more cases of ovarian cancer diagnosed at any age
- Male breast cancer.

BRCA2: The BRCA2 tumor suppressor gene is also associated with high rates of breast and ovarian cancer. The lifetime risk of breast cancer has been reported to be similar to that of BRCA1 (55-85%), while the lifetime risk of ovarian cancer is estimated to be 10-20%. BRCA2 is also associated with a 5-6% risk of male breast cancer, as well as increased risk of pancreatic cancer and melanoma.[18] BRCA2 features are similar to those outlined for BRCA1, but also include a family history of pancreas cancer in addition to breast and/or ovarian cancer.[19]

Hereditary non-polyposis colorectal cancer (Lynch syndrome II)

Hereditary non-polyposis colorectal cancer (HNPCC), also known as Lynch syndrome II, is a hereditary syndrome most commonly characterized by an increased risk for colorectal cancer. The lifetime risk of colorectal cancer is 80%, and is typically diagnosed in the individual's mid-40s.[20] The risk of endometrial (uterine) cancer associated with HNPCC is approximately 40%, while the risk of ovarian cancer is 10%.[21] Other associated cancers include stomach, small bowel, urinary tract, and biliary tract.

Germ line mutations of mismatch repair (MMR) genes have been demonstrated in individuals with HNPCC causing widespread genomic instability, or a hypermutable state, which provides the background for an accelerated accumulation of mutations. Genetic testing is available for HNPCC, but is complex because five causative genes have been identified, thus far. Again, genetic counseling is advised. Features strongly suggestive of HNPCC include (The Amsterdam II Criteria) [22,23]

1. At least three members of family must have been diagnosed with a cancer associated with HNPCC—cancer of the colon, endometrium, small bowel, ureter, or renal pelvis. (Note: Not all relatives must have the same kind of cancers.)
2. One of the three family members must be a first-degree relative (parent, offspring, or sibling) of the other two.

3. At least two successive generations of family should be affected.
4. At least one of these relatives must have been diagnosed with cancer before age 50.
5. Familial adenomatous polyposis (or FAP, the other hereditary colon cancer syndrome) as the cause of colon cancer should be ruled out.

Although not as strongly suggestive, HNPCC should be considered in a family with one case of early-onset colorectal cancer and one case of ovarian cancer diagnosed at any age.

Site-specific ovarian cancer

Limited data are available on the site-specific ovarian cancer syndrome. This is the least common of the three hereditary cancer syndromes, and is characterized by an increased risk of ovarian cancer. Findings from one group of investigators suggested that most families with this syndrome are linked to mutations in the BRCA1 gene.

Q.11. How does an ovarian cancer metastasize?

Ans:

- **Direct:** The spread occurs to adjacent organs like uterus and fallopian tubes.
- **Transcoelomic:** Metastasis occurs to intra-peritoneal organs and omentum.
- **Lymphatic-** Lymphatic dissemination to pelvic and para-aortic lymph nodes is common especially in advanced stages. According to a series,[1] the rate of dissemination to para-aortic nodes is 18% in stage I, 20% in stage II, 42% in stage III and 67% in stage IV.
- **Hematogenous** spread is less common. Spread to vital organ like lungs and liver occurs in 2% to 3% patients.

Q.12. What are the prognostic factors of ovarian malignancy?

Ans:

Clinical factors: Preoperative clinical factors like age of patient and performance status, intra-operative factors like stage of disease, the volume of ascitis and postoperative factors like the extent of the residual disease after surgery are independent prognostic variables.

Pathological factors: The morphologic and histologic pattern, including the architecture and grade of the lesion, are important prognostic variables. Clear cell carcinoma are associated with prognosis worse than other histologic types.

Biological factors: Diploid tumors have longer survival rate than those with aneuploid tumors. HER-2/neu expression has been associated with poorer prognosis. The tumor suppressor genes evaluated in ovarian malignancy are p53, PTEN and ras.

Q.13. What are the histopathological types of epithelial ovarian tumors?

Ans:

Histologic type	*Cellular type*	*Percent (%)*
Serous	Endosalpingeal	75%
Mucinous	Endocervical	20%
Endometrioid	Endometrial	2%
Clear cell	Mullerian	<1%
Brenner	Transitional	<1%
Mixed epithelial	Mixed	<1%
Undifferentiated	Anaplastic	<1%
Unclassified	Mesothelioma, etc.	-

Q.14. What are borderline ovarian tumors?

Ans: They are tumors of low malignant potential. They tend to remain confined to the ovary for long periods. The criteria for diagnosis of borderline tumors are as follows:

- Epithelial hyperplasia
- Nuclear atypia and increased mitotic activity
- Detached cell clusters
- Absence of destructive stromal invasion

Q.15. What is the management of borderline ovarian tumors?

Ans: The principal treatment of borderline tumor is surgical resection of primary tumor. After a frozen

section has determined that the histology is borderline, premenopausal patients who desire preservation of ovarian function may undergo a conservative surgery, which is usually a unilateral oophorectomy. This needs to be confirmed by detailed histopathology and such patients must be kept under close surveillance as distant metastasis are known to occur even with borderline tumors.

Q.16. What is palpable ovary syndrome?

Ans: In patients who are 1 year past menopause, the ovaries should have become atrophic and not palpable. It has been proposed that any pelvic mass in these patients should be considered potentially malignant, a situation that has been referred to as the postmenopausal palpable ovary syndrome.

This concept has been challenged because only 3% of palpable masses measuring < 5 cm have been reported to be malignant.

Q.17. What are the guidelines for management of an enlarged ovary?

Ans: The guidelines for management of ovarian enlargement are as follows:

- Any ovarian enlargement of > 8 cm during child-bearing period needs careful follow-up.
- In postmenopausal women any ovarian enlargement should be assessed by serum CA-125 and TVS. Cysts that are simple, unilocular and < 8 cm in diameter with normal serum CA-125 can be managed conservatively. 4 monthly follow-up should be done in these patients.

Q.18. What is debulking or cytoreductive surgery?

Ans: A patient with advanced ovarian malignancy who is medically stable should undergo a cytoreductive surgery to remove as much of the tumor and its metastasis as possible. The surgery typically involves the performance of a total abdominal hysterectomy and bilateral salpingo-oophorectomy, along with an infracolic omentectomy and resection of any metastatic lesions from the peritoneal surfaces or from the intestines. Patients whose disease has been completely resected to no macroscopic residual disease (only microscopic disease) have the best overall survival. 60% will be free of disease at the end of 5 years. This should be performed by a gynecologic oncologist at the time of initial laparotomy. The volume of residual disease at the completion of surgery represents one of the most powerful prognostic factors. Patients with advanced ovarian cancer are classified in three groups as follows, based on the postoperative residual tumor:

- **Good risk:** Microscopic disease outside the pelvis (stage IIIa).
- **Intermediate risk:** Macroscopic disease less than 2 cm outside the pelvis only after surgery
- **Poor risk:** Macroscopic disease more than 2 cm after surgery or disease outside the peritoneal cavity.

Q.19. What is interval debulking?

Ans: Interval debulking is performed in patients in whom adequate debulking is not able to be performed at the time of initial surgery. Such patients receive 3 cycles of chemotherapy after initial surgery and approximately 60% of patients are subsequently able to undergo optimal resection. This interval debulking is followed by 3 more cycles of chemotherapy. Interval debulking surgery may also be considered in those patients in whom an initial debulking surgery was not attempted and chemotherapy was given without any staging laparatomy. CA-125 levels are also a good indicator of the volume of residual disease.

Q.20. Which patients of ovarian malignancy require chemotherapy?

Postoperative chemotherapy is indicated in all patients with ovarian cancer except those who have surgical-pathologic stage I disease with low-risk characteristics. Literature suggests that post-

operative platinum-based chemotherapy prolongs both progression-free survival and overall survival in the majority of patients with early stage ovarian cancer. In patients with early stage disease (Stage I and II) the risk of recurrence may be classified as follows:

Low risk for recurrence is indicated by the following:

- Grade 1 or 2 disease
- No tumor on external surface of the ovary
- Negative peritoneal cytology
- No ascites
- Tumor growth confined to the ovaries

High risk for recurrence is indicated by the following:

- Grade 3 disease
- Preoperative rupture of the capsule
- Tumor on the external surface of the ovary
- Positive peritoneal cytology
- Ascites
- Tumor growth outside of the ovary
- Clear cell tumors
- Surgical stage II and beyond

Q.21. What are the chemotherapeutic regimens used in ovarian malignancy?

Ans: Standard postoperative chemotherapy is combination therapy with platinum based and paclitaxel. Cisplatin and paclitaxel or carboplatin and paclitaxel are commonly used. Randomized studies have proven that both regimens result in equivalent survival rates. However, because of an improved toxicity profile, the combination of carboplatin and paclitaxel is preferred. If patients are treated with cisplatin, paclitaxel should be administered as a 24 hours infusion to decrease the risk of neurotoxicity. Another alternative is to combine carboplatin with docetaxel. Cisplatin, carboplatin, and paclitaxel are chemotherapy agents approved for the initial treatment of ovarian cancer. Results from randomized studies have shown that platinum-containing regimens are superior to those that do not contain platinum.

The combination of paclitaxel and carboplatin is customarily given every 3 weeks (day 1 of a 21-day cycle).

Intraperitoneal chemotherapy: Results from randomized clinical trials suggest that in patients with optimally debulked disease, intraperitoneal administration of chemotherapy (cisplatin) is superior to intravenous administration. Recent meta-analyses confirm that intraperitoneal administration of chemotherapy is associated with an improvement in survival. However, this approach is also associated with more toxicity. The national cancer institute supports the use of intraperitoneal chemotherapy in optimally debulked ovarian cancer.

Neoadjuvant chemotherapy: Patients with advanced ovarian cancer who are not candidates for surgical cytoreduction may be treated initially with 2-3 cycles of conventional chemotherapy and can then be re-evaluated for surgical cytoreduction. However, initial optimal cytoreduction remains the standard of care for most patients.

Maintenance chemotherapy: Most patients with ovarian cancer achieve a complete clinical response after debulking surgery and platinum-based chemotherapy. However, 50% experience relapse and ultimately die of the disease. Therefore, strategies to decrease the risk of recurrence have been investigated. A phase III randomized trial exploring the impact of 12 monthly cycles of paclitaxel as maintenance chemotherapy was discontinued by the Data Safety and Monitoring Committee when a prospectively defined interim analysis revealed a highly statistically significant improvement in progression-free survival; an ongoing phase III trial is addressing the question of whether this maintenance strategy has a significant effect on overall survival.

Second-line chemotherapy: Recurrent ovarian cancer is classified into 2 categories, depending on the length of time the patient remained disease-free after completing chemotherapy:

1. Relapse that occurs more than 6 months after initial chemotherapy is considered platinum-sensitive;
2. Relapse that occurs before 6 months is considered platinum-resistant. Patients with platinum-sensitive disease may exhibit a good response if retreated with a platinum-based regimen. The probability of response increases with the duration of the disease-free interval.

   Results from clinical trials suggest that combination chemotherapy offers an improvement in response rate, progression-free survival, and overall survival. Several chemotherapy agents elicit a response in patients whose disease is resistant to platinum-based therapies. These include liposomal doxorubicin, topotecan, oral etoposide, gemcitabine, docetaxel, and vinorelbine. Other agents that may be used are ifosfamide, 5-fluorouracil with leucovorin, and altretamine (Hexalen). Tamoxifen, an oral antiestrogen, exhibits modest activity but has a favorable toxicity profile.

Q.22. What is the role of radiotherapy in ovarian malignancies?

Ans: Evidence that radiation therapy is an effective adjuvant therapy in certain stages of ovarian cancer has been proven in several trials. For early and intermediate stage disease, trials have shown that radiotherapy to the whole abdomen following surgery to be more effective than certain chemotherapy and pelvic radiation. Although there have been no randomized trials comparing platinum based chemotherapy to whole abdominal therapy, platinum based chemotherapy has largely supplanted the use of radiotherapy in the United States. However, radiotherapy does have a role in both cure and symptom control in patients with ovarian cancer.

Surgery followed by whole abdominal radiotherapy has shown favorable results in patients with high risk stage I patients, as well as stage II and stage III patients having no residual disease or less than 2 cm of residual disease. Currently, chemotherapy is the standard of care after surgery due to the lack of large prospective randomized trials involving postoperative radiotherapy. Radiation may be utilized as salvage therapy in patients who have failed surgery followed by chemotherapy. Optimal results have been found in patients who have microscopic residual disease or disease confined to the pelvis. Radiotherapy can also be considered as consolidative therapy following optimal cytoreductive surgery and platinum based chemotherapy for select individuals with intermediate or high risk of relapse. For patients with advanced disease that is unresectable and chemoresistent, radiotherapy has been shown to have an important palliative role in reducing symptoms, such as controlling vaginal or rectal bleeding, pulmonary metastasis, and pain control.

Q.23. What is the role of immunotherapy?

Ans: Immunotherapy (sometimes called biological therapy, biotherapy, or biological response modifier therapy) is one of the innovative ovarian cancer treatment options. Biotherapy utilizes immune system either directly or indirectly against cancer cells. Ovarian cancer may develop when the immune system breaks down or is not functioning adequately. Biotherapy is designed to enhance the natural immune responses. Aside from fighting ovarian cancer, biotherapy may help strengthen the body against side effects caused by conventional ovarian cancer treatments. Biotherapy can be used as a stand-alone ovarian cancer treatment, or it may be used in conjunction with other modalities such as surgery, radiation therapy and chemotherapy. Cytokines have been used extensively in second line therapy and the activity of interferon-α, interferon-γ, and interleukin-2 has been demonstrated. Biotherapy/immunotherapy may be used to:

- Halt or interfere with the growth process of ovarian cancer cells

- Make ovarian cancer cells more recognizable, and therefore more susceptible, to destruction by immune system
- Boost the killing power of immune system cells, including T-cells, NK-cells and macrophages
- Alter ovarian cancer cells' growth patterns to normal
- Block or reverse the process that changes a normal cell or a pre-cancerous cell into a cancerous cell
- Enhance ability to repair or replace normal cells damaged or destroyed by other forms of ovarian cancer treatment (e.g. chemotherapy, radiation)
- Prevent ovarian cancer cells from spreading to other parts of body.

The observation that the presence of certain immune cells in tumors is associated with improved survival, suggests that stimulation of anti-tumor immune responses, i.e. immunotherapy, might be a useful approach to improve prognosis of ovarian cancer. In this review, the feasibility of antigen-specific active immunotherapy is evaluated. Antigen-specific active immunotherapy aims at the induction of tumor-directed immune responses through the administration of a tumor-antigen, a molecule that is preferentially expressed by tumor cells and can induce immune responses.

Q.24. What is the role of hormone therapy?

Ans: There is no evidence that hormone therapy alone is appropriate primary therapy for advanced ovarian cancer. The use of progestational agents in the treatment of recurrent well-differentiated endometrioid carcinoma is supported by current data. A trial of tamoxifen in combination with multiagent chemotherapy is being conducted. Leuprolide acetate and aromatase inhibitors are also being studied. The study, published in Clinical Cancer Research, has proved for the first time that the targeted use of an antiestrogen drug could prolong the life of some patients by up to three years, and delay the use of chemotherapy in others.

Q.25. How is the follow-up done in ovarian cancer patients?

Ans: Regular follow-up is essential for all ovarian cancer patients. This includes patients whose disease is in remission after treatment. Although most women who develop a recurrence do so within the first 2 years after treatment, ovarian cancer can reappear up to 20 years later. Patients should be examined every 3 months for the first 2 years. Thereafter, follow-up visits may be scheduled every 4 to 6 months. During each visit, serum CA-125 level should be checked. If the CA-125 level is increased, tests such as CT scan, biopsy and peritoneal lavage may be performed to locate the new cancer site.

Q.26. What is the role of second look operation?

Ans: Second-look surgery is performed after a procedure or course of treatment to determine if the patient is free of disease. If disease is found, additional procedures may or may not be performed at the time of second-look surgery.

A second-look procedure is sometimes performed to determine if a cancer patient has responded successfully to a particular treatment. Examples of cancers that are assessed during second-look surgery are ovarian cancer and colorectal cancer. In many cases, before a round of chemotherapy and/or radiation therapy is started, a patient will undergo a surgical procedure called cytoreduction to reduce the size of a tumor. This debulking increases the sensitivity of the tumor and decreases the number of necessary treatment cycles. Following cytoreduction and chemotherapy, a second-look procedure may be necessary to determine if the area is cancer-free.

An advantage of second-look surgery following cancer treatment is that if cancer is found, it may be removed during the procedure in some patients. In other cases, if a tumor cannot be entirely removed, the surgeon can debulk the tumor and improve the patient's chances of responding to

another cycle of chemotherapy. However, second-look surgery cannot definitively prove that a patient is free of cancer as some microscopic cancer cells can persist and begin to grow in other areas of the body. Even if no cancer is found during second-look surgery, the rate of cancer relapse is approximately 25%.

Q.27. What is the survival rate in these patients?

Ans: The 5 years survival rates of patients with ovarian malignancy depend on the stage of the disease. The stage-wise 5 years survival rates are as follows:

a. Stage I-73%
b. Stage II-45%
c. Stage III-21%
d. Stage IV-Less than 5%

Q.28. How would you have modified your management if your patient was 26-year-old?

Ans: Germ cell tumors (GCT) are the more common ovarian malignancies present in the younger age group. GCT predominantly affect young women, but they sometimes occur in infants and older women. GCT account for over 60% of ovarian neoplasms in children and adolescents, one-third of which are malignant. Hence, apart from the investigations already mentioned, tumor markers specific for germ cell tumors need to be done. These tumor markers are as follows:

Tumor	*Tumor marker*
Dysgerminoma	10% have elevated hCG (Human chorionic gonadotropin), serum lactate dehydrogenase
Embryonal carcinoma	Pure tumors do not secrete hCG or AFP (Alpha feto-protein)
Endodermal sinus tumor	AFP, alpha-1 anti-trypsin
Choriocarcinoma	hCG
Teratoma	hCG or AFP
Mixed	Depends on elements present

The treatment of a patient with germ cell malignancy will depend upon the stage of the disease and her desire to preserve fertility. In advanced stages, management is the same as in epithelial malignancies, i.e. staging laparotomy with panhysterectomy followed by chemotherapy. But in early stages, fertility preserving surgeries should be offered. Treatment also depends on whether the tumor is dysgerminoma or another type of germ cell tumor.

- In young patients **surgery** should ideally be conservative in order to preserve fertility if the stage of the disease allows. Consequently unilateral salpingo-oophorectomy is performed for all stages of GCT. Even if extraovarian disease is present, the contralateral ovary and uterus should not be removed as these tumors are curable with chemotherapy. However, if fertility is not of concern, total abdominal hysterectomy and bilateral salpingo-oophorectomy, together with removal of as much tumor tissue as possible, is recommended for stage II, III and IV of GCT.
- **Chemotherapy** is preferable, despite these tumors being highly radiosensitive (except endodermal sinus tumor (EST) and embryonal carcinoma), in order to preserve ovarian function. All patients irrespective of tumor histology, except those with immature teratomas (stage IA, grade1), receive postoperative chemotherapy, for adjuvant or curative purposes. Adjuvant chemotherapy is given to patients with completely resected stages I, II or III ESTs, mixed cell tumors, embryonal carcinomas, choriocarcinomas and immature teratomas due to high recurrence rates. All GCT receive the same chemotherapy regimes based on a combination cisplatin therapy. Combination therapies include vinblastine, bleomycin, and cisplatin (VBP); bleomycin, etoposide and cisplatin (BEP) and also etoposide and cisplatin (EP). Combination chemotherapy is given to

patients with bulky residual disease, extra-abdominal metastases, or those who failed primary treatment with a curative intent. Survival rates for ovarian germ cell malignancies have increased dramatically with the use of platinum-based combination chemotherapy. Approximately 15-25% of dysgerminomas recur, but these are usually treated with a curative outcome by newer chemotherapy regimes.

Q.29. How does a patient of germ cell tumor present?

Ans: Most GCT are benign and unilateral, with the exception of dysgerminomas. Patients usually present at stage I. Abdominal pain or adnexal torsion is the commonest presenting symptom of GCT, however they may be asymptomatic. The mass may cause acute pain due to torsion, rupture, or hemorrhage. Patients may also have abdominal distension, vaginal bleeding or fever. Teratomas are usually diagnosed in premenopausal women without presenting symptoms. Complications of mature cystic teratoma (dermoid cyst) include torsion, rupture, infection and hemolytic anemia. Approximately 50% of prepubertal girls with nongestational choriocarcinoma are isosexually precocious. Only 1-2% of dermoid cysts become malignant, usually in postmenopausal women. Patients with ESTs frequently present following spontaneous rupture and hemorrhage.

Q.30. What is the prognosis of ovarian germ cell tumor?

Ans: Malignant ovarian germ cell tumors are very aggressive, but the prognosis is still good provided it is treated without delay with combination chemotherapy.

- The survival rates for dysgerminomas presenting at early and advanced stages are 95% and >80% respectively.
- The survival rates for stage I and II ESTs are reported to be 60-100%, whereas for those with stage III or IV disease the prognosis is less favorable (50-75%).
- Survival rates for embryonal carcinoma are slightly higher than those for ESTs.
- The prognosis of immature teratomas is governed by grade and stage. Grade 1, stage 1 have 100% survival rate, whereas stage III, grade 1 has only a 50% chance of survival. Meanwhile, most patients with mature teratomas show long survival times.
- The prognosis is better for gestational choriocarcinoma than non-gestational carcinoma.
- The prognosis for mixed GCT is dictated by the proportion of the more malignant component and the stage.

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Raksha Arora, Neha Gupta

25 Management of Abnormal Pap Smear and Cervical Cancer

Screening is a public health intervention based on a population at risk or target population. Screening is not undertaken to diagnose a disease, but to identify individuals with a high probability of having or of developing a disease. Women targeted for screening of cervical cancer may actually feel perfectly healthy and may see no reason to visit a health facility.

Pap smear (cytology) is a time tested method of screening and has reduced incidence and mortality of cervical cancer in developed countries.

Q.1. What are the other screening tests which may be more practicable for our country?

Ans:

I. Visual inspection after acetic acid (VIA)
II. Visual inspection after Lugol's Iodine (VILI)
III. HPV DNA test

Q.2. What is liquid based cytology (LBC)?

Ans: It is a refinement of conventional cytology in which the specimen from the cytobrush/spatula is transferred to a preservative solution instead of smearing of the scraped cervical cells from the transformation zone on a slide. The specimen is sent to a laboratory where the slide is prepared. It is more expensive and laboratory staff needs special training, however: it has few advantages over the conventional Pap smear:

- False-negative rate is low because the specimen obtained is more representative of the areas sampled.
- Fewer unsatisfactory smears.
- Increased efficiency and cost effectiveness due to a shorter interpretation time.
- The material collected can also be tested for HPV DNA (reflex HPV testing)

Q.3. Sometimes we get the reports of Pap smear as CIN, Carcinoma *in situ* or dysplasia, LSIL and HSIL? What is the difference between all these terminologies?

Ans: All these terminologies point towards pre-invasive lesions of the cervix. The concept of precursors was brought out way back in 1888 when certain areas of non invasive atypical changes were recognized in tissue specimens adjacent to invasive cancers. The term carcinoma *in situ* (CIS) was introduced in 1932 for those lesions in which undifferentiated malignant cells involved the full thickness of the epithelium without disruption of basement membrane (Borders). Subsequently, association between carcinoma *in situ* and invasive cancer was reported.

The term 'dysplasia' was introduced in the late 1950s to designate the cervical epithelial atypia that is intermediate between normal epithelium and CIS (Regan, 1953). Dysplasia was further categorized

into mild, moderate and severe, depending on the degree of involvement of the epithelial thickness by the malignant cells.

Later on, a direct correlation of progression and histological grade was observed on the basis of follow-up studies. This led to the concept of a single continuous disease process by which normal epithelium evolves into preinvasive and then to invasive cancer. On this basis, the term cervical intraepithelial neoplasia (CIN) was introduced to denote the whole range of cellular atypia confined to the epithelium. CIN 1 corresponds to mild, CIN 2 to moderate and CIN 3 to both severe dysplasia and carcinoma *in situ*. The Bethesda System (TBS) was introduced in 1991 and 2001 in which the term CIN was replaced by squamous intraepithelial lesion (SIL). The correlation between all these systems is elaborated in Table 25.1.

CASE 1

Mrs Laxmi (name changed), 30 years old P 4+2 had a normal vaginal delivery one year back. She came to gynecology OPD with complaint of vaginal discharge. Per speculum examination showed cervical erosion (ectopy) and moderate amount of mucoid vaginal discharge. She also brought a Pap smear report of ASC-US.

Q.4. How will you manage such a case?

Ans: The algorithm of management of ASC-US is provided by the American Society of Colposcopy and Cervical pathology (ASCCP), 2007.[1] According to ASCCP, reflex HPV DNA testing should be advised for a combined triage provided that it is affordable. In circumstances in which it is not available, two repeat Pap smear at 6 months interval is advised, as the negative predictive value of two consecutive negative Pap smear after an ASC-US is quite high. After this, she can return to routine screening. However, if one of the Pap report is again same or higher, colposcopy is indicated. Third opinion is that if patient can not come back for a six monthly follow-up, colposcopy should be done. If colposcopy does not show any abnormal findings, she can be followed up with Pap smear after one year. Routine use of diagnostic excisional procedure is unacceptable.

Q.5. Is the management same if Mrs Laxmi's age was less than 20 or if she was pregnant?

Ans: No. For a woman who is in the adolescent age group (20 or below), management of ASC-US and LSIL is conservative; colposcopy or HPV DNA testing need not be done because high-risk HPV DNA is likely to be positive in this age group and

Table 25.1: Correlation between original CIN, modified CIN and Bethesda system

Dysplasia terminology terminology	*Original CIN terminology*	*Modified CIN*	*Bethesda system*
Normal	Normal	Normal	Within normal limits Benign Cellular changes (infection or repair) ASC-US, AG-US
Atypia	Koilocytic atypia Flat condyloma without epithelial changes	Low grade CIN	LSIL
Mild dysplasia or dyskeratosis	CIN 1	Low grade CIN	LSIL
Moderate dysplasia or dyskeratosis	CIN 2	High grade CIN	HSIL
Severe dysplasia or dyskeratosis	CIN 3	High grade CIN	HSIL
Carcinoma *in situ*	CIN 3	High grade CIN	HSIL
Invasive carcinoma	Invasive carcinoma	Invasive carcinoma	Invasive carcinoma

is of no clinical use. She should be called for repeat Pap smear after every 6 months for a year. If she was pregnant, options would be to allow for deferral of colposcopy until 6 weeks after delivery because the risk for invasive cancer following ASC-US, LSIL and CIN I is very low.[1]

CASE 2

35 years old, Mrs Ratna (name changed), P 2+0, comes to OPD with a Pap smear report of ASC-H. She had no symptoms of vaginal discharge or inter menstrual bleeding.

Q.6. How will you manage her?

Ans: Since the prevalence of CIN 2 and 3 is higher in such situation, colposcopy is indicated straight away. If that is normal (i.e. no CIN 2 or 3), she can be followed up with HPV DNA testing at 12 months or Pap smear at 6 months interval for a year. If HPV is positive at the follow-up visit at one year or again has ASC-US or greater on cytology, again colposcopy should be done. If HPV is negative or 2 repeat cytology reports are normal, this patient can return to routine cytologic screening.[1]

Q.7. Why HPV DNA testing is not considered as one of the options in the initial management of ASC-H as in the case of ASC-US?

Ans: Recent studies have shown high rates (37-100%) of positive high-risk HPV DNA among women with ASC-H. Since the prevalence of CIN 2or 3 is very high in such women and there is high rate of HPV positivity, testing of HPV DNA will not be of any clinical value in the initial management in this case.[2]

CASE 3

Mrs Anju (name changed), 40 years old woman, complaining of persistent vaginal discharge comes to OPD with a Pap smear report of LSIL or mild dysplasia.

Q.8. How will you manage?

Ans: As given in the algorithm of ASCCP,[1] colposcopy is indicated for this patient. If colposcopy shows no identifiable lesion or it is an unsatisfactory colposcopy, endocervical sampling should also be done to rule out pathology in the endocervix. If colposcopy shows an abnormal area, targeted biopsy should be taken along with endocervical sampling. If no CIN 2 or 3 is found after colposcopy, either call her for high-risk HPV DNA after one year or repeat cytology after 6 and 12 months. If HPV DNA test is negative or two consecutive Pap smears are negative, she can be kept for routine screening. Colposcopy is again to be done if follow-up HPV test comes positive.

Previously, if CIN 1 was detected in a woman with unsatisfactory colposcopy, then a diagnostic excisional procedure was recommended but in 2006, this recommendation was removed. Diagnostic excisional or ablative procedures are unacceptable in the initial management of LSIL according to ASCCP guidelines.

Q.9. What will you do if colposcopy directed biopsy report shows CIN 2?

Ans: If the histopathology report is CIN 2 or 3 i.e. high grade lesion, there is 1.44% chance of cervical cancer in the two year time. So she must receive treatment in the form of ablative or excisional procedure.

Q.10. What are the different ablative and excisional procedures? How to decide which procedure to choose?

Ans: Different ablative procedures are cryotherapy, laser electrofulguration or cold coagulation. Excisional procedures include loop electrosurgical excisional procedure, cold knife conisation, laser conisation. Ablative therapies are not appropriate if colposcopy is unsatisfactory, if the entire squamocolumner junction or entire lesion is not seen, if the lesion is large (covers three or more

quadrants of cervix) or if innasive cancer is suspected. In such situations excisional procedure is preferred. The biggest advantage of excisional procedure is that tissue sample is obtained for histopathology.

Q.11. What are the advantages and disadvantages of ablative procedures?

Ans. Advantages are:

a. Easy to perform
b. Equipment needed is inexpensive
c. No risk of acute bleeding
d. Useful in low resource setting

Disadvantages:

a. No tissue is obtained for histopathology
b. Cryotherapy can cause profuse watery discharge for 2-4 weeks and many patients may experience cramping or vasonagal symptoms during the procedure.

Q.12. Is the management different in postmenopausal with a LSIL report?

Ans: Yes. She should be managed in the similar manner as premenopausal woman who has ASC-US report, i.e. triage with HPV testing, immediate colposcopy or serial cytology. Repeat cytology after course of intravaginal estrogen is no more recommended according to 2006 guidelines.[2] If HPV DNA is negative or colposcopy is normal, repeat cytology is done after 12 months. If HPV is positive or if repeat cytology reveals ASC-US or greater, then colposcopy is recommended. If two consecutive repeat cytology smears are negative, she can be followed up by routine screening.

CASE 4

A 35 years old Mrs Aman (name changed) brings with her a report of HSIL with the presenting symptom of white discharge per vaginum. She belongs to a poor socioeconomic status and has come from outside Delhi.

Q.13. How will you manage?

Ans: As per ASCCP guidelines,[1] colposcopy is indicated in this patient. Endocervical curettage at the time of colposcopy and directed biopsy from any abnormal lesion is also done. Since this patient has come from a distant place and may not be able to come, immediate treatment with a loop electrosurgical excisional procedure may be a better alternative.

Q.14. Would the management be the same if she was pregnant?

Ans: No. Colposcopy is done and biopsy should be taken only if CIN 2 or worse is suspected. Cervical dysplasia should not be treated during pregnancy because pregnancy does not hasten the course of disease and moreover, regression rate for CIN after pregnancy is high. Route of delivery also does not affect the process of regression. Endocervical curettage is never done during pregnancy.

Q.15. What would be the management for a HSIL report in a younger patient (20 years or less)?

Ans: According to ASCCP guidelines,[1] colposcopy is recommended but see and treat policy by surgical excisional procedure is not accepted. If colposcopy does not show CIN 2 or 3, she is simply followed up by repeat colposcopy and cytology every 6 months for two years. If colposcopy is not satisfactory or endocervical sampling is positive for dysplasia, only then diagnostic excisional procedure is done. The rationale behind the conservative management is that although HPV infection is common in young adolescent woman, cervical cancer is uncommon and most of dysplasia would regress spontaneously.

Q.16. What would be the management if colposcopy directed biopsy of Mrs Aman does not show CIN 2 or 3?

Ans: In that situation, according to the guidelines. A diagnostic excisional procedure may be performed as the risk for having CIN 2 or 3 is very high. Even the Pap smear slide and histopathology report can be reviewed by the pathologist and managed accordingly. If this can not be done, patient can be followed up with Pap tests and colposcopy every 6 months for a year. If any of the tests is positive, diagnostic excisional procedure must be done. If the Pap test results and colposcopies are negative both times, the patient can be returned to routine Pap smear screening. Any patient who is 20 years or older with a Pap smear report of HSIL and unsatisfactory colposcopy, straightaway diagnostic excisional procedure is done.

CASE 5

Forty years Mrs Tina (name changed) brings the Pap report showing atypical glandular cells (AGC). She is obese multiparous and complains of menorrhagia.

Q.17. What is AGC and what is the difference between AGC and AGUS and how will you manage such a case?

Ans: In the revised Bethesda system (2001), AGUS terminology has been replaced by AGC. The glandular abnormalities are expressed as AGC (specify endocervical, endometrial, not otherwise specified) and AGC (favors neoplasia). The underlying significant neoplasia rate changes from 9 to 50%. According to the current management for AGC, coloposcopy and directed biopsies, endocervical curettage and HPV DNA testing is recommended. This multimodality testing is necessary to detect the lesions which are in gland crypts and may escape detection by sampling devices and visual methodology. This patient will also require endometrial sampling since she is above 35 years and has menorrhagia. If no abnormality is found on colposcopy and endocervical/ endometrial sampling and HPV DNA test is negative, she will be called for follow-up for repeat cytology and HPV DNA test in 12 months. If only HPV test is positive in the initial evaluation, repeat cytology and HPV DNA testing should be done after 6 months.

Q.18. What will be the management if the same woman's report is AGC (favors neoplasia)?

Ans: Since these are atypical endometrial cells, endometrial biopsy and endocervical sampling is first done. If it is negative, complete cervical evaluation is done by colposcopy and HPV DNA testing.

In a postmenopausal woman, evaluation of endometrial thickness by ultrasound may be a logical alternative before doing endometrial biopsy because thickness of less than 5 mm has a high negative predictive value. If ultrasound or endometrial biopsy does not reveal neoplasia, D and C and hysteroscopy may be necessary.

Q.19. What will be the management in postmenopausal woman if the Pap smear results show AGC (favor neoplasia or adenocarcinoma *in situ* (AIS)?

Ans: The management of cytology smear showing AGC (favors neoplasia) or AIS is same, i.e. endocervical curettage. The initial evaluation is done the same way as in AGC. If no lesion is found or only CIN 1 is found, it is necessary to perform excisional biopsy because the chances of underlying cancer rate are high. If a significant lesion is found, treatment should be directed by histopathology report.

CASE 6

A 38 years old, Mrs Nagma (name changed) brings the Pap smear report of benign appearing endometrial cells. She has no complaints.

Q.20. What is its significance and how to manage?

Ans: Benign appearing endometrial cells, endometrial stromal cells or histiocytes in an asymptomatic patient are not associated with significant neoplasia. So this patient does not require any further evaluation.

If the same woman was postmenopausal, endometrial evaluation should be done even if she is asymptomatic because underlying rate of hyperplasia or malignancy may be found in 7% of these cases. A recent review (ref) has shown the incidence of hyperplasia as 20%, atypical hyperplasia 8% and that of cervical carcinoma as high as 15%.[3]

Q.21. What would you advise if the cytology report shows adenocarcinoma?

Ans: Initial evaluation by HPV DNA, colposcopy, endocervical and endometrial sampling by excisional biopsy and D and C/ hysteroscopy is done. If all are negative, USG imaging of pelvis is recommended. Even CT scan, Ca 125 may be necessary if clinical suspicion of underlying malignancy is confirmed by second review.[1]

CASE 7

A 40 years old woman complaining of persistent white discharge per vaginum for the last two years, on per speculum examination shows a hypertrophied cervix with ectropion. Pap smear was done which shows malignant cells.

Q.22. How do we interpret such a report? What is the action plan for such a patient?

Ans: The morphology of sqaumous cell carcinoma can vary in the degree of differentiation and presence or absence of keratinization. Some appear identical to HSIL on Pap test. False positive pap diagnosis of squamous cell carcinoma is possible because of some overlap in key morphologic features. Markedly atypical keratinization can be seen in invasive tumors but can also overly a keratininzing dysplasia. Invasive squamous cell carcinoma can demonstrate the presence of prominent nucleoli; however, that feature can also be seen in CIN 3.

The action plan for such a patient has just to be same as for HSIL, i.e. colposcopy with endocervical curettage even if the colposcopy is satisfactory. Loop excisional procedure is done only if colposcopic features are not suggestive of invasive carcinoma. In that case, punch biopsy can be taken from the most abnormal area or even four quadrant biopsy can be taken if no abnormal lesion is seen on colposcopy.

Q.23. This patient comes back with the histopathology report of CIN 3. Discuss the further management.

Ans: In this patient cone biopsy will be a preferred approach since there is discrepancy between the Pap smear report and histopathology report. Pap smear has reported malignant cells, so taking a bigger biopsy is essential to rule out the involvement of stroma beyond the epithelium.

Q.24. What is the recommended management of a woman with CIN 1?

Ans: CIN 1 preceded by ASC-US, ASC-H or LSIL can be followed with HPV DNA every 12 months or cytology every six months. Colposcopy should be done if HPV is positive or cytology report is ASC-US or greater. If CIN 1 persists for two years, ablative procure (if colposcopy is satisfactory) and excisional procedure (if colposcopy is unsatisfactory), should be done. However, if CIN 1 is preceded by HSIL or AGC-NOS, diagnostic excisional procedure should be done.[2]

Adolescent and pregnant women with CIN 1 should be followed up with repeat cytology.

Q.25. What is the recommendation for managing CIN 2 or 3?

Ans: A diagnostic excisional procedure is recommended for women with a histological diagnosis of CIN 2/3. Hysterectomy as primary therapy is unacceptable.[2]

Follow-up should be with HPV DNA at 6-12 months or combination cytology and colposcopy at 6 month interval. Further management depends upon reports.

Q.26. What are the situations in which cone biopsy is indicated?

Ans: The indications of cone biopsy are as follows:

- The lesion extends into the endocervical canal and it is not possible to confirm the exact extent.
- The lesion extends into the canal and the farthest extent exceeds the excisional capability of the LEEP cone technique (maximum deapth of 1.5 cm).
- The lesion extends into the canal and the farthest extent exceeds the excisional capability of the colposcopist.
- The cytology is repeatedly abnormal, suggests neoplasia, but there is no corresponding colposcopic abnormality of the cervix or vagina on which to perform biopsy.
- Cytology suggests a much more serious lesion than that which is seen and biopsy confirmed.
- Cytology shows atypical glandular cells that suggest the possibility of glandular dysplasia or adenocarcinoma.
- Colposcopy suggests the possibility of glandular dysplasia or adenocarcinoma.
- Endocervical curettage reveals abnormal histology.

CASE 8

A 40 years P5L5, comes to the OPD with complaint of blood stained discharge per vaginum. On per speculum examination, there is a growth on the anterior lip of the cervix and it bleeds on touch. On per vaginum examination, hard growth is felt on anterior cervical lip, uterus is bulky, bilateral fornices are free.

Q.27. What is the differential diagnosis of a granulomatous growth on cervix?

Ans:

- Carcinoma cervix
- Tuberculosis
- Schistosomiasis
- Coccidoidomycosis
- Crohn's disease
- Brucellosis
- Actinomycosis
- Sarcoidosis
- Syphilis (ulcerative/ excavating growth)

Q.28. From where should biopsy be taken in such a case?

Ans: Biopsy should be taken from the margin of the growth, not from the center because of less blood supply to that area, making it necrotic.

CASE 9

45 years old, Kamla (name changed), P5L5, married at the age of 16 years, comes to the gynecology OPD with complaint of postcoital bleeding and foul smelling discharge per vaginum. On examination, she is thin built and pale. On per speculum examination, there is a fungating growth seen on the anterior lip of the cervix. On per vaginum examination, same growth is felt, uterus is retroverted, normal size and bilateral fornices are free. Punch biopsy taken from the growth shows moderately differentiated sqaumous cell carcinoma.

Q.29. What are the symptoms with which, patient can present in early cervical cancer?

Ans: In early stage of invasive cervical cancer, presenting symptoms can be excessive vaginal discharge which may sometimes be foul smelling, irregular bleeding (intermenstrual), postcoital

bleeding, postmenopausal bleeding. Unfortunately, women in our country do not seek medical help in the early stage. Eighty percent of them come in late stage. When they present with blood stained vaginal discharge which may be very foul smelling, backache or lower abdominal pain, urinary frequency and urgency or even decreased urinary output, urinary or fecal incontinence, swelling of lower limbs or even breathlessness.[4]

Q.30. How will you manage further?

Ans: Once a histological diagnosis of cervical cancer has been made; next step is to stage the disease to formulate the most effective therapy. Cervical cancer is clinically staged, supplemented by a limited number of investigations.

FIGO Staging of Cervical Cancer, 2009

Stage I The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded).

IA invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤ 5 mm and largest extension ≥ 7 mm.

IA1 measured stromal invasion of ≤ 3.0 mm in depth and extension of ≤ 7.0 mm.

IA2 measured stromal invasion of > 3.0 mm and not > 5.0 mm with an extension of not > 7.0 mm.

IB clinically visible lesions limited to the cervix uteri or preclinical cancers greater than stage IA*.

IB1 clinically visible lesion ≤ 4.0 cm in greatest dimension.

IB2 Clinically visible lesion > 4.0 cm in greatest dimension.

Stage II Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina.

IIA without parametrial invasion.

IIA1 clinically visible lesion ≤ 4.0 cm in greatest dimension.

IIA2 clinically visible lesion > 4 cm in greatest dimension.

IIB with obvious parametrial invasion.

Stage III The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney.**

IIIA tumor involves lower third of the vagina, with no extension to the pelvic wall.

IIIB extension to the pelvic wall and/or hydronephrosis or non-functioning kidney.

Stage IV The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV.

IVA spread of the growth to adjacent organs.

IVB spread to distant organs.

Q.31. How will you evaluate the case further before formulating a management plan?

Ans: Pretreatment evaluation will include[4]

- Complete blood count
- Urine for albumin, sugar, microscopy, culture and sensitivity.
- Chest X ray
- IVP/ ultrasound to rule out renal involvement.

Cystoscopy/ barium enema/ sigmoidoscopy if bladder or rectal involvement is suspected.

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*All macroscopically visible lesions—even with superficial invasion—are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of not > 7.00 mm. Depth of invasion should not be > 5.00 mm taken from the base of the epithelium of the original tissue—superficial or glandular. The depth of invasion should always be reported in mm, even in those cases with "early (minimal) stromal invasion" (~1 mm).

The involvement of vascular/lymphatic spaces should not change the stage allotment.

**On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause.

CT scan or MRI should be done, if available, to determine disease status with regards to its extent. This might change the proposed treatment modalities; however, it does not change the clinical stage of the disease.

Q.32. How will you counsel the patient?

Ans: We will tell the patient about the different treatment modalities:

- Surgery (total hysterectomy with bilateral salpingo-oophorectomy with lymph node dissection).
- Radiotherapy (radical or palliative).

Q.33. What are the indications of surgery?

Ans:

- Associated PID
- Associated fibroid, ovarian tumor, prolapse uterus, endocervical carcinoma
- Stump carcinoma
- Radioresistant adenocarcinoma of cervix
- Young patient
- Recurrence after radiation therapy.

CASE 10

Mrs A had come from outside with Pap smear report of severe dysplasia and colposcopic directed biopsy report showed CIN 2. Cone biopsy was done and histopathology report showed microinvasive carcinoma.

Q.34. How will you manage?

Ans: Management of patient will depend upon age and parity. If the patient wants fertility preservation, we need to discuss the histopathology report with the pathologist, for a comment on the margins of the specimen and involvement of lymphovasular space and depth of invasion. If the margins are clear and there is no involvement of the lymphovascular space and depth of invasion is up to 3 mm, patient can be kept on follow-up.

If the invasion is more than 3mm and up to 5 mm and < 7 mm in horizontal spread (stage IA2), then, type II radical hysterectomy (modified radical) with pelvic lymph node dissection should be done since the incidence of lymph node involvement is up to 5% or more. Same treatment would also be advisable if on discussion with the pathologist, depth of invasion is not certain.

Q.35. How will the management differ if the patient was 35 years old and multiparous?

Ans: In this patient, total hysterectomy (abdominal or vaginal) will be the ideal management. Lymph node dissection is not required as the incidence of involvement is very low (< 1% in stage IA 1). Ovaries should be conserved and preferably transposed above the pelvic brim.

CASE 11

Forty-five years old, Mrs Rani (name changed) came with history of inter menstrual bleeding. On examination there was a small growth on the anterior lip of the cervix, vagina and parametrium were free. Biopsy taken from the growth showed a histopathology report of moderately differentiated large cell keratinizing sqaumous cell carcinoma.

Q.36. What is the management?

Ans: As this patient is stage IB 1, different treatment options which can be offered to her are:

- Type III radical hysterectomy with bilateral pelvic lymph node dissection
- Radiation therapy
- Concurrent chemoradiation.

Q.37. What are the treatment options for stage IB 2 and IIA?

Ans: The treatment options are:

- Type III radical hysterectomy with bilateral pelvic lymph node dissection

- Radiation therapy (external + intracavitary)
- Radiation combined with chemotherapy (chemoradiation)
- Neoadjuvant chemotherapy followed by surgery or radiation.

Q.38. What are the criteria which decide the choice of treatment modality?

Ans:

- Age of the patient
- Associated gynecological problem (fibroid, ovarian tumor, prolapse)
- Associated co-morbid condition
- Facilities and expertise available
- Patient's choice.

Q.39. What are the advantages of surgery over radiotherapy?

Ans: The advantages are:

- Preservation of ovarian function
- Assessment of extent and spread of disease
- No risk of secondary uterine cancer
- Complications that occur after surgical treatment are more readily correctable than that of radiotherapy.

Q.40. In this patient, radical surgery has been done. What criteria in the histopathological report of the specimen, will indicate the need for adjuvant therapy?

Ans: The criteria are: Positive lymph nodes and positive surgical margins, parametrial extension (high-risk category)

Deep invasion of cervical stroma, lyphmovasular space invasion, tumor size more than 4 cm at the last two of the above criteria must be present for requiring adjuvant therapy (intermediate risk). In patients not having any of the above criteria, adjuvant therapy is not recommended (low risk).

Q.41. Explain about the radiotherapy options available.

Ans: Radical radiotherapy in cervical cancer comprises of teletherapy and brachytherapy. In teletherapy, radiation is given from a distance with the help of a radioactive source such as cobalt 60 or linear accelerator targeting the primary disease as well as the probable draining nodes.

In brachytherapy, the tumor and surrounding areas are treated by direct contact of high energy small wire like or pellet like sources which move into the hollow tubes placed in the vagina and in the uterine cavity or in the substance of the cervix. The dose is calculated according to the amount of radiation received at two arbitrary points.

Point A: It is 2 cm above external os and 2 cm lateral to cervical canal. It is point of crossing over of ureter by uterine artery.

Point B: It is 3 cm lateral to point A. This point is on the lateral pelvic wall at the obturator gland.

Intracavitary radiotherapy gives 7,000 rads at point A (over a period of three weeks) 2,000 rads at point B. Supplementation is done by external beam radiation. Telegamma therapy gives 4,000 rads at point B (over next three 200 rads/ day). Thus, point B receives 6,000 rads in six weeks which is cancericidal for parametrium and pelvic lymph nodes.

Q.42. How will you follow-up after treatment?

Ans: Women who have been treated with surgery alone should have three monthly follow-up consultations for a period of first 2 years and then annually for the rest of the life. With careful recording of symptoms, particularly bleeding, discharge or pelvic pain. During the consultations, the following examinations should be performed:

- Speculum examination and visualization of the vaginal vault
- Cytological smear of the vault and of any abnormality noted on examination
- Bimanual vaginal and rectal examination to palpate for recurrence of disease
- Chest X-ray should be done every year.
- Other investigations depending on the clinical findings and resources available. Recurrent disease in these women can be treated with radiation.

Q.43. How will the management differ if the patient was pregnant?

Ans: Management of carcinoma cervix in pregnancy will depend upon stage of the disease as in a non-pregnant patient.

In stage IA1, pregnancy can be followed till term and vaginal delivery can be allowed. Vaginal hysterectomy can be done, 6 weeks later, if pregnancy is not desired.

In stage IA2, continue pregnancy till fetal maturity followed by cesarean section and modified radical hysterectomy with pelvic lymph node dissection.

For stage IB1, do not delay treatment for more than 4 weeks to attain fetal maturity. Do classical cesarean section and radical hysterectomy with lymph node dissection.

In stage II to IV, if the fetus is viable deliver by classical cesarean section and follow-up with radiotherapy immediately.

In the first trimester and stage II-IV disease start external beam radiotherapy, wait till fetal maturity, if second trimester.

Key Points and Good Clinical Practice

- According to revised ASCCP guidelines (2007), there are three options for women with cytology report of ASC-US; repeat cytology, HPV DNA testing or colposcopy. HPV DNA testing is ideal but management depends upon resources available and patient affordability. Follow-up is done with repeat HPV at 12 months or cytology every six months until two consecutive reports are negative after which patient can return to routine screening.
- For all Pap smear reports showing ASC-H or above, colposcopy should be done.
- HPV DNA testing is useful for ASC-US and not ASC-H as there is high prevalence of oncogenic HPV and high grade cervical intra-epithelial neoplasia in the latter.
- In adolescent (< 20 years) girls who have abnormal Pap smear report and histology, observation by yearly cytology is favored according to recent guidelines.
- In adolescent girls triage with HPV DNA for cytology report of ASC-US is not recommended as recurrent HPV infection is common in this age group.
- Screening guidelines are similar in pregnant patients. Colposcopic examination may be deferred until postpartum period unless there is suspicion of invasive cancer.
- Therapeutic conization is contraindicated in pregnancy. Indications of diagnostic conization are: Microinvasion/AIS on punch biopsy, strong suspicion of invasive cancer on colposcopy or cytology.
- ECC is contraindicated in pregnancy.
- Recommended management of AGC is colposcopy and directed biopsy, ECC and endometrial evaluation.
- If cytology report is AGC- favors neoplasia or AIS then ecxisional biopsy is preferred.
- Symptoms of early cervical cancer are intermenstrual bleeding, postcoital or postmenopausal bleeding and persistent excessive vaginal discharge. All sexually active women must be asked about these symptoms to detect cervical cancer at an early stage.
- Histological confirmation of cervical cancer must be done before planning the treatment.
- There are few changes in clinical [FIGO] staging of cervical cancer in 2009, i.e. deletion of stage O and stage II A to be divided into into II A1 and II A 2.
- Pretreatment evaluation includes IVP or abdominal ultrasound, cystoscopy, chest X-ray and ECG in addition to the routine blood and urine investigations. CT scan MRI and PET scan may be done if affordable to tailor the management.

- Surgery, radiotherapy, and concurrent chemo-radiation are the main modalities of treatment, the choice of which depends upon different criteria, e.g. age of the patient, stage of the disease, associated gynecological problem, comoirbidities, facilities available and patient preference.
- Follow-up after treatment is same after both surgery and radiotherapy, i.e. vault smear, bimanual vaginal and rectal examination and other investigations depending upon the clinical findings.

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26 Postmenopausal Bleeding

Bleeding from genital tract occurring after 12 months of amenorrhea in a woman of post-menopausal age (other than cyclical bleeding that occurs in women taking sequential hormone replacement therapy) is known as postmenopausal bleeding. For most women, menopause is in late 40's or early 50's.

CASE 1

Mrs X, a 60 years old postmenopausal lady complains of bleeding per vaginum off and on for one month. How will you manage this case?

After taking history and doing clinical examination, work up of the patient to exclude genital cancers will be done.

Q.1. What is important to elicit in history and examination?

Ans:

A.

a. Age of the patient is noted. As the age advances, risk of endometrial cancer increases. It is 1% at 50 years and 25% at 80 years of age.
b. Details of duration and severity of bleeding are noted, in addition to whether it is related to trauma, intercourse, recent genital tract surgery, etc.
c. History of radiation, HRT (oestrogen use without progestins in postmenopausal women increases the risk of endometrial cancer 4-8 times), topical oestrogen, Tamoxifen (four fold increase in endometrial cancer after 5 years of use), and any drugs especially for hypertension, hypothyroidism, diabetes should also be elicited. Risk is increased in diabetes due to increased oestrogen levels, hyperinsulinemia or insulin like growth factor.
d. It is important to note whether the patient was having regular screening with Pap smear or not, as another important cause of postmenopausal bleeding can be cervical cancer.
e. Associated symptoms like pain, fever, changes in bladder and bowel function (to exclude pyometra).
f. Urinary frequency, burning micturition, hematuria and h/o piles or bleeding per rectum or pain during defecation (fissure in ano) should also be elicited to find out whether bleeding is not vaginal.

B. **Menstrual history:** Age of menarche and menopause should also be noted. In late menopause the risk is increased 2-3 times. It is important to note whether the patient had any treatment for polycystic ovarian disease, anovulation or endometrial hyperplasia or oestrogen use for gonadal dysgenesis or treatment for granulose theca cell tumors, as cancer is more common in conditions with high

oestrogens (see risk factors). 25% to 43% cases of atypical hyperplasia have associated endometrial cancer.

C. **Obstetrical history:** Parity should be noted. Endometrial cancer is more common in nulliparous (2-3 times ↑ risk) and infertile, while multiparous women are at risk for cervical cancer.

D. **Past history:** History of treatment of any other cancer like breast or cervical cancer.

E. **Family history** of bleeding disorders; breast, colorectal or endometrial cancer or others associated with hereditary nonpolyposis colorectal cancer should be elicited. Women with hereditary nonpolyposis colorectal cancer syndrome (HNPCC) with germline mutations in mismatch repair genes MLH1, MSH2 and MSH6 have 40-60% life-time risk of endometrial as well as colon cancer.

F. ***General examination:*** Note BMI. In obesity, there is 3-fold increase in risk of endometrial cancer because androstenedione, (85% produced from adrenals and 15% from the ovary), is converted into oestrone in peripheral fat and there is lesser binding of steroids due to decreased levels of sex hormone binding globulin. Features of hypothyroidism should also be noted. Assess pallor, blood pressure, note lymphadenopathy, pedal edema, thyroid and breast abnormalities. Do systemic examination including heart and lung examination to exclude co-existing medical disorders or distant metastasis as the patient may require surgery.

G. Per abdomen examination: Any organomegaly or lump/ascites should be noted.

H. Local examination: Any growth, ulceration, abnormality should be noted on vulva, perineum, urethra, suburethral region and anus.

I. Per speculum: Cervix, vagina should be inspected for discharge, ulcer, or growth and any abnormalities like white patches, warts, varicosities, atrophic changes in vagina (like loss of rugae, dry vagina, inflammation and petechiae) and atrophic changes on cervix, whether flushed with vagina, bleeding through cervical os, whether stenotic and approach to cervix should be noted.

J. Per vaginum: Check uterine size, mobility, adnexal mass and feel for nodularity in pouch of Douglas and thickening or induration in parametrium.

K. P/V/R: Confirm P/V findings and check for mass, nodularity in the pouch of Douglas, parametrial thickening and whether rectal mucosa is free or not.

This patient, Mrs X had menopause at 50 years, is obese, hypertensive Para$_{1+0}$ and has no other positive history or findings on general examination.

On P/S, cervix is healthy, flushed with vagina, os stenotic, upper vagina narrow with difficulty in exposing cervix.

On P/V, bleeding through os is present, and on P/V/R, uterus is anteverted, normal size, mobile, adnexae free, parametrium and POD free. What would be your most probable diagnosis?

Since this patient has no local lesion on examination, and bleeding is seen through the os, it is likely to be uterine bleeding. Endometrial cancer should be suspected as she has low parity, is obese and hypertensive (which are risk factors for carcinoma endometrium), uterine bleeding is present and no other positive findings are present on examination.

Q.2. What investigations should be done?

Ans: Complete blood count, blood sugar (fasting and postprandial), blood urea, Pap smear, X-ray chest, ECG, and urine microscopy should be done. Transvaginal sonography should be done to exclude any pelvic pathology and note the endometrial thickness.

It is traditional to do differential curettage under GA to obtain tissue for histopathology. Alternatively, endometrial biopsy from all walls, aspiration biopsy from endometrium with endocervical curettings or office hysteroscopy and biopsy can be done in OPD setup. Pipelle sampling has a failure rate of 3% and there is insufficient sampling in 5%. If reports are negative for cancer on endometrial biopsy, then detailed D and C or hysteroscopic directed biopsy should be done. These are indicated when USG is nondiagnostic, i.e.,

a. Endometrium cannot be visualised in totality
b. Endometrial thickness is >5 mm
c. Focal endometrial abnormality
d. Margins of endometrium are indistinct

Endometrial cancer is present in 10% cases while polyps, hyperplasia and fibroids are present in 40% cases. SIS (saline infusion sonography) or hysteroscopy can better delineate endometrial cavity, but tissue biopsy is mandatory for planning any definitive treatment.

Q.3. Is TVS required in all cases?

Ans: It is an optional complementary modality but tissue biopsy is mandatory.

Q.4. What is the correlation between endometrial thickness and endometrial cancer?

Ans: Endometrial cancer is seen in 0.8% cases when thickness is < 4 mm. At 5 mm thickness sensitivity of TVS for endometrial disease is 92% and endometrial cancer is 96%. TVS is as sensitive as endometrial biopsy and can complement when EB is not possible or nondiagnostic.

Differential curettage revealed proliferative endometrium and endocervical curettings were scanty and inadequate for reporting. TVS showed endometrial thickness of 4 mm. Patient was put under observation and reported recurrent bleeding after 6 months. Her BP was 170/100 mm Hg and she was investigated further by TVS, hysteroscopy, cystoscopy and sigmoidoscopy after adjusting antihypertensive drugs. No abnormality was found and the patient was instructed to take her antihypertensives regularly and is fine for last one year.

Alternatively, we could consider the patient for hormonal therapy in the form of medroxyprogesterone for 2 weeks every cycle for 3 months as her endometrium was showing proliferative changes. As her bleeding stopped after D and C, nothing more than antihypertensives were given after the first episode. Progestins (10-30 mg/day medroxyprogesterone acetate) can be given in simple hyperplasia without atypia but hysterectomy is recommended when there is associated atypia.

Q.5. What will you do in case she comes with recurrence again?

Ans: It is safer to do laparotomy and hysterectomy as none of the investigations can exclude pathology with 100% certainty (Table 26.1).

Q.6. What are the Type I and Type II endometrial cancer?

Ans:

Type I – Endometrial cancers that are typically of endometroid pathology, low grade and associated with exposure to unopposed estrogens. These are diagnosed at an early stage and have an excellent prognosis. They account for 90% of endometrial cancers.[1]

Type II – Endometrial cancers that are typically high grade, estrogen independent and often of papillary serous or clear cell pathology. They tend to be diagnosed at a later stage, but have a poor prognosis even if diagnosed at an early stage.[1]

Q.7. What are the high-risk factors for developing endometrial malignancies?

Ans: Most high-risk factors are related to presence of prolonged, unopposed estrogen stimulation of endometrium.[2,3]

Table 26.1: Important causes of postmenopausal bleeding

HRT	Exclude endometrial malignancy and, if fine, continue with medroxyprogesterone 10 mg for 12 days along with conjugated oestrogen 0.625 mg daily
Atrophy or senile vaginitis/endometritis	HRT
DUB – Hyperplasia without atypia - Hyperplasia with atypia	Medroxyprogesterone acetate Hysterectomy
Inflammation	Treat infection, HRT
Pyometra	Drain and do endometrial and endocervical curettage after one week
Foreign body	Remove foreign body and treat infection
Trauma vagina	Treat infection and stitch in fresh case, or packing in old case
Decubitus ulcer	Vaginal packing, pessary or surgical treatment of prolapse after the healing of ulcer
Polyp	Polypectomy and D and C, and histopathological examination
Cervical cancer	Stage and treat by chemoradiation or surgery
Endometrial cancer	Staging laparotomy/panhysterectomy, lymphadenectomy – pelvic and para-aortic, omentectomy if indicated. Radiotherapy postoperatively (see text)
Ovarian cancer	Staging laparotomy and panhysterectomy + lymphadenectomy + omentectomy, or debulking depending on stage
Fallopian tube cancer	Staging laparotomy and panhysterectomy + lymphadenectomy + omentectomy
Diseases of adjoining organs like piles, fissure in ano, etc.	Surgical consultation and referral for appropriate treatment

Factor	**Relative Risk**
1. Atypical endometrial hyperplasia	8-29%
2. Nulliparous women	2-3 times
3. Infertility	8 times the risk
4. Irregular cycles/anovulatory cycles/PCOS	2-3 times
5. Late menopause (>52yrs)	2-4 times
6. Obesity	
21-50 pounds overweight	3 times
>50 pounds overweight	10 times
7. Exogenous HRT (estrogens without progestins)	4-8 times
8. Tamoxifen for breast cancer	2-4 times
9. Diabetes/Hypertension	1.3-2.8 times
10. Functioning ovarian tumors	3.5-27 times
11. Genetic predisposition (Lynch II Syndrome)	20%
12. Higher socio-economic class, white women	Increased risk
13. Endometrial hyperplasia	Increased risk (as below)

Endometrial hyperplasia may precede or occur simultaneously with endometrial cancer. The risk of progression to cancer in hyperplasia is as follows:

- Simple cystic hyperplasia without atypia 1%
- Complex adenomatous hyperplasia without atypia 3%
- Simple cystic hyperplasia with atypia 8%
- Complex adenomatous hyperplasia with atypia 29%

25-43% of patients with atypical hyperplasia detected in an endometrial biopsy or curettage specimen will have an associated, usually well-differentiated endometrial cancer detected during hysterectomy.

Certain factors which have been associated with **decreased risk of endometrial cancer** include multiparity, smoking, consumption of isoflavnes and lignans, diet rich in fruits, vegetables and fibers, physical activity and oral contraceptive use (50% reduction in endometrial cancer perhaps secondary to net progestational effect due to use of the pill).

Table 26.2: Various methods available for cancer evaluation

Method	*Advantages*	*Disadvantages*	*Sensitivity*	*Specificity*
Pap smear	Easy, available, no patient discomfort	Non-sensitive, not-specific, pick up rate only 30-50%		
Office endometrial aspiration biopsy	Cost-effective, disposable, no anaesthesia needed	Small risk of perforation, patient discomfort	83-94%	98-99%
Differential curettage	Cost-effective	Small risk of perforation, patient discomfort, can miss the lesion in 10% cases		
TVS	Non-invasive, NPV 99%, detects co-existent disease	Not cost-effective, PPV 9%, histopathological examination is still required for treatment	Asymptomatic patients: 90% Patients with bleeding: 82%	48% 80%
CT, MRI		Not cost-effective		
Tumor markers CA-125, CA 19-9		not suitable		
Hysteroscopy	Allows direct visualization of endometrial cavity, useful in focal lesions and recurrent PMB	Not feasible, invasive, requires anesthesia	86.4%	99.2%
Saline infusion sonography (SIS)	Allows identification of polyps/fibroids distorting endometrial cavity	Cannot diagnose malignancy, histopathological examination is still required for diagnosis and treatment		

In the endometrium, progesterone stimulates estradiol 17-β dehydrogenase enzyme, which converts oestradiol to less potent estrone. The relative risk is 0.2 after 10 years use of oral contraceptives, and reduced risk lasts for 20 or more years after discontinuation.

Q.8. What is the role of universal screening in endometrial cancer? What are the possible methods of screening?

Ans: Universal screening for endometrial cancer should not be undertaken because of lack of an appropriate, cost-effective test and acceptable test that reduces mortality. Although many risk factors for endometrial cancer have been described, screening the high-risk cases could at best detect only half of all cases. It is also not warranted as more than 95% of patients are symptomatic and present with abnormal peri- or post-menopausal bleeding at an early stage. Thus, screening for low-risk population is not recommended.

Screening for endometrial cancer or its precursors may be justified in certain high-risk women such as:[2]

i. Women receiving postmenopausal estrogen therapy without progestins
ii. Members of families with Hereditary non-polyposis colon cancer (HNPCC)

(No benefit has been demonstrated from routine screening with transvaginal ultrasound or endometrial biopsy in women taking tamoxifen).

Q.9. How can the diagnosis of carcinoma endometrium be confirmed?

Ans: The diagnosis of carcinoma endometrium can be confirmed on histopathologic examination of endometrial tissue. Various endometrial sampling procedures are:

Endometrial aspiration biopsy with endocervical curettage is the accepted first step in evaluation of a patient with abnormal peri- or postmenopausal bleeding. It is done using a No.4 Karman's cannula with a 20 or 50 ml syringe. Other instruments which can be used are vabra aspirator, Pipelle, Novak curette, Z sampler. The diagnostic accuracy of an office EB is 90-98%, and if it is negative, the patient should have differential curettage.

In-patient techniques include fractional curettage, differential curettage, and hysteroscopic directed endometrial biopsy. These should be reserved for cases where cervical stenosis or patient tolerance does not permit adequate evaluation by aspiration biopsy, in cases with negative endometrial biopsy or the specimen obtained on biopsy is inadequate, or EB and TVS reports don't tally. Hysteroscopy is more accurate in identifying polyps and submucous myomas than EB or D and C (see Table 26.2).

Q. 10. Discuss the various histological types of endometrial cancer.

Ans: The histological classification of endometrial carcinoma is as follows[2] (Table 26.3):

Table 26.3: Histological classification

Endometroid adenocarcinoma	Accounts for 80% of endometrial cancer
Variants: Villoglandular or papillary	Accounts for 2%
Secretory	1%
With squamous differentiation	15-25%
Mucinous carcinoma	5%, good prognosis
Papillary serous carcinoma	3-4%, high grade, associated with deep myometrial and lymphvascular space invasion, poor prognosis
Clear cell carcinoma	<5%, very aggressive, overall survival 33-64%
Squamous carcinoma	Rare, poor prognosis, 36% survival rate in stage I
Undifferentiated carcinoma	
Mixed carcinoma	

Q.11. What is the incidence of synchronous endometrial and ovarian cancer?

Ans.: 1.4 to 3.8%. Mostly both endometrial and ovarian cancers are well-differentiated adenocarcinoma of low stage with excellent prognosis.

Q.12. What is the role of imaging modalities in diagnosis?

Ans: Various imaging modalities used in diagnosis of endometrial cancer are:

Ultrasound, especially transvaginal ultrasound is a simple non-invasive method. The findings suspicious of carcinoma endometrium are:

1. Endometrial thickness more than 4-5 mm in a postmenopausal lady. TVS has a sensitivity of 100% and specificity of 96% for identifying endometrial abnormalities.
2. Polypoidal endometrial mass.
3. Collection of fluid in the uterus.

Saline infusion sonography increases the sensivity to detect endometrial polyps from 35% to 75%. Myometrial invasion can be detected in 75% cases on USG.

MRI: The accuracy of MRI to diagnose endometrial cancer and depth of myometrial invasion varies from 70-97%.

CT scan has 84-88% accuracy in picking up enlarged lymph nodes, though not as sensitive as MRI for picking myometrial invasion.

Q.13. What is the role of tumor markers in carcinoma endometrium?

Ans: Various tumor markers include CA-125, CA 19-9, CA 15-3.

- Little role in screening – not cost effective.
- CA-125 useful in prognosticating, predicting myometrial invasion and extrauterine spread and in follow-up of patients with advanced and recurrent cancer. It is specially useful in follow-up if initial values are high.

CASE 2

Mrs Y,a 60-year old obese patient comes with recurrent postmenopausal bleeding of 6 months duration. Endometrial biopsy shows moderately differentiated endometroid adenocarcinoma.

Q.14. How will you work up this patient pre-operatively?

Ans: After the diagnosis is confirmed by histopathology, thorough pre-surgical evaluation is performed to assess operability and the best approach to management by taking into consideration history, clinical examination and following investigations.[3]

Routine investigations:

- Blood tests: Blood grouping and cross-matching, Hemogram, LFT, KFT, serum electrolytes, blood sugar, optional CA-125
- Urine analysis and culture
- ECG
- Pap smear
- Endocervical and endometrial sampling is already done
- Imaging studies:
  - Chest X-ray
  - Contrast enhanced MRI abdomen/pelvis can be used to assess myometrial invasion and cervical involvement pre-operatively and plan the procedure with regard to need for lymph node sampling. Sensitivity for myometrial invasion is 80-100% and specificity 70-100%. It can also assess depth of invasion in parametrium, and ureteral, vascular and nerve entrapment. It is specially useful in management of young patients with low grade cancer, who desire conservative therapy to preserve the uterus.
  - CT abdomen/pelvis – not indicated as it is expensive, poor predictor of nodal disease, depth of invasion and cervical involvement.
  - Barium enema, cystoscopy/IVP – not indicated unless dictated by patient symptoms or clinical findings.

(Barium enema, colonoscopy and proctosigmoidoscopy should be done in cases with suspected HNPCC.)

Q.15. How do you stage endometrial carcinoma?

Ans: Patients with endometrial cancer should undergo surgical staging based on 2008 FIGO system:

2008 FIGO surgical staging for endometrial cancer[4]

Stage I *		Tumor confined to corpus uteri
	IA*	No or less than half myometrial invasion
	IB *	Invasion equal to or more than half of the myometrium
Stage II *		Tumor invades cervical stroma, but does not extend beyond the uterus**
Stage III*		Local and/or regional spread of the tumor
	III A	Tumor invades the serosa of the corpus uteri and/or adnexae#
	III B	Vaginal and/or parametrial involvement
	III C	Metastasis to pelvic and/or para-aortic lymph nodes
	III C 1	Positive pelvic lymph nodes
	III C 2	Postive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV*		Tumor invades bladder and/or bowel mucosa, and/or distant metastasis
	IV A	Tumor invasion of bladder and/or bowel mucosa
	IV B	Distant metastasis, including intra-abdominal metastasis and/or inguinal lymph nodes

* - Either G1, G2 or G3

** - Endocervical glandular involvement only should be considered as stage I and no longer stage II

- Positive cytology has to be reported separately without changing the stage

G1 - 5% or less of tumor shows a non-squamous or non-morular (solid) growth pattern

G2 – 6-50% of the tumor shows a non-squamous or non-morular (solid) growth pattern

G3 – More than 50% of the tumor shows a non-squamous or non-morular (solid) growth pattern

At minimum, the surgical staging procedure should include:

i. Sampling of peritoneal fluid for cytological evaluation
ii. Systematic exploration of abdomen and pelvis with biopsy or excision of any extra-uterine lesions suggestive of metastatic cancer
iii. Extrafascial hysterectomy and bilateral salpingo-oophorectomy
iv. The uterine specimen should be opened and tumor size, depth of myometrial invasion and cervical extension assessed.
v. Any suspicious pelvic and para-aortic lymph nodes should be removed for pathologic examination. In addition, clinically negative retroperitoneal lymph nodes should be sampled in the cases with any of the following risk factors:
   - Serous/clear cell or high grade histology
   - Myometrial invasion > 50%
   - Tumor size >2 cm
   - Cervical or isthmus involvement
   - Adnexal or pelvic extension of disease
   - Enlarged lymph nodes

Q.16. Is there any role of clinical staging in this patient?

Anss: If the medical conditions (diabetes and hypertension) in this patient are well-controlled, surgical staging is preferred for management as clinical staging may not be as accurate. According to 1971 FIGO staging system, clinical staging should be performed in patients unsuitable for surgery because of poor medical condition or spread of disease (gross cervical involvement, parametrial spread, invasion of bladder or rectum, or distant metastasis).

FIGO clinical staging of endometrial carcinoma (1971)

Stage I		Confined to corpus, including isthmus
	Ia	Length of uterine cavity <8 cm
	Ib	Length of uterine cavity >8 cm
Stage II		Involves corpus and cervix, but has not extended outside the uterus
Stage III		Extends outside the uterus, but not outside the true pelvis
Stage IV		Extends outside the true pelvis or involvement of mucosa of bladder/ rectum
	IVa	Spread to adjacent organs
	IVb	Spread to distant organs

Q.17. What are the prognostic factors in endometrial carcinoma?

Ans:

- **Age:** Younger women with endometrial cancer have a better prognosis than older women. There is a higher incidence of grade 3 tumors or unfavorable histological subtypes in older women.
- **Histological type:** Nonendometroid histological subtypes account for 10% of endometroid cancers and carry an increased risk for recurrence and distant spread. In contrast to the 92% survival rate among patients with endometroid tumors, the overall survival rate for patients with these more aggressive subtypes, is only 33%.
- **Histological grade:** Increasing tumor anaplasia is associated with a worse prognosis.
- **Tumor size:** It is a significant prognostic factor for lymph node metastasis and survival in patients with endometrial cancer. Lymph node metastasis has been reported in 4% cases with tumor $\leq$ 2 cm, 15% cases with tumor > 2 cm, and in 35% with tumor involving the entire uterine cavity. Reported 5-year survival is 98%, 84% and 64%, respectively.

- **Myometrial invasion:** Increasing depth of invasion is associated with increased risk of extrauterine spread and recurrence. The distance from tumor-myometrial junction to the uterine serosa is a sensitive indicator of survival. Risk of recurrence and death is much higher when the distance is < 5 mm.
- **Lymph-vascular space invasion:** 83% 5-year survival rate has been reported for patients without LVSI, compared with 64.5% in those with LVSI.
- **Isthmus-cervical extension:** This is associated with increased risk of extrauterine disease and lymph node metastasis, and thus is a poor prognostic factor.
- **Adnexal involvement:** Most of these patients have other poor prognostic factors.
- **Lymph node metastasis:** It is the most important prognostic factor in clinically early stage endometrial cancer. Patients with lymph node metastasis have a 6-fold higher risk of developing recurrent cancer. 5-year survival rate in patients with lymph node metastasis is reported as 54%, compared to 90% for patients without lymph node metastasis.
- **Intraperitoneal tumor:** Extrauterine spread of the disease is associated with poor prognosis and decreased 5-year disease free survival.
- **Peritoneal cytology:** Positive peritoneal cytology has an adverse effect on survival only if endometrial cancer has spread to adnexa, peritoneum or lymph nodes; not if the disease is confined to the uterus (5-yr survival 90%).
- **Hormone receptor status:** Patients whose tumors are positive for estrogen and/or progesterone receptors have longer survival rates than patients whose carcinomas lack these receptors.
- **DNA ploidy status/proliferative index**: Aneuploid tumors tend to be poorly differentiated, metastatic and associated with decreased survival.
- **Genetic, molecular tumor markers:** The presence of mutations of K-*ras* is an unfavorable prognostic factor. Alteration of tumor suppressor gene *p53* is also associated with advanced stage, papillary serous subtype and poor prognosis. Expression of *MIB-I (Ki-67)*, a proliferative marker, is associated with extrauterine disease spread and decreased survival. On the other hand, microsatellite instability, PTEN mutation and absence of p53 overexpression predict a favorable outcome.

Q.18. Describe the steps of surgery in this patient.

Ans: This patient should undergo staging laparotomy as follows:

Abdominal route:

1. Abdomen should be opened by low midline incision.
2. Peritoneal washings should be taken with 50-100 ml saline and collected in heparinised sterile container.
3. Paracolic gutters, ascending colon, hepatic flexure, liver, hemi-diaphragm, transverse colon, splenic flexure and spleen, descending colon, omentum, and kidneys should be inspected and palpated.
4. Retroperitoneum and para-aortic area should be inspected and palpated.
5. Any suspicious adhesions or implants should be biopsied.
6. Uterus, tubes and ovaries should be thoroughly explored.
7. Extrafascial total abdominal hysterectomy along with removal of vaginal cuff, and bilateral salpingo-oophorectomy should be done.
8. Partial omentectomy should be considered in uterine papillary serous and Mixed mullerian tumors which have a high-risk of intra-abdominal spread and upper abdominal recurrence.
9. Any suspicious pelvic and para-aortic lymph nodes should be removed for pathologic

examination. Clinically negative retroperitoneal lymph nodes should be sampled in cases with any of the high-risk factors mentioned earlier.

Complete excision of lymph nodes located around the iliac vessels and above obturator nerve allows identification of 90% of node positive patients. Isolated involvement of para-aortin nodes is rare. If pelvic nodes are positive on frozen section, then para-aortic lymph nodes up to the inferior mesenteric artery should be removed.

The decision on whether to undertake lymphadenectomy should not be based on palpation of nodal area because less than 10% of patients with nodal metastasis have grossly enlarged lymph nodes.

Q.19. Is there any role of vaginal hysterectomy or laparoscopic surgery in this case?

Ans: *Role of vaginal hysterectomy in cases of endometrial cancer:*

Vaginal hysterectomy with BSO may be done in extremely obese patients or those with uterine prolapse, who are at low risk for extra-uterine spread (clinical stage I, well-differentiated tumor). For those where extensive dissection is required, it may add to the morbidity as approach to upper abdomen and para-aortic lymph nodes is compromised. Pertitoneal washings are taken when the posterior pouch is opened. These patients are usually given post-operative radiotherapy because appropriate surgical staging is not done.

Role of laparoscopic surgical staging:

Laparoscopic assisted vaginal hysterectomy (LAVH) with BSO and laparoscopic retroperitoneal lymph node sampling/removal for staging and treatment of patients of endometrial cancer can be used in selected group of patients. It has been shown to result in shorter hospital stay, lower complication rates and no difference in recurrence rates when compared to laparotomy. Manipulation of the tumor (including macroscopically involved lymph nodes) should be avoided to prevent the rare occurrence of port-site metastasis.

Q.20. What information is required from the histopathologic examination of the specimen?

Ans:

i. Histologic subtype and grade
ii. Ploidy status
iii. Estrogen and progesterone receptor status
iv. Myometrial invasion
v. Isthmus/cervical extension
vi. Parametrial spread
vii. Adnexal involvement
viii. Lymph node involvement

Q.21. This patient, Mrs Y is found to have well-differentiated endometroid adenocarcinoma involving >50% of myometrium, with normal adnexa, negative lymph nodes and peritoneal cytology. How will you further manage the case?

Ans: The histopathology suggests Stage Ib G1 disease. This patient should receive pelvic radiotherapy and vaginal boost following surgery.

Post-operative therapy should be based on prognostic factors determined by surgical and pathological staging. Patients can be classified into three treatment categories as follows:

Post-surgical treatment of endometrial cancer based on surgical-pathological findings and stage

Surgical-pathological findings	*Post-operative treatment*
Stage I, G1/2, no myometrial invasion	None (Observe and follow up)
G3, no myometrial invasion Stage I G1/2, <50% myometrial invasion	Vaginal cuff radiation
Stage I, >50% myometrial invasion Grade 3, any myometrial invasion and pelvic extension Lymph node metastasis	Pelvic irradiation plus vaginal cuff boost Isthmus, cervical
Positive para-aortic/common iliac lymph nodes	Pelvic irradiation + vaginal cuff boost + Extended field radiation

Contd...

Contd...

Positive peritoneal cytology	Progestins
Adnexal/parametrial spread completely resected	Whole abdominal radiation Intraperitoneal disease or chemotherapy
Bladder/rectal invasion	Pelvic and vaginal irradiation

Q.22. How would your treatment differ if there was no or minimal myometrial invasion?

Ans: This correlates with stage Ia disease, which has excellent prognosis. Only observation and regular follow up is recommended after surgery. 100% disease free 5 yr survival has been reported after appropriate surgery. No recurrences have been reported so far.

Q.23. What is the role of hormone receptor status?

Ans: Estrogen and progesterone receptor levels have shown to be prognostic indicators, independent of grade.

Patients whose tumors are positive for one or both receptors have longer survival times than those lacking the receptors. Even metastatic tumors which are receptor positive have improved prognosis.

Progesterone receptor levels appear to be better predictors of survival than estrogen receptor levels. The higher the absolute level of receptors, better the prognosis.

Q.24. What is the significance of knowing the histological grade?

Ans: Histological grade is strongly associated with prognosis. In a study of patients with stage I disease:

Grade	*Recurrence*	*5 years survival*
Grade I	7.7%	92%
Grade II	10.5%	86%
Grade III	36.1%	64%

Increasing tumor anaplasia is associated with deep myometrial invasion, cervical extension, lymph node metastasis and local and distant metastasis.

Q.25. What cases require post-operative vaginal vault therapy and how is it given?

Ans: Post-operative vaginal irradiation reduces the incidence of vaginal recurrence in patients with tumors confined to the uterus from 15% to 1-2%.

Procedure: Earlier this was administered using low dose radium or caesium sources via colpostats to deliver a surface dose of 6000 to 7000 cGy to upper vagina. Recently, afterloading outpatient techniques using high dose rate iridium sources have been employed.

Side-effects: It is associated with low morbidity. Vaginal stenosis and dysparunia may be a problem for postmenopausal patients in the absence of regular vaginal dilatation.

Q.26. What cases will need external pelvic radiation?

Ans:

- Stage Ib, grade 3 (Stage I, grade 1/2 with deep myometrial invasion)
- Cervical involvement
- Adnexal or parametrial involvement
- Pelvic lymph node metastasis
- Large tumors >2 cm with high grade
- Any grade of tumor with lymph vascular space invasion

Benefits: Reduces locoregional recurrence, improves disease free survival

In a recent GOG trial (2004), including cases of intermediate risk endometrial cancer, disease recurrence was reduced by 58% with the use of post-operative pelvic irradiation.

Technique of post-operative whole pelvic external beam radiation: 4500 to 5040 cGy in 180 cGy fractions over 5 to 6 weeks, to a field encompassing upper-half of vagina inferiorly, lower border of L4 superiorly and 1cm lateral to margin of bony pelvis. Vaginal apex usually boosted to 6000 to 7000 cGy.

Side-effects: Most frequent side-effects are gastro-intestinal, usually abdominal cramps and diarrhea.

More serious complications such as bleeding, proctitis, bowel obstruction and fistula formation can occur, and may require surgical correction. Hematuria, cystitis or vesico-vaginal fistulae may also occur. Overall complication rate ranges from 25 to 40%. The rate of serious complications requiring surgical intervention is 1.5 to 3%.

Q.27. When is extended field radiation given?

Ans: Extended field radiation is given in patients with histologically proven para-aortic nodes metastasis, who have no other evidence of disease outside the pelvis. The entire pelvis, common iliac lymph nodes, and para-aortic lymph nodes are included within the radiation field. Para-aortic radiation dose is limited to 4500-5000 cGy.

Q.28. What is the role of whole abdomen radiation?

Ans: Whole abdominal radiation is given in:

- Patients with stage III/IV disease (adnexal or upper abdominal disease such as in the omentum, that has been completely excised)
- Papillary serous/mixed Mullerian tumor with propensity for upper abdomen recurrence.

It should not be used in patients with gross residual intraperitoneal disease.

Dose: 3000 cGy in 20 daily fractions of 150 cGy. Renal shielding is done at 1500-2000 cGy. Additional 1500 cGy is delivered to para-aortic nodes and 2000 cGy to pelvis.

Side-effects: Gastrointestinal side-effects, e.g. nausea, vomiting and diarrhea are common. Hematological toxicity may occur and is usually mild. Late complications (mainly chronic diarrhea and small bowel obstruction) occur in 5-10% cases.

Q.29. How would you manage a case of stage II disease?

Ans: Pre-operative assessment of cervical involvement is difficult. Endocervical curettage has high false positive (50-80%) and false negative rates. Ultrasound or MRI may suggest cervical invasion. Thus, histological proof of cancer infiltration of cervical stroma or presence of obvious tumor on the cervix is the only reliable means of diagnosing cervical involvement.

In patients with stage II cancer endometrium, the incidence of pelvic lymph node metastasis is 30-40%. Thus, treatment should include management of pelvic lymph nodes.

Two approaches may be used for management in this case:

a. *Initial surgical staging laparotomy followed by RT:* The best approach is initial surgical staging followed by irradiation. This confirms the correct stage of the disease, which is important as there are discrepancies in clinical and surgical staging in up to 50%.

   The surgical staging includes exploratory laparotomy, peritoneal washings for cytology, modified radical hysterectomy with bilateral salpingo-oophorectomy, resection of iliac and lower para-aortic lymph nodes. This is followed postoperatively by pelvic or extended field radiation depending on surgico-pathological stage. The reported 5-yr survival following this management is 70%. Some surgeons do only extrafascial hysterectomy, as post-operative RT is required.

b. *Initial RT followed by surgery:* In patients who are unsuitable for extensive surgery (obese, elderly, medical problems, ballooned up cervix), the preferred approach is initial external and intracavitary radiotherapy followed within 6 weeks by less extensive surgery (TAH with BSO). Reported 5-yr survival rates are 60-65%.

c. *Radiation alone:* In patients unsuitable for surgery, radiotherapy alone may be used but 5-yr survival rates are reduced to 50%.

Q.30. How would you manage this patient if she was found to have stage III endometrial cancer?

Ans: Stage III cancer accounts for 7-10% of all cases of endometrial cancer. Treatment needs to be

individualised. Surgery should be performed with the aim of determining extent of the disease and to remove the bulk of the disease if possible. Preferred treatment is extrafascial hysterectomy with BSO and partial omentectomy, peritoneal washings, peritoneal biopsy from suspicious areas and selective pelvic and para-aortic lymphadenectomy and partial omentectomy.

Post-operative radiotherapy is tailored according to the extent of the disease. Patients treated with surgery and radiotherapy both, fare better than those treated with radiation alone.

Q.31. How will you manage stage IV endometrial cancer?

Ans: Stage IV tumor is found in 3% of all cases. Management needs to be individualized. The primary aim is control of symptoms and local control of tumor to provide palliative relief of bleeding, discharge and complications involving bladder and rectum. It usually involves a combination of surgery, radiotherapy and systemic hormonal or chemotherapy. Several reports have noted a positive impact of cytoreductive surgery on survival, median survival being 3 times greater with optimal cytoreduction (18-34 months versus 8-11 months, respectively).

If pulmonary metastasis is present, further imaging of abdomen and pelvis by CT or MRI is needed. If no other site of disease is found, treatment includes TAH with BSO, progestogens, and adjuvant RT if pelvic and para-aortic lymph nodes are involved. The management of metastatic disease is variable depending on factors such as co-morbidities, tumor grade, performance status, and prior treatment. Hormonal therapy and cytotoxic chemotherapy have traditionally been used. Surgical resection of lung metastasis has also been found to improve survival rates.

Q.32. How will you follow up this patient after treatment is completed?

Ans: There is no single accepted strategy for follow up of patients with endometrial cancer. Routine follow-up visits at 3-6 months with vaginal cytology at each visit and annual chest X-ray is neither clinically productive, nor cost-effective.[1] 60-75% patients will be symptomatic at the time of recurrence, and most patients with curable recurrence had vaginal bleeding from a vaginal lesion. Despite this, a periodic examination provides psychological reassurance to the patient.

Thus, routine post-treatment surveillance for patients with endometrial cancer should include:[1]

- Education of the patients regarding symptoms of recurrence (vaginal bleeding, abdominopelvic or back pain, leg swelling, abdominal bloating, cough or shortness of breath). Symptomatic patients should be instructed to report promptly for evaluation and treatment.
- ACOG recommends follow-up of patients every 3-4 months for 2-3 years, then every 6 months. After 5 years, patients can return to routine annual follow-up.
- At each visit, history and clinical examination (including general physical, systemic, abdominal and pelvic examination, with careful inspection and palpation of whole length of vagina, parametrium and rectovaginal examination) should be done.
- Routine Pap smear and chest X-ray cannot currently be recommended.
- CT scan, USG, MRI, IVP is done only if clinically indicated.
- CA-125: Elevated levels are seen in advanced and recurrent disease, and correlate with clinical course. CA-125 is helpful in monitoring patients with uterine papillary serous carcinoma, or those with high-risk of recurrence/previously elevated levels.
- Patients treated with radiation and/or chemotherapy need more intensive follow-up

to monitor them for long-term complications of therapy.

Q.33. What are the overall 5-yr survival rates?

Ans: The overall 5-yr survival rate in endometrial cancer is *approximately* 75%.

Stage	*5 years survival rates*
I	82% (in well-differentiated)
II	65%
III	44%
IV	15%

Q.34. She comes back after 1 year with vaginal bleeding and examination and investigations reveal recurrent vaginal disease. How would you manage? What are the common sites of recurrence?

Ans: About one-fourth of the patients treated for cancer endometrium develop recurrent disease. 50% recurrences develop in 2 yrs and three-fourths occur within 3 years of initial treatment. In patients treated with surgery alone, most recurrences tend to be vaginal/pelvic. While patients treated with combined surgery and radiotherapy tend to have distant metastasis (70%) involving lung, abdomen, lymph nodes (aortic, supraclavicular, inguinal), liver, brain and bone. Vaginal bleeding is the most common symptom associated with local recurrence, and pelvic pain is most often present with pelvic recurrence.

Patients with initial well-differentiated tumors and recurrence occurring 3 yrs after primary therapy have better prognosis.

Management: Pelvic or vaginal recurrence in patients who have not received prior pelvic irradiation is best treated with external irradiation followed by brachytherapy boost to deliver a total tumor dose of at least 6000 cGy. Reported survival rates in patients with isolated vaginal recurrence treated with irradiation range from 24 to 45%. Survival rates are better in cases where the initial endometrial cancer was grade 1, with younger age at recurrence, recurrent tumor ≤ 2 cm, time from initial treatment to recurrence more than 1 year, and in cases that have received brachytherapy vaginal boost.

Role of surgery in recurrent disease:

1. Surgical resection of a metastatic vaginal nodule >2 cm prior to radiation may improve local control.
2. Few patients with intraperitoneal recurrence may need surgery to relieve intestinal obstruction.
3. Tumor reductive surgery may be performed before administration of whole abdomen radiation therapy or systemic hormonal or chemotherapy.
4. In patients with isolated central pelvic recurrence after irradiation, exploratory laparotomy and pelvic exenteration may be done if there is no evidence of disease outside the pelvis and no lymph node metastasis.

Site of recurrence	*Treatment available*
Vaginal vault recurrence	After primary surgery, treated with radiation (EBRT + ICRT – 6000 cGy). Surgical resection of a metastatic vaginal nodule >2 cm prior to radiation may improve local control.
Lymph nodes	Radiation therapy Long-term progestin therapy if progesterone receptor positive
Lung metastasis	Long-term progestin therapy

Q.35. What is the role of hormonal therapy in endometrial cancer? What agents are used?

Ans: Indications:

i. Advanced/Recurrent endometrial cancer
ii. Metastatic disease

Agents:

i. Oral medroxy-progesterone acetate 50-100 mg TDS
ii. Megestral acetate 160-320 mg/day
iii. MPA (depo provera) 500-1000 mg im weekly
iv. Tamoxifen, 20-40 mg/day

Progestins are currently recommended as initial treatment for all patients with recurrent endometrial tumors which are hormone receptor positive. Response depends on estrogen and progesterone receptor status. Response is better if tumor is progesterone receptor positive. If a response is obtained, the progestin should be continued for as long as the disease is static or in remission. In cases with relative contra-indication to high-dose progestin therapy (e.g. prior or current thromboembolic disease, severe heart disease, or inability to tolerate progestins), tamoxifen 20 mg BD is recommended. Failure to respond to hormonal therapy is an indication for initiating chemotherapy.

Q.36. What is the role of chemotherapy in management of adenocarcinoma endometrium? What chemotherapeutic agents are available?

Ans: Chemotherapy has a palliative role in advanced/metastatic disease. Most active chemotherapeutic agents are doxorubicin (50-60mg/m^2 every 3 weeks), cisplatin (60-75mg/m^2 every 3 weeks), carboplatin (350-400 mg/m^2 every 4 weeks) and paclitaxel (250 mg/m^2 as a 24-hr infusion or 175 mg/m^2 as a 3-hr infusion every 3 weeks). Response rates reported with paclitaxel alone are 36%, while those with mono-agent chemotherapy using other mentioned agents are 21-29%. Combination chemotherapy (with cyclophosphamide, doxorubicin, and cisplatin or cispatin/carboplatin + paclitaxel) results in response rates ranging from 38-76%. Despite this, the median survival time has been less than 12 months.

Q. 37. What is the prognosis if histopathology shows papillary serous and clear cell carcinoma?

Ans: These account for only 10% cases, but are associated with 50% relapse. 5-yr survival for papillary serous carcinoma is 30% and for clear cell carcinoma 40%. These are not estrogen dependent. Recommended treatment is extensive surgical staging including pelvic and para-aortic lymphadenectomy, and partial omentectomy.

For patients with stage Ia, no further treatment is needed. For patients beyond stage Ia, give pelvic RT and CAP regimen. Only pelvic radiation is not enough.

Q.38. What is the role of estrogen replacement therapy after treatment of endometrial cancer?

Ans: Post-surgery, many women may suffer from menopausal symptoms. There has been concern regarding use of estrogen replacement in treated cases of endometrial cancer because occult disease may be activated by estrogen.

ACOG states that for women with history of endometrial cancer, hormone replacement therapy could be used, but selection of appropriate candidates should be based on prognostic indicators and the risk she is willing to assume. Most authorities do not prescribe estrogens for 1 year after surgery since recurrences appear within 1-3 years. If all disease has been removed by surgery or destroyed by RT, then HRT may be given after explaining the risk of occult disease.

Alternatively, topical estrogen alone can be used to treat vaginal symptoms. Symptomatic relief of hot flushes patients can be achieved by giving only progestins like:

i. MPA 20 mg OD
ii. MPA 150 mg IM every 3 months
iii. Non-hormonal agents like clonidine, venlafaxine.
iv. SERMS like raloxifene and weight bearing exercises can reduce bone loss.

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Gauri Gandhi, Neha Singh

27 Carcinoma Vulva

Carcinoma vulva is an uncommon malignancy accounting for 2-5% of the malignancies of the genital tract. Although this cancer appears most frequently in women aged 65-75 years (usually associated with lichen sclerosis and squamous hyperplasia), it can appear in patients younger than 40 years. These young patients tend to have early microcarcinomas, which may be associated with diffuse intraepithelial neoplasia of the vulva and human papillomavirus.

The most common presentation is a pruritic lesion of the vulva or a mass detected by the patient herself. However, early vulvar cancer may be asymptomatic and recognized only with careful inspection of the vulva. A biopsy should be performed on all visible lesions on the vulva. A delay in diagnosis appears to occur mainly because the patient does not seek medical attention for many months or because the lesion is treated medically for months, without biopsy for definitive diagnosis. Hence, there is need for awareness regarding early diagnosis and proper management of carcinoma vulva in both patients and the physicians.

CASE 1

Mrs X, a 64-year old postmenopausal lady presented with complaints of itching in the vulvar area.

Q.1. What are the important points in history?

Ans:

- History of discharge or bleeding from vulva
- History of discharge or bleeding per vaginum as vulvar malignancies can be associated with malignancies of vagina and cervix due to 'field phenomenon'.
- History of sexually transmitted diseases.

Vulvar cancer is occasionally associated with syphilis, Lymphogranuloma venerum and granuloma inguinale. These patients develop the disease at an earlier age and have more poorly differentiated lesion.

HPV infection is associated with VIN and basaloid or warty type of vulvar cancer. DNA of HPV is found in 89% of VIN3 and up to 86% of basaloid or warty type of carcinoma vulva, although it is present in <10% of keratinizing type.

- History of treatment received for cervical precancer or cancer and VIN
- History of any mass in the groin
- History of HIV/ AIDS or immunosuppressant therapy as this is a risk factor for carcinoma vulva.
- History of diabetes and hypertension should be elicited as these diseases are more common in this age.

Q.2. How would you proceed to examine the case?

Ans:

- A general physical examination is done.

- A systemic examination should be done including examination of thyroid and breasts, CVS, CNS, respiratory system.
- A per abdominal examination is done to rule out any abnormality. The inguinofemoral region should be examined for any lymphadenopathy.
- Local examination: Examine the vulva for any leukoplakia, raised areas, growth or ulcerative lesion. Vulvar cancer may present as an exophytic growth, an ulcerative lesion or a raised flat area. It may be pigmented, fleshy, and may sometimes be tender. The lesion may be merging in the surrounding area of vulvar dystrophy. In keratinizing carcinoma, associated lichen sclerosis or squamous hyperplasia is found in 80% cases, although their causative role remains controversial.

A careful assessment of location and size of lesion should be done and also assess whether it is unifocal or multifocal.

- Extension of the tumor to adjacent mucosal structures like vagina, urethra, bladder base or anus should be noted.
- Vulvar cancer is often associated with other squamous intraepithelial and invasive lesions of lower genital tract, therefore do careful speculum examination of cervix and vagina.
- It may be sometimes necessary to examine under anesthesia if palpation of tumor is very painful.

On local examination of Mrs X, an exophytic growth of about 3 × 3 cm was present, tender, not fixed to underlying bone. There were no palpable lymph nodes. P/S – NAD. P/V- NAD.

Q.3. What is the diagnosis?

Ans. The first clinical diagnosis is carcinoma vulva. The differential diagnosis includes:

- Tuberculosis of vulva
- Condyloma accuminata

If the lesion is ulcerative, the differential diagnosis would include syphilitic ulcer, chancroid.

Q.4. What is the incidence of carcinoma vulva?

Ans: Vulvar cancer is not so common and represents 2-5% of the malignancies of the female genital tract. The estimated incidence is 1-2/100,000 women.

Q.5. How will you confirm the diagnosis?

Ans: The diagnosis should be confirmed by taking a wedge biopsy under local or regional anesthesia. The biopsy should be taken from an area where there is transition from normal to malignant tissue. The biopsy should include sufficient underlying dermis to assess the depth of invasion.

If the lesion is less than 1 cm, then an excisional biopsy with a 1 cm margin all around is preferable.

Q.6. What are the histological types of vulvar cancer?

Ans: Squamous cell carcinoma is the most common histological type of carcinoma vulva occurring in 85-90% patients. It can be of the following two types:

a. Basaloid or warty type: They tend to be multifocal, occur in younger age, and are associated with HPV, VIN and cigarette smoking.
b. Keratinizing type: They tend to be unifocal, occur in older age, and are associated with lichen sclerosis and squamous metaplasia.

Other histological types of carcinoma vulva are-

– Melanomas	2-4%
– Basal cell carcinoma	2-3%
– Bartholin gland carcinoma (adenocarcinoma)	1%
– Sarcoma	< 1%
– Verrucous carcinoma	< 1%
– Metastatic carcinoma	< 1%

The biopsy has come out to be keratinizing squamous cell carcinoma, invading >1 mm.

Q.7. How will you stage the lesion?

Ans: In 1988, FIGO approved a surgico-pathological system for staging carcinoma vulva.

This staging has been revised by FIGO in 2008 and published in 2009. Although the previous stage IA remains unchanged because this is the only group of patients with a negligible risk of lymph node metastasis, the previous stages I and II have been combined because many studies have demonstrated that the size of the lesion (with negative lymph nodes) is no longer a prognostic factor in previous stages I and II. Moreover, the number and morphology (size and extracapsular spread) of positive lymph nodes have been taken into account because they have been shown to be important prognostic factors, whereas the bilaterality of positive nodes have been discounted due to controversy from previous studies.

The revised FIGO staging for carcinoma vulva is:

- **Stage I** Tumor confined to the vulva
  - **IA** Lesions < 2 cm in size, confined to the vulva or perineum and with stromal invasion <1.0 mm*, and no nodal metastasis
  - **IB** Lesions >2 cm in size or with stromal invasion >1.0 mm*, confined to the vulva or perineum, with negative nodes.
- **Stage II** Tumor of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes
- **Stage III** Tumor of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with positive inguinofemoral lymph nodes.
  - **IIIA** (i) With 1 lymph node metastasis ≥5 mm, or
    (ii) 1-2 lymph node metastasis <5 mm
  - **IIIB** (i) With 2 or more lymph node metastases ≥5 mm
    (ii) 3 or more lymph node metastases <5 mm diameter.
  - **IIIC** With positive nodes with extracapsular spread
- **Stage IV** Tumor invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures
  - **IVA** Tumor invades any of the following:
    (i) Upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or
    (ii) Fixed or ulcerated inguinofemoral lymph nodes
  - **IVB** Any distant metastasis including pelvic lymph nodes

Since the growth of the patient is >2 cm but does not involve adjacent perineal structures and no palpable nodes are present, it appears to be Stage IB according to the new staging (and earlier would have been Stage II)

Q.8. What other investigations should be done?

Ans:

1. The following investigations should be done to rule out surrounding vulvar dystrophies and other genital malignancies
   - Pap smear
   - Colposcopy of cervix and vagina
   - Vulvoscopy for lesions at other sites on vulva
2. Pre-operative investigations, which include–
   - Complete blood count
   - LFT, KFT
   - Blood sugar
   - Serum electrolytes
   - Chest X-ray, ECG
   - Urine-albumin, sugar, microscopy and culture
   - Special investigations for co-morbid conditions in elderly

* The depth of invasion is defined as the measurement of the tumor from the epithelialstromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

3. Imaging:
   - Ultrasound pelvis to rule out other pelvic pathology
   - CT/MRI scan of groin, pelvis and abdomen may be done to see the extent and resectability of the tumor and involvement of lymph nodes

   If the lesion is large and locally advanced, the following investigations may be required:
   - Cystourethroscopy – if bladder or urethra seems involved
   - Intravenous pyelography – if bladder base is involved
   - Proctosigmoidoscopy – if anus or rectum seems involved

Q.9. What are the routes of spread of vulvar cancer?

Ans: Vulvar cancer spreads by the following routes:

1. *Direct extension*, to involve adjacent structures such as vagina, urethra and anus
2. *Lymphatic spread:* Lymphatic metastases may occur early in the disease. Initially, spread is usually to the inguinal lymph nodes, which are located between Camper's fascia and fascia lata. From these superficial groin nodes, the disease will spread to the deep femoral nodes, which are located medially along the femoral vessels. Cloquet's or Rosenmuller's node, situated beneath the inguinal ligament, is the most caphalad of the femoral node group. Metastases to the femoral nodes without involvement of the inguinal nodes have been reported and the lymphatics of the vulva from either side form a rich network of anastomoses along the midline. Lymphatic drainage from the clitoris, anterior labia minora and perineum is bilateral. For lateral tumors, metastases to contralateral lymph nodes in the absence of ipsilateral nodal involvement is rare.

   From the inguinofemoral nodes, the cancer spreads to the pelvic nodes, particularly the external iliac group. The overall incidence of inguino-femoral lymph node metastases is about 30%. Metastases to pelvic nodes occur in about 12% cases. Pelvic nodal metastases is rare (0.6%) in the absence of groin node involvement.
3. *Hematogenous spread* to ditant sites, including the lungs, liver and bone. Hematogenous spread usually occurs late and is rare in the absence of lymph node metastasis.

Q.10. What is the treatment for this patient?

Ans: Surgery is the mainstay of treatment.

Earlier radical vulvectomy with bilateral inguinofemoral lymphadenectomy by *en bloc* dissection was the standard therapy for Stage IB. However, the disadvantages of *en bloc* dissection are:

- Large loss of vulvar tissue with psychosexual sequelae
- A 50% wound breakdown rate
- A high incidence of lower extremity lymphedema

The *en bloc* dissection has now been replaced by the **triple incision technique**. Separate incisions are given for vulvectomy and lymphadenectomy. This results in significant reduction in wound morbidity.

Radical Vulvectomy

This is done by two elliptical incisions on the vulva. The outer one is placed on the labiocrural folds and anteriorly brought across the mons pubis and posteriorly across the perineal body. The inner incision circumscribes the vaginal introitus and vulvar vestibule. The dissection is carried down to the deep perineal fascia. The aim should be to have 2cm tumor free margin. Once dissection is complete, the levator ani muscles should be approximated to prevent rectocele formation. After achieving hemostasis, the skin is sutured to vaginal mucosa by interrupted sutures.

Lymphadenectomy

Bilateral inguinofemoral lymphadenectomy is done by separate longitudinal incisions centered midway between the femoral artery and pubic tubercle, extending from one inch above to two inch below the inguinal ligament. The skin and subcutaneous tissue is incised. The superficial inguinal lymph nodes lie above the cribriform fascia and associated with saphenous vein and its tributaries (superficial circumflex, superficial external pudendal and superficial epigastric). These tributaries of saphenous vein are first identified and ligated and superficial inguinal lymph nodes are removed. The saphenous vein is identified and ligated at its entry to the femoral vein. A segment of the saphenous vein along with the longitudinal group of lymph nodes is removed. All lymph nodes around the saphenofemoral junction should be removed and any prominent deeper lymph node (Cloquet node) medial to the femoral vein should also be removed. This can be used as the sentinel node and sent for frozen section. *If positive*, extraperitoneal pelvic lymphadenectomy may be done. The alternative treatment for positive inguinofemoral nodes is postoperative radiotherapy to the pelvis and groin.

Q.11. What is the role of sentinel node mapping?

Ans: The sentinel node is the initial site of metastatic disease and the histology of the sentinel node reflects the histology of the rest of the lymph nodes in that basin.

- The inguinal femoral lymph nodes are the sentinel nodes for carcinoma vulva
  - Sentinal node can be identified by lymphatic mapping using the isosulfan blue dye or technetium-99m-labelled nanocolloid. Lymphoscintigraphy is done preoperatively and intra-operatively to identify nodes with metastases.
  - When negative by frozen section, the risk of metastasis to pelvic lymph nodes is negligible. The negative predictive value of this method is 97%.
  - If positive, pelvic lymphadenectomy or pelvic LN radiation can be done.
  - The advantage of this method is that extensive lymphadenectomy is avoided in cases where sentinel node is negative.
  - Sentinel node mapping is still under trial.

Q.12. What is the role of unilateral groin dissection?

Ans. This has been done in **well lateralized early** tumors that are **well differentiated**, with no capillary or lymphatic space involvement and negative ipsilateral inguinal lymph nodes. Stehman et al (1992), in a GOG study reported 3 out of 121 patients undergoing unilateral lymphadenectomy had a recurrence in contralateral lymph nodes but all these tumors were poorly differentiated.

Q.13. When can groin dissection be omitted?

Ans: This can only be done in non midline tumors <2 cm, with no capillary or lymph space involvement which are well differentiated and have stromal invasion less than or equal to 1 mm (Stage IA).

Q.14. What is the treatment according to the stage?

Ans: The management of carcinoma vulva according to the stage is:

Stage IA (tumor < 2 cm with stromal invasion < 1 mm, no nodal metastasis)

- Wide local excision with 1-2 cm normal tissue margin is usually sufficient
- Lymph node dissection may be omitted **except** when the following high-risk factors are present:
  a. poorly differentiated tumor
  b. capillary or lymphatic space involvement
  c. multifocal lesions

- Proper follow up is necessary as there is risk of recurrence

Stage IB (tumor > 2 cm or stromal invasion > 1 mm with no nodal metastasis):

Various factors have to be considered to decide the surgical approach. These include the patient's age, size of tumor and site of lesion.

a. **Radical local excision with inguinofemoral lymphadenectomy**:
   - It is suitable for younger patients with a well-localized small unifocal lesions.
   - Recommendation is to resect the primary tumor with a 2 cm margin of normal tissue and to carry the dissection up to the deep perineal fascia of the urogenital diaphragm.
   - In tumors < 2 cm size, radical local excision results in 90% survival rate.
   - In well-lateralized early tumor that is well differentiated, with no capillary or lymphatic space involvement ipsilateral inguinofemoral lymphadenectomy is done. These are sent for frozen section. If positive, then contralateral and pelvic lymph node dissection is done. If negative, no further dissection or postoperative radiotherapy is needed.
   - Bilateral lymph node dissection should be done in tumors involving midline structures (clitoris or labia minora or perineal body) or within 2 cm of midline.

b. **Radical vulvectomy with bilateral inguinofemoral lymphadenectomy:**
   - Radical vulvectomy with bilateral inguinofemoral lymphadenectomy by triple incision technique which has been described earlier.

Treatment of Advanced Vulvar Cancer

Stage II Tumor involving adjacent perineal structures, i.e. lower 1/3 urethra**,** lower 1/3 vagina, anus).

Stage III (stage I or II with positive inguinofemoral lymph nodes).

Advanced vulvar cancer can be managed by

a. Ultra-radical surgery
b. Radiotherapy
c. Combined modality using chemotherapy and radiotherapy

a. **Ultra-radical vulvectomy** with bilateral **inguinofemoral lymphadenectomy** by triple incision technique.

   When tumor involves the *distal urethra, vagina or anus,* but is still resectable by partial resection of these structures may be done. If >1 cm of urethra is excised then risk of urinary incontinence is there. Partial resection of the external anal sphinter in combination with radical local resection of perianal tissue is associated with a significant rate of subsequent fecal incontinence. Careful sphincter reapproximation and levator muscle placation are done in an effort to minimize incontinence. This surgery should be done in highly selected cases which are clearly respectable with none or 1 or 2 lymph nodes positive.

b. **Radiotherapy**

   This may be the only option in medically unfit patients or unresectable disease. The current high energy radiotherapy techniques have relative skin sparing effect. Teletherapy at a dose of 45-55 Gy to the whole pelvis, including vulva and groins, is given. This can be combined with 65-70 Gy to the tumor bed by a single direct electron beam or interstitial needles, but this local treatment is highly morbid. A more effective method is to combine preoperative chemoradiation followed by a more limited resection. Megavoltage radiotherapy causes regression of advanced cancer to a point where limited resection can be done, with sparing of organ function and better quality of life. Surgery is performed 2-6 weeks after completion of external beam radiotherapy, delivering 50 Gy to whole pelvis.

Stage IV Tumor invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures

The options available are:

a. Ultra-radical surgery - pelvic exenteration
b. Radiotherapy (Teletherapy of pelvis including the vulva and groin has been done at a dose of 45 to 55 Gy), followed by limited resection if possible
c. Combination modality using chemoradiation and surgery 5-flurouracil, cisplatinum, mitomycin and bleomycin have been used for chemotherapy.

Q.15. What is the role of radiation in the treatment of cancer vulva?

Ans: Radiotherapy for cancer vulva is indicated in:

a. Preoperatively in patients with advanced disease who would otherwise require pelvic exenteration, as described earlier.
b. Postoperatively to treat the pelvic and groin lymph node of patients with positive groin nodes.
c. To prevent local recurrence in patients with close surgical margins (<5 mm).
d. As primary therapy for young patients with small primary tumor involving clitoral and periclitoral lesions.

Q.16. What is the role of neoadjuvant chemotherapy?

Ans: Neoadjuvant chemotherapy for vulvar cancer may be considered for tumors that manifest with bowel or bladder involvement that would require extensive or exenterative surgery.

Except in the neoadjuvant setting, chemotherapy for vulvar cancer is palliative or when combined with radiotherapy. Bleomycin, cisplatin and 5-flurouracil have been used for chemotherapy.

Q.17. What are the recent modifications in the surgical management?

Ans: There has been a paradigm shift towards a more conservative surgical approach without compromised survival and with markedly decreased physical and psychosexual morbidity. The changes include:

1. Individualization of treatment for all patients with invasive disease.
2. The use of separate incisions for groin dissection to improve wound healing
3. Modified radical vulvectomy/wide radical resection : This refers to the removal of the **portion** of vulva containing the tumor ensuring that 2 cm tumor free skin margin is removed. The types of modified radical vulvectomy include anterior or posterior hemivulvectomy or lateral hemivulvectomy with clitoral sparing. Sparing of as much normal tissue as possible is likely to reduce sexual dysfunction and disfigurement of the vulva as compared to radical vulvectomy.
4. Omission of groin dissection for patients with Stage IA and no risk factors.
5. Omission of contralateral groin dissection in patients with lateral lesions < 2 cm and negative ipsilateral nodes
6. Elimination of routine pelvic lymphadenectomy if inguinofemoral nodes are negative.
7. The use of postoperative radiation therapy to decrease the incidence of groin recurrence in patients with multiple positive groin nodes.

Q.18. How will you manage the patient after radical vulvectomy and what are the post-operative complications?

Ans: Surgery is usually well-tolerated by these patients despite their old age and associated medical conditions. The patients are advised to have:

- Bed rest for 3-5 days
- A low residue diet can be started from the second day
- Perineal hygiene to be maintained
- Frequent dry dressing of the local wound

- Self-retaining foley catheter till the patient is ambulatory or longer if the lower portion of urethra is removed.
- Pneumatic calf compression or subcutaneous heparin can be used to prevent deep vein thrombosis.

The postoperative complications may be early or late:

Early complications

a. *Wound breakdown:* Groin wound infection, necrosis and breakdown is seen in about 50% patients having 'en bloc excision' and is reduced to about 20% with the 'triple incision technique'.
b. *Lymphocyst formation* may occur in the femoral triangle in 10-20% cases. Periodic sterile aspirations may be required.
c. *Femoral nerve injury* is a rare but debilitating complication of inguinofemoral lymphadenectomy. It can be prevented by avoiding dissection lateral to the femoral artery.
d. *UTI:* It responds to antibiotics.
e. *Thromboembolic complications:* Deep vein thrombosis and pulmonary embolism may occur due to immobilization. Prophylactic low molecular weight heparin is given in high-risk patients to avoid this compication.
f. *Osteitis pubis* is rare. Treatment includes bed rest and nonsteroidal anti-inflammatory drugs.

Late complications:

a. *Lower limb edema* is seen in 7-10% patients.
b. *Recurrent lumphadenitis or cellulitis* of leg occurs in 10% patients. It usually responds to antibiotics.
c. *Dyspareunia* can occur due to stenosis of the introitus. It can be minimized by limiting tissue resection.
d. *Stress incontinence or misdirection of urinary stream* can occur in 10% cases due to poor alignment of urethra. Urethra should be suspended if distal urethra is to be excised.
e. *Posterior vaginal wall prolapse* if levators are not approximated.
f. *Inguinofemoral hernia* after lymphadenectomy can be prevented by proper closure of femoral canal with suture from inguinal ligament to Cooper's ligament.
g. *Pubic osteomyelitis* and *rectovaginal fistula* are rare complications.

Q.19. What is the prognosis of carcinoma vulva?

Ans: The overall 5-year survival rate in *operable* cases is 70-80%

Prognosis of the disease depends on:

a. *Stage of the disease*: The 5-year survival rates of vulvar cancer according to the stage of the disease are:
   Stage I - 95-98%
   Stage II - 80-85%
   Stage III - 40-50%
   Stage IV - 20-40%
b. *Lymph node status:* The number of positive groin nodes is the most important prognostic factor. Patients with one microscopically positive lymph node have a prognosis similar to those with negative nodes, whereas patients with more than 3 positive nodes have poor prognosis with a two-year survival rate of 20%. The survival rate also varies with the nodal group involved. With negative groin nodes, the 5-year survival for invasive carcinoma is about 90%, which falls to about 50% for patients with positive groin nodes. With positive pelvic nodes, the survival falls further to about 11%.
c. *Tumor ploidy* is the second most important prognostic factor after lymph node status. Aneuploid tumors have 23% and diploid tumors have 62% five-year survival.
d. *Depth of stromal invasion* and *lymph vascular space involvement.*
e. *Histologic grade of the tumor.*

Q.20. How will you follow up?

Ans: After completion of treatment for vulvar cancer, a long-term follow up is needed. It is

reasonable to examine these women at least every 6 months for the first 5 years and annually thereafter.

- Follow up is directed at early detection of local recurrence or later, a new primary vulvar tumor and recurrence in the groin nodes, and any distant metastasis.
- Look for any treatment related complications listed earlier.
- Surveillance for associated malignancies of vagina and cervix by Pap smear and colposcopy.

Q.21. What is the rate of recurrence and its management?

Ans: Incidence: 15-35%.

- Majority are seen within 2 years of initial surgery.
- The sites are:
  vulva (70%)- commonest site of recurrence
  groin (24%)
  pelvis (15%)
  distant organs (18%)
  – Status of surgical margins is the most powerful predictor of recurrence, with almost 50% recurrence risk with margins closer than 0.8 cm.
  – *Therapy*: depends on the location and extent of recurrence
    - Localized to vulva- wide local excision or combination of external beam and interstitial radiotherapy.
    - Groin – radical groin dissection and/or radiotherapy
    - Advanced beyond vulva – pelvic irradiation/chemotherapy/palliative surgery

  Distant recurrences are difficult to manage and have poor prognosis.

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