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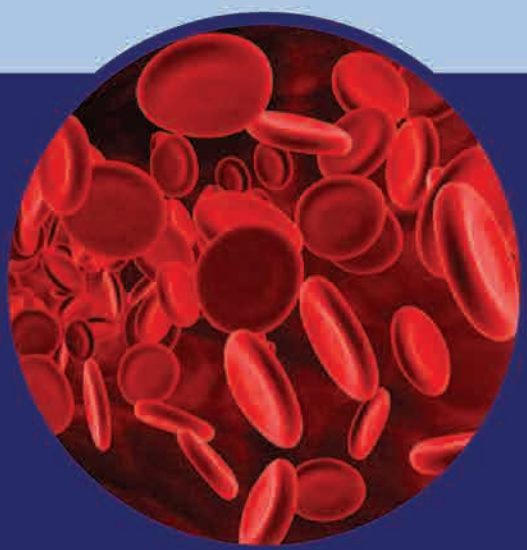
MEDICAL DISORDERS IN PREGNANCY



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Medical Disorders in Pregnancy

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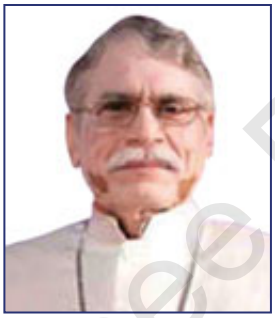

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Message

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Dear FOGSIANS,

Greetings,

There is an increasing trend of multiple pregnancies especially with assisted reproductive technology and though pregnancy is a physiological state it can be complicated by many medical and surgical disorders. Physiological changes occurring during pregnancy are essential for the successful outcome of pregnancy but many medical disorders may interfere with these adaptations and complicate the pregnancy. In some conditions, pregnancy is contraindicated while in others early termination may be warranted for the health of mother and fetus. Pregnancy itself can also have an adverse impact in the preexisting or new onset medical conditions. Maternal complications of multiple pregnancies include increased risk of pregnancy-induced hypertension, gestational diabetes, peripartum hemorrhage, operative delivery, postpartum depression, and heightened symptoms of anxiety and parenting stress. Multiple pregnancy are also associated with a six-fold increase in the risk of preterm birth, which is a leading cause of infant mortality and long-term mental and physical disabilities, including cerebral palsy, learning difficulties, and chronic lung disease.

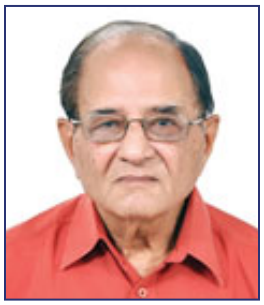
"It's double the giggles and double the grins, and double the trouble if you're blessed with twins."

Complications during pregnancy and childbirth are a leading cause of death and disability among women of reproductive age in developing countries and I feel that all the causes leading to multiple pregnancies and also detection and sensitization for preexisting disease, which can exacerbate and have unwarranted outcome of pregnancy, should be avoided, after all at the end of the day, it is the live and healthy mother and child which are important. My heartiest congratulations to Dr MC Patel and team Ahmadabad for organizing this wonderful conference of high impact in today's scenario and I hope each one who attends will benefit immensely. Looking forward to seeing you all soon.

Happy reading!

Jaideep Malhotra

Foreword



Rohit Bhatt MD DCH FAMS FICOG
Former FOGSI President
Chairperson of ICOG
Chairperson of Safe Motherhood Committee

Professor Jeffcoate described journey through 4 inches of birth canal as most difficult journey. It is rightly said that delivery is NORMAL only in retrospect. Modern obstetrician is supposed to be well versed with not only obstetrical intricacies but also must possess adequate knowledge of medical disorders during pregnancy.

It must be realized that pregnancy can be associated with medical issues too. Pregnant woman is as likely to suffer from medical disorders as in a nonpregnant state. Medical disorders in pregnancy are also important cause of maternal morbidity and maternal mortality. Obstetrician cannot have expertise in all medical disorders but at least he must be able to suspect these disorders so that such women can be referred to expert care. Obstetrician is expected to possess basic knowledge about diagnosing and treating common medical disorders in a pregnant woman. Common medical disorders seen in pregnancy are anemia, hypertension, diabetes, respiratory problems, viral infections, urinary tract infection, heart conditions, jaundice, epilepsy, endocrine disorders, and mosquito born diseases. In India, as in many emerging nations, we have different levels of obstetric care.

1. Obstetricians with MBBS degree running a maternity care hospital in rural areas
2. Obstetricians with MD or diploma holding doctors in districts and smaller towns
3. Obstetricians in big cities where all diagnostic and therapeutic facilities are available.

Medical disorders are a very big branch with so many subspecialties. It is not possible for an obstetrician to know everything about medical disorders in pregnancy. Therefore, obstetrician in limited medical facility must try to update his/her knowledge of common medical disorders. He must be ready to refer to the specialist medical care doctor when his treatment does not improve the condition. The super specialties in medicine are expanding at a very rapid rate and average obstetrician may not be able to remain updated with advances in these fields. In India, working in medicine department is not compulsory for MD. In many Western countries, the rules require them to work in medical ward for 6 months before they can be certified. Therefore, in patient's interest and to avoid legal problems, obstetrician must know when the standard protocol for medical disorders is not improving patient's condition and should be referred to specialists.

It would not be desirable to refer the pregnant woman for common medical disorders. However, obstetrician should seek help from specialists in times of need. There is no problem in medical colleges and big corporate hospitals because help from all specialists is easily available. Problem is in smaller places, villages, and districts. A good obstetrician should be able to suspect and diagnose common medical disorders. Some investigations at first antenatal visit may help in early diagnosis of medical conditions. Such investigations are blood count, Rh and ABO grouping, serum thyroid stimulating hormone, random blood sugar, human immunodeficiency virus test, and ultrasound. Other investigations may be ordered according to need.

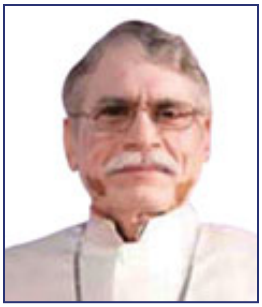
I congratulate FOGSI office bearers for bringing updated version of medical disorders in pregnancy. The authors of various chapters have sound knowledge of medical disorders. They have supplied guidelines for "good clinical practice."

This FOGSI Focus will be very useful to all practicing obstetricians and postgraduates

Words of Caution

As in every field, half-life of knowledge is short and, therefore, all guidelines represent present way of approach. Maybe guidelines may change in future if more information is available.

Preface



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Dear fellow FOGSI colleagues,

To have healthy and successful pregnancy with favorable outcome is a dream of every patient, her relatives, and family. To come to know about pregnancy first time is the happiest moment for any patient and family.

Pregnancy itself is complex physiology. It becomes much complex and complicated if associated with any medical disorder. It also becomes troublesome not only to the patient but to the treating doctors as well. In era of medicolegal problems, it invites one more area of worry for doctors.

Our ultimate goal is to check maternal and fetal mortality and morbidity, as it is matter of great concern and worry.

Obstetrician is expected and supposed to have basic knowledge about diagnosing and treating common medical disorders in a pregnant woman and to refer in time to specialist or intensive care unit to deal with accordingly in given situation, if needed.

This FOGSI focus would be of much help to update knowledge of the given disorders and management guidelines to deal with the situation in time, which is the purpose of this focus.

We congratulate all the authors who are learned and masters in their respective field with basic work and experience. We thank all the authors for sparing their valuable time to contribute chapters for this focus.

Wish you all tension-free, litigation-free practice.

Contents

1

CHAPTER

HELLP Syndrome

Beenu K Singh

INTRODUCTION

Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome refers to a serious complication occurring during pregnancy and consists of a triad of hemolysis with a microangiopathic blood smear, elevated liver enzymes, and a low platelet count.[1] Weinstein recognized it first as a separate entity which is most of the times associated with severe preeclampsia/eclampsia.[2] It is a rare disorder with an incidence of 1–2% of all pregnancies and up to 10–20% in preeclampsia/eclampsia. Although, most commonly it presents as a complication of severe preeclampsia/eclampsia but in as many as 15–20% of cases of HELLP syndrome may not have antecedent hypertension or proteinuria from preeclampsia.[3-5] Early identification and management are important as it may be associated with serious hepatic manifestations, including infarction, hemorrhage, and rupture.

ETIOPATHOGENESIS

All risk factors associated with preeclampsia/eclampsia may be responsible for causing HELLP syndrome as well, only that multiparity is an important risk factor unlike preeclampsia/eclampsia, also that its presence in previous pregnancy increases the risk many fold.[6]

Abnormal placental development and widespread endothelial injury is the basic pathology, same as in pre-eclampsia/eclampsia[6,7] but with greater hepatic system vasospasm, hepatic inflammation, and greater activation of the coagulation system than in preeclampsia.[8] Very rarely it may be caused by genetic factors like fetal deficiency of long-chain 3-hydroxyacyl CoA dehydrogenase (LCHAD).[9,10]

CLINICAL FEATURES

Eighty percent cases of HELLP syndrome present during late second trimester through 34–36 weeks of pregnancy but it may also be seen during early and mid-second trimester or even during postpartum period.[11] It may have a variable presentation, most common symptom being; upper abdominal pain and tenderness with or without nausea and vomiting, less commonly it may also present with headache and visual symptoms.[11,12]

Hypertension (defined as blood pressure ≥140/90 mmHg) and proteinuria are present in approximately 85% of cases, but it may be absent even in severe HELLP syndrome as mentioned above.[13]

DIAGNOSIS

Diagnosis of HELLP is made on the basis of presence of three laboratory findings which is called as basic triad of HELLP syndrome (Tennessee classification):

1. Microangiopathic hemolytic anemia with schistocytes on blood smear and/or other features suggestive of hemolysis; include an elevated indirect bilirubin level (Total bilirubin >1.2 mg/dL), raised LDH levels (>600 U/L) and a low serum haptoglobin concentration (≤25 mg/dL).
2. Serum aspartate/alamine aminotransferase (AST/ALT) >2 times upper limit of normal for the local laboratory (usually >70 international units/L).
3. Platelet count <100,000/mm^3

Women who do not meet all of the above laboratory criteria are considered to have partial HELLP syndrome, these patients may progress to complete HELLP syndrome on further monitoring.

CLASSIFICATION ACCORDING TO SEVERITY OF HELLP SYNDROME

Mississippi classification system is often used to prognosticate HELLP syndrome, it is described as follows:

- Class 1: Most severe form—platelet <50,000/mm^3, AST/ALT ≥70 U/L, LDH ≥600 U/L
- Class 2: Platelet 50,000–100,000/mm^3, AST/ALT ≥70 U/L, LDH ≥600 U/L
- Class 3: Platelet 100,000–150,000/mm^3, AST/ALT ≥70 U/L, LDH ≥600 U/L.

COMPLICATIONS

HELLP syndrome when severe may result in significant maternal morbidity and mortality (up to 20–25%), typical maternal mortality in cases of HELLP is 1–5%. Maternal complications associated with HELLP include pulmonary edema, acute renal failure, disseminated intravascular coagulation (DIC), hepatic rupture, sudden hypotension, cerebral hemorrhage and stroke, and death. Perinatal complications are even higher (up to 30–40%) as it may result in premature delivery, placental insufficiency, intrauterine growth restriction (IUGR), abruption placentae and sudden intrauterine death.

DIFFERENTIAL DIAGNOSIS

Because of its varied clinical presentation, HELLP syndrome may be confused with many other diseases complicating pregnancy (Box 1). Out of all these, acute fatty liver of pregnancy (AFLP) and thrombotic angiopathy caused by hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) need a special mention because they mimic HELLP very closely, although they can be distinguished by a thorough clinical history and laboratory testing.

Acute Fatty Liver of Pregnancy

The clinical presentation of AFLP commonly includes nausea and vomiting, abdominal pain, malaise, polydipsia/polyuria, jaundice/dark urine, encephalopathy, and hypertension/preeclampsia which is very close to HELLP, their time of presentation during pregnancy is also same.[14] It is very important to differentiate between the two as AFLP can rapidly deteriorate in to liver failure and encephalopathy. Detailed laboratory testing should be performed. Coagulation derangement which is reflected as prolongation of the prothrombin (PT) and activated partial thromboplastin time (aPTT), severe hypoglycemia, and elevated creatinine concentration are more common in women with AFLP while hypertension is more common in HELLP. Rarely AFLP may need confirmation by liver biopsy, but clinical diagnosis is usually good enough. Moreover, the information gained, does not change management (i.e., delivery of the fetus) while the procedure itself may turn out to be more risky to the mother.

Thrombotic Microangiopathy

Differential diagnosis of TTP and/or HUS along with HELLP, should always be considered in all pregnant women with severe thrombocytopenia, severe anemia, and elevated LDH levels with minimal elevation of AST/ALT.[15-20] The distinction between TTP, HUS, and severe preeclampsia or HELLP is important for therapeutic and prognostic reasons. Time of onset may suggest one disorder over the other. The onset of TTP tends to be earlier in gestation than the onset of preeclampsia or HELLP.[21] In severe preeclampsia with HELLP, a history of proteinuria and hypertension is usually present prior to onset of symptoms of HELLP. HUS is generally characterized by severe renal insufficiency. On Lab investigations, a high LDH level with only modest elevation of AST is more consistent with TTP than HELLP, also percentage of schistocytes on peripheral smear is often higher in TTP (2–5%) than in HELLP (<1%).[20]

BOX 1 Differential diagnosis of the HELLP syndrome

- Acute fatty liver of pregnancy (AFLP), viral hepatitis
- Hyperemesis gravidarum, gastroenteritis
- Gastritis, cholecystitis, appendicitis, pancreatitis
- Pyelonephritis, kidney stone disease, glomerulonephritis
- Diabetic kotoacidosis, SLE
- Hemolytic uremic syndrome
- Thrombotic thrombocytopenic purpura

MANAGEMENT

After the diagnosis is confirmed, the initial steps in management are to stabilize the mother, assess the fetal condition, and take decision for timing of delivery. Apart from supportive treatment, severe hypertension is treated with antihypertensive therapy and magnesium sulfate is given to prevent eclampsia and also for neuroprotection of neonates at 28–32 weeks of gestation. Once the maternal condition is stabilized, decision for timing of delivery is important as this is the only definitive treatment available.

Timing of delivery—indications for immediate delivery are as follows:

- Pregnancies ≥34 weeks of gestation or <28 weeks of gestation
- Fetal demise, nonreassuring tests of fetal status
- Severe maternal disease: Multiorgan dysfunction, DIC, liver infarction or hemorrhage, pulmonary edema, renal failure, or abruptio placenta.

For pregnancies >28 and <34 weeks of gestation in which maternal and fetal status are reassuring, a waiting period of 48 hours is acceptable before delivering the fetus, a course of corticosteroids is meanwhile given to accelerate fetal pulmonary maturity.

Role of Expectant Management

Although this is not a usual approach, there are few studies which have focused on expectant management of HELLP syndrome. In these studies, in a subset of patients, where the laboratory abnormalities of HELLP syndrome reversed, were managed expectantly with careful monitoring and timely intervention.[22,23] However, there is no strong evidence demonstrating improvement in overall perinatal outcome. As a general rule if maternal conditions permit and if fetus is between 28 and 34 weeks, a wait of 48 hours only is permissible for the corticosteroids to act effectively.

Route of Delivery

Vaginal delivery is desirable for all if possible; regardless of gestational age labor can be induced in women with favorable cervices or pregnancies at least 30–32 weeks of gestation. Cesarean delivery is performed only for the usual obstetrical indications (e.g., breech, nonreassuring fetal status). However, for gestations less than 30–32 weeks with an unfavorable cervix, cesarean delivery is preferable or if the cervix is unfavorable

for induction, and there are signs of fetal compromise (growth restriction, abruptio placenta, oligohydramnios), as the induction process may take time which can prove life threatening to the mother or the fetus.

Special Precautions during Labor and Cesarean Section Delivery

- Thrombocytopenia and coagulation abnormalities contraindicate use of neuraxial analgesia/anesthesia for labor and delivery. Intravenous opioids can be used for this purpose without risk of maternal bleeding
- There is no contraindication to perineal infiltration of an anesthetic for performing an episiotomy or repairing the perineum
- Maintaining a platelet count of at least 50,000/mm^3 is must for performing CS delivery. Because of the high risk of subfascial and wound hematoma in these women, placement of a subfascial drain at cesarean delivery is advisable.

Indications for Platelet Transfusion[13]

- Actively bleeding patients with thrombocytopenia should be transfused with platelets
- Platelet transfusion is generally indicated to prevent excessive bleeding during delivery if the platelet count is less than 20,000/mm^3
- If cesarean delivery is planned, platelet transfusion is required to achieve ≥50,000/mm^3
- Although minimum count before a neuraxial procedure requiring placement of epidural catheter is controversial but maintaining a level of ≥80,000/mm^3 is generally suggested.

Management of Hepatic Complications

HELLP syndrome may be complicated by life-threatening conditions like hepatic hematoma, infarction and rupture. Despite of best of treatment, it is associated with very high maternal mortality (up to 80%).[24]

When complicated by hematoma, it may remain contained, or may rupture resulting in bleeding in to the peritoneal cavity. These patients present with sudden onset epigastric pain, shoulder pain, nausea, and vomiting.[25] If hepatic rupture occurs, swelling of the abdomen from hemoperitoneum and shock rapidly ensue. The aminotransferases are usually modestly elevated. Imaging using CT or MRI is more reliable than ultrasonography. The management of a contained hematoma is mainly supportive, with volume replacement and blood transfusion. In hemodynamically stable patients, percutaneous embolization of the hepatic arteries is first-line therapy of hepatic rupture.[26,27] Surgical intervention is indicated if there is hemodynamic instability, persistent bleeding, increasing pain, or continued expansion of the hematoma.[28] Operative management includes packing, drainage, hepatic artery ligation, and/or resection of affected areas of the liver. Rarely for intractable hemorrhage administration of recombinant factor VIIa[29] and liver transplantation[30,31] may be required as a last resort.

Hepatic infarction is rare in HELLP syndrome and is usually associated when woman has a thrombophilic tendency, like in antiphospholipid syndrome.[32,33] Clinical findings include marked elevation in serum aminotransferases (usually 1,000–2,000 international unit/L or higher) with right upper quadrant pain and fever; infarction can be followed by hemorrhage. The diagnosis is supported by characteristic hepatic imaging (MRI or CT). Treatment consists of supportive therapy along with anticoagulation, if required.

Role of Dexamethasone for Treatment of HELLP

- Although, initial observational studies and small randomized trials suggested use of glucocorticoids for improvement of platelet counts in patients of HELLP[34,35] but were not supported by subsequent large, well-designed randomized, double-blind, placebo-controlled clinical trials[36,37]
- Cochrane review of 11 trials comparing corticosteroids with placebo/no treatment in women with HELLP syndrome found no difference between groups in rates of maternal death, maternal death or severe maternal morbidity, or perinatal/infant death and concluded there was no clear evidence of benefit on substantive clinical outcomes[38]
- The American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy opined that dexamethasone may be justified before 34 weeks of gestation to raise the maternal platelet count.

Postpartum Recovery

Initially after delivery laboratory values may worsen. An upward trend in platelet count and a downward trend in LDH concentration is generally seen by the fourth postpartum day in the absence of any other complications. Recovery may be delayed in women severe disease, such as those with DIC, platelet count <20,000/mm^3, renal dysfunction, or ascites.[17,39]

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2

CHAPTER

Preeclampsia: When to Refer to a Tertiary Care Obstetric Critical Care Unit

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"Realize deeply that the present moment is all that you have. Make the NOW the primary focus of your life."

— Eckhart Tolle

INTRODUCTION

Eclampsia is still killing women in India in the prime of their life. Since past several decades, eclampsia is showing same incidence with a high case fatality rate. Eclampsia usually follows preeclampsia. To prevent eclampsia, we have to prevent preeclampsia. Apart from the direct medical causes of death such as pulmonary edema, cardiac failure, DIC, HELLP syndrome, there are several indirect factors that contribute to the high mortality rate. Inadequate health care delivery system including subnormal doctor-patient ratio and delay in referral to tertiary health care set-up are some of the important contributory factors.

Hypertensive disorders of pregnancy, including pre-eclampsia, complicate up to 10% of pregnancies in India and world-wide, constituting one of the greatest causes of maternal and perinatal morbidity and mortality. A basic, precise and practical classification categorizes hypertension in pregnancy into four classes: preeclampsia-eclampsia, chronic hypertension (of any cause), chronic hypertension with superimposed preeclampsia and gestational hypertension.

DEFINITION

Preeclampsia is a pregnancy-specific hypertensive disease with multisystem involvement. It usually occurs after 20 weeks of gestation, most often near term, and can be superimposed on other hypertensive disorders. Preeclampsia is the commonest form of high blood pressure that complicates pregnancy. It is primarily defined as new onset hypertension with new onset proteinuria.

The American College of Obstetricians and Gynecologists (ACOG) Task Force on Hypertension in Pregnancy published its report "Hypertension in Pregnancy" in November 2014. According to the new ACOG guidelines, the diagnosis of preeclampsia no longer requires the detection of high levels of protein in the urine (proteinuria). It has been observed that end-organ problems with the kidneys and liver can occur even without proteinuria, and that the amount of protein in the urine does not predict how severely the disease will progress.

Hypertension in pregnancy is defined as either a systolic blood pressure (SBP) of 140 mmHg or greater, or a diastolic blood pressure (DBP) of 90 mmHg or greater, or both.

Mild to moderate high blood pressure (140–159 mmHg systolic or 90–109 mmHg diastolic measured on two occasions at least 4 hours apart) warrants close evaluation and monitoring.

High blood pressure ≥160 mmHg systolic or ≥110 mmHg diastolic is a feature of severe preeclampsia.

Proteinuria in pregnancy is diagnosed when 24 hours excretion equals or exceeds 300 mg/dL in 24 hours, or the ratio of measured protein to creatinine (protein:creatinine ratio) in a single void urine measures or exceeds 3.0 mg/dL.

Preeclampsia is a complex disease. Its clinical evolution varies, and can result in a wide variety of—in many cases, unpredictable—clinical manifestations, as well as adverse health outcomes for both the mother and the fetus. Hence, it is necessary that several healthcare providers should interact continuously and in a coordinated manner to provide proper health care. However, standardizing criteria to treat patients with preeclampsia is difficult and severe flaws have been observed in the management of the disease ultimately leading to morbidity and mortality.

WHERE IS THE WEAK LINK?

Obstetric patients are generally young and healthy. However, the potential for catastrophic complications is real, and despite the therapeutic advances of the last few decades, maternal morbidity and mortality continue to occur. This may be related to the pregnancy itself, aggravation of a preexisting illness, or complications of the (operative) delivery.

Maternal mortality ratio (MMR) of India (2015) is 174/100,000 live births ranging from 300 in Assam to 61 in Kerala. The infant mortality rate (IMR) is 34/100,000 live births with Madhya Pradesh having highest IMR 47 and Goa having lowest at 8. Although both these indicators are showing a decline, they are still significant compared to the global averages.

All research and publication data is hospital based. Hence, we may not get the true picture of the community. Since the introduction of National Rural Health Mission (NRHM) in April 2005 and Government of India's Policy regarding hospital delivery (all deliveries should be hospital delivery) and giving incentives for coming for hospital delivery, more and more pregnant ladies are coming for hospital delivery. This may be one of the factors for increasing incidence of PE-eclampsia and decline in MMR.

Managing preeclampsia remains a challenge for physicians and health care services. Physicians make clinical decisions on an individual basis and combining intuition with concepts of probability, utility and the expected value of decision making.[1] Meanwhile, health care service organizations attempt to meet the health needs of patients by using human and physical resources effectively and efficiently.

Different strategies have been proposed and tested for preventing preeclampsia. These include low-dose aspirin, as well as antioxidants, zinc, magnesium, and calcium supplementation. While some studies have shown promising results,[2] large multicenter studies are inconclusive.[3] In addition, because attempts to develop a reliable test to predict preeclampsia have not been successful, health care providers concentrate on early identification and diagnosis of disease through the assessment of risk factors and biomarkers.[4] The predominant mode for treating hypertensive disorders in pregnancy includes, depending on the stage of disease, antihypertensives, anticonvulsants, and the interruption of pregnancy.[5,6]

In institutional health care settings, different providers at different levels of care must interact in an ongoing and coordinated manner to provide service. Many times lack of communication between various levels of healthcare providers leads to mismanagement of the patient.

Two aspects should be taken into account when treating a case of preeclampsia:

- First, the team of obstetricians, physicians and other healthcare providers must consider the well-being and progress of the individual woman and her fetus
- Second, institutional settings should establish guidelines for the management of such patients to provide uniform, high quality health services, efficiently and effectively, as well as to ensure to physicians the availability of appropriate resources to manage patients.

This balance is complicated since physicians must take into account possible variations in the development and severity of preeclampsia on an individual basis, and because health care services differ in terms of their resources, criteria, and demand for services. Because suboptimal clinical management of preeclampsia can have serious consequences, a strategy to formulate and to implement clinical practice guidelines must be developed.

Previous attempts at developing a logical stepwise management structure for treating patients with severe preeclampsia have highlighted the importance of screening all pregnant women and ensuring continuity of care.[7] However, these management structures do not offer guidelines for clinical decision-making based on patient health outcomes. The Canadian Hypertension Society Consensus Conference developed and proposed a complete and comprehensive set of evidence-based recommendations and criteria to define,[8] manage and treat hypertensive disorders in pregnancy.

The following shortcomings have been identified in the care of women with preeclampsia:

- Inaccuracy in screening and diagnostic procedures that can lead to misclassification of patients, (i.e., inaccurate diagnosis of the presence/absence of hypertension during pregnancy)
- Delay on the part of the patient in seeking prenatal care (only 30% of pregnant women consult for prenatal care in the first trimester), lack of compliance to medical recommendations, and irregular attendance at routine prenatal care visits
- Failures in the process of care:
  - Deficiency in the information provided to the patient regarding her disease
  - Untimely referral among the different levels of care
  - Delay in the provision of care when the patient is referred from primary level set-up (General Practitioner or periphery areas)
  - Inaccurate diagnosis or inappropriate treatment during hospitalization, the period of labor or delivery.

Any weak link in the chain of health care services could jeopardize the patient's health and lead to catastrophic complications for both baby as well as the mother.

PHYSICAL EXAMINATION

Physical examination of the patient must be done at each visit to assess the onset of new hypertension and also predict patients who might be at risk of developing preeclampsia (Table 1).

Patient should be examined and following points should be noted:

- Blood pressure
- Height
- Weight
- Body mass index (BMI)
- Uterine size
- Fetal movements.

HOW TO MEASURE BLOOD PRESSURE IN PREGNANCY

By definition, hypertension in pregnancy is:

- SBP ≥140 mmHg or DBP ≥90 mmHg
- Mean arterial pressure (MAP) >106 mmHg
- Increase of 30 mmHg of SBP or increase of DPB above 15 mmHg above baseline
- The patient should be seated or lying at 45° angle, with arm at level of the heart and external stimuli should be eliminated
- Mercury sphygmomanometers are preferable to automated blood pressure monitors. If automated devices are used they should be calibrated, and checked regularly, against a mercury sphygmomanometer

TABLE 1: Criteria to classify the hypertensive disorders of pregnancy second and third levels of care (responsible: obstetrician-gynecologist)

Entity	*Blood pressure*	*Clinical data (one or more of the symptoms)*
Mild preeclampsia	• DBP ≥90 to <110 mmHg • MAP ≥106 to <126 mmHg	• Mild symptoms such as headache, nausea etc. or no symptoms • Protein excretion in 24 hours urine collection >0.3 g to <3 g
Severe preeclampsia	• DBP ≥110 mmHg • MAP >126 mmHg	• Frontal headache, blurred vision, severe nausea and vomiting, persistence of abdominal pain (right upper quadrant), dizziness, tinnitus, drowsiness; and/or ONE of the following: Elevated liver enzymes • Thrombocytopenia (<100,000 × 10^9/L) • Oliguria (< 500 mL/d) • Proteinuria >3 g
Severe morbidity	DBP ≥90 mmHg	Same conditions as above and/or: • Convulsions (eclampsia) • HELLP syndrome • Abruptio placentae • Pulmonary edema • Deterioration in the level of consciousness • Coma • Acute renal failure • Cerebral bleeding • Disseminated intravascular coagulation • Adult progressive respiratory distress syndrome • Hepatic bleeding

- Use an appropriate size cuff
- Record blood pressure to the nearest 2 mmHg
- Measure blood pressure twice on the left arm, using the disappearance of the sound (5th Korotkoff sound) to measure diastolic blood pressure.

IDENTIFYING RISK FACTORS

At every antenatal visit, risk stratification of the patient is to be done (Box 1).

BOX 1 Risk factors for the development of preeclampsia

- Primigravidity/primipaternity
- History of preeclampsia/eclampsia in previous pregnancies: Recurrent preeclampsia occurs, on average, between zero and 4 weeks later than in the first pregnancy ≥3 pregnancies
- Family history of preeclampsia/eclampsia in first degree relative
- Obesity (get data from physical exam; obesity criteria: BMI >27)
- ≥10 years since previous pregnancy
- ≥40 years of age
- Body mass index ≥35 at booking
- Diastolic blood pressure ≥80 mmHg at booking
- Proteinuria at booking in: Asymptomatic proteinuria at booking should be confirmed by a 24-hour urine sample as it may be an indicator of an underlying renal disease which in itself is a risk factor for preeclampsia
- Multiple pregnancy
- Underlying medical condition:
  - Chronic hypertension
  - Renal disease
  - Diabetes
  - Presence of antiphospholipid antibodies
- Migraine
- Change of partner
- Donor egg/donor insemination

Share and discuss information with the woman and her partner in a manner that enables informed choice and consent and supports woman centered care. Discuss the woman's preferences for management. The BRAND acronym (Benefits, Risks, Alternatives, Do Nothing, Discuss) may be useful in communicating care options with woman and their families:

- What are the Benefits?
- What are the Risks?
- What are the Alternatives?
- What happens if we do Nothing?
- Discuss decisions.

WHAT TO DO AFTER THE RISK ASSESSMENT

Referral of patients before 20 weeks to obstetrician for their antenatal care plan if they have one of the following (Table 2):

1. Previous preeclampsia
2. Multiple pregnancy
3. Underlying medical conditions:
   a. Preexisting hypertension or diastolic blood pressure ≥90 mmHg at booking
   b. Preexisting renal disease or proteinuria (≥+ on more than one occasion or ≥300 mg/24 h) at booking

TABLE 2: Warning signs and symptoms of severe preeclampsia that should prompt urgent referral to the intensive care unit

Headache ++	Nausea ++
Drowsiness ++	Vomiting ++
Epigastric pain	Hepatic tenderness
Sudden blindness	Scotomas
Hematemesis	Oliguria/anuria
Proteinuria (identified by dipstick)	Shortness of breath
Seizures (indicates severe morbidity)	Hematuria/hemoglobinuria

c. Preexisting diabetes
d. Presence of antiphospholipid antibodies

4. Any two other risk factors.

WHAT TO DO AFTER 20 WEEKS

At every assessment, identify the presence of any of the following signs and symptoms of the onset of preeclampsia:

- New hypertension: Hypertension at or after 20 weeks' gestation in women with a diastolic blood pressure <90 mmHg before 20 weeks
- New proteinuria: Presence of proteinuria as shown by ≥+ (300 mg/L) on dipstick testing, a protein to creatinine ratio of ≥30 mg/mmol on a random sample, or a urine protein excretion of ≥300 mg in 24 hours
- Symptoms of headache or visual disturbance, or both
- Epigastric pain or vomiting, or both
- Reduced fetal movements, small for gestational age infant–fetal compromise.

Assess all women presenting with new hypertension after 20 weeks gestation for signs and symptoms of preeclampsia. The earlier the gestation at presentation and the more severe the hypertension, the higher is the likelihood that the woman with gestational hypertension will progress to develop preeclampsia or an adverse pregnancy outcome.[12]

If the patient is classified as severe preeclampsia or severe morbidity, she should be immediately referred to a tertiary care center where obstetric intensive care unit (OICU) facility is available to begin treatment (Table 3).

The main goals of management of mild preeclampsia at secondary care hospitals are to monitor the patient and the fetus, to recover and/or maintain clinical stability, to identify progression of the disease to severe preeclampsia or severe morbidity in a timely manner. Medical treatment[9-11] is also described for this level of care. The patient must be seen every 3 days in ambulatory care, and she and the fetus should be monitored to verify that the disease has not progressed. When the disease shows signs of progression, patient should be referred to tertiary care center with intensive care unit facility.

MILD PREECLAMPSIA

Evidence tells us that preeclampsia is a dynamic process. Diagnosing a woman's condition as "mild preeclampsia" is not helpful because it is a progressive disease, progressing at different rates in different women. Roughly, mild preeclampsia may be categorized as:

- Clinically stable: Patients showing no irregular increase in DBP (>95 but <110 mmHg) and/or proteinuria, without CNS symptoms. They can be ambulatory and under monitoring every 3 days at a secondary level health care (Table 4)
- Clinically unstable: Patients showing irregular increase in DBP (>95 mmHg but <110 mmHg) and/or proteinuria, beginning of CNS symptoms. They should be hospitalized at a secondary or tertiary level health care (Table 5).

Women with new hypertension before 32 weeks have a 50% chance of developing preeclampsia.[13] At 24–28 weeks, new hypertension is predictive of severe preeclampsia.[14] On an

TABLE 3: Actions to be taken by referring healthcare providers in various type of patients presenting with hypertension

Definition	*Action to be taken by referring healthcare provider*
New hypertension without proteinuria	
Diastolic ≥90 mmHg and <100 mmHg	Refer to secondary level hospital set up within 48 hours
Diastolic ≥90 mmHg and <100 mmHg with any warning symptoms	Refer same day to secondary level hospital set-up
Systolic ≥160 mmHg	
Diastolic ≥100 mmHg	
New hypertension with proteinuria	
Diastolic ≥90 mmHg and new proteinuria ≥+ on dipstick	Refer same day to secondary level hospital set-up
Diastolic ≥110 mmHg and new proteinuria ≥+ on dipstick	Arrange immediate admission tertiary level hospital with obstetric intensive care unit facility
Systolic ≥170 mmHg and new proteinuria ≥+ on dipstick	
Diastolic ≥90 mmHg and new proteinuria ≥+ on dipstick and any warning symptom	
New proteinuria without hypertension	
Reading on dipstick:	
+	Repeat preeclampsia assessment within one week
++ or more	Refer to secondary level hospital set up within 48 hours
+ with any warning symptom/sign	Refer same day to secondary level hospital set-up
Maternal symptoms or fetal signs and symptoms without hypertension or proteinuria	
Symptoms along with diastolic blood pressure <90 mmHg and trace or no protein:	
Headache, visual disturbances or both	Refer to secondary or tertiary level hospital same day. Follow local protocols for investigation. Consider reducing interval before next assessment
Epigastric pain	
Reduced fetal movements or SGA infant	

TABLE 4: Clinically stable mild preeclampsia: ambulatory treatment

	Clinical	*Examination*	*Treatment*
Mother	• Blood pressure • Weight • Look for CNS, renal, cardiovascular or gastrointestinal symptoms at every visit	• Blood count (including platelet count) • Urinalysis (proteinuria) every 3rd day or dipstick liver function tests (bilirubin, AST, ALT)	• Bed rest • Antihypertensives: ○ Methyldopa ○ Nifedipine ○ Hydralazine
Fetus	• Fetal movements • Fetal heart rate	Cardiotocography: No-stress testing (every 5–7 days) Ultrasonography (measure fetal growth, maturity and placental location and amniotic fluid index)	Induction of pulmonary maturity using dexamethasone or betamethasone in patients with gestational age less than 34 weeks

TABLE 5: Clinically unstable mild preeclampsia: hospitalization

	Clinical	*Examination as often as needed*	*Treatment*
Mother	• Blood pressure • Weight • CNS, renal, cardiovascular, GI symptoms at every visit	• Blood count (platelets) • Urinalysis (proteinuria) • Liver function tests (bilirubin, AST, ALT)	• Bed rest • Antihypertensives: Methyldopa, Nifedipine, Hydralazine • Anticonvulsants: Magnesium sulfate
Fetus	• Fetal movements • Fetal heart rate	• Cardiotocography: nonstress testing • Ultrasonography: Fetal growth, placenta (site, maturity), amniotic fluid volume (AFI)	• Induction of pulmonary maturity using dexamethasoneor betamethasone in gestational age <34 weeks

average, a rise in diastolic blood pressure that does not reach 90 mmHg at any time during pregnancy is associated with an uncomplicated pregnancy.[15] Eclampsia is not always associated with severe hypertension; in a UK population study, 34% of eclamptic women had a maximum DBS of ≤100 mmHg.[16]

New proteinuria with new hypertension is strongly associated with poor fetal and maternal outcome.[17,18]

Women may progress rapidly: 25–55% of women with hypertension of ≥160 mmHg systolic or ≥110 mmHg diastolic with new proteinuria (≥+) required delivery within 48 hours of admission.[19]

PREVENTION OF PREECLAMPSIA

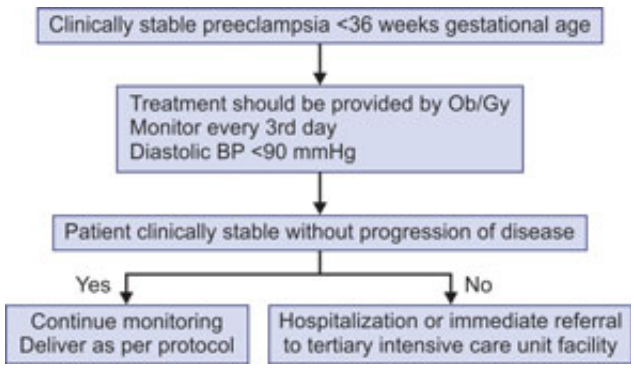
Primary prevention of preeclampsia is not satisfactorily possible. However, certain interventions have been studied to identify the high risk cases earlier in pregnancy and to delay the onset as well as alleviate the course of the disease. Several interventions have been studied including, low dose aspirin, high dose calcium, antioxidants such as vitamin C and E, low salt diet, heparin, etc.

Recent evidence suggests that giving low-dose aspirin to women at high risk of preeclampsia can reduce the prevalence of the severest form of preeclampsia by more than 60%, but the treatment must be started before 16 weeks' gestation. Therefore, early detection is key.

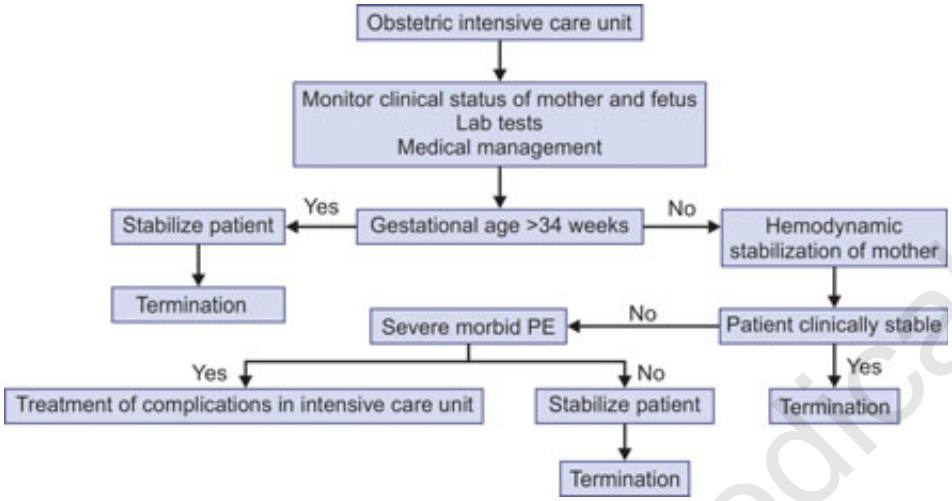
In the UK, identification of high-risk women who could benefit from aspirin is based on a checklist of maternal characteristics and medical history as defined by the National Institute for Health and Care Excellence (NICE) guidelines. An alternative approach combines known risk factors with the results of various maternal biophysical and biochemical measurements taken at 11–13 weeks' gestation: mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), and serum placental growth factor (PlGF); known as the first-trimester combined test. The detection rates of the NICE checklist for all-PE and preterm preeclampsia were 30.4% and

BOX 2 Indications for birth

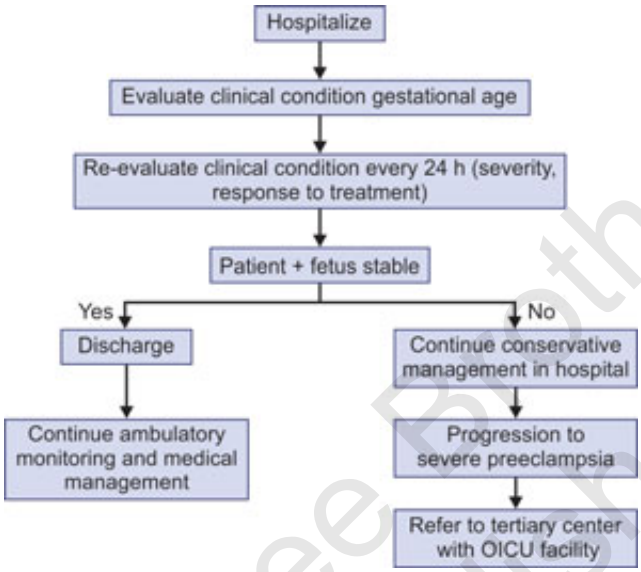
- Nonreassuring fetal status
- Severe fetal growth restriction
- ≥37 weeks
- Eclampsia
- Placental abruption
- Acute pulmonary edema
- Uncontrollable hypertension
- Deteriorating platelet count
- Deteriorating liver and/or renal function
- Persistent neurological symptoms
- Persistent epigastric pain, nausea, and vomiting



Flowchart 1: Management of mild preeclampsia at secondary level.



Flowchart 2: Management of severe preeclampsia at tertiary care facility.



Flowchart 3: Management of clinically unstable preeclampsia.

40.8%, respectively. If screening was carried out by the first-trimester combined test, the detection rates for all-PE and preterm preeclampsia were increased to 42.5% and 82.4%, respectively.[20]

The SPREE (Screening program for preeclampsia) showed that the performance of screening is substantially improved by a method combining maternal factors with biomarkers like MAP, PAPP-A, UtA-PI, PlGF in prediction of preterm PE requiring delivery <37 weeks of gestation.

If these tests are put to universal use, the early detection rate of patients at risk of developing preeclampsia may improve. And this risk stratification may help timely referral of patients to health care units that are well equipped to handle critical care Obstetric cases and neonates.

CONCLUSION

Hypertensive disease in pregnancy complicated by pre-eclampsia/eclampsia requires proper antenatal care, early recognition and referral, adequate treatment, and timely delivery. The lack of protocols for disease management or failure to follow clinical protocols of care contributes toward avoidable medical factors. Factors associated with high rates of Eclampsia and Maternal Mortality and Morbidities in the Developing Countries as compared with developed countries include lack of and/or poor prenatal care, delay in early diagnosis, progression to severe preeclampsia, delay in treatment, lack of access to hospital care, lack of access to transportation to clinic, lack of transport from clinic to hospital, lack of transport from hospital to tertiary facility, lack of well-trained staff and personnel, lack of proper resources, medications, equipment, laboratory, intensive care unit.

Timely delivery and prompt initiation of antihypertensive therapy for severe hypertension form the mainstay of care in preeclampsia. Emphasis on early detection of maternal problems and prompt referral to tertiary centers with intensive care unit facilities to provide optimum care of the circulation, blood pressure, and respiration at an early stage could minimize the prevalence of multiple organ failure and mortality in critically ill obstetric patients. Doctors working in peripheral hospitals and midwives should have periodic training in the management of preeclampsia and eclampsia. There should be more involvement of midwives and accredited social health activist (ASHA) workers in rural areas. We need to strive to reduce the maternal mortality rate of our country further. Care should be taken that no maternal or perinatal morbidity or mortality occurs due to a delay in referral to appropriate health care facility.

"There are far too many silent sufferers. Not because they don't yearn to reach out, but because they've tried and found no one cares."

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3

CHAPTER

Fetal Surveillance in Pregnancy Induced Hypertension

Rajat Ray

INTRODUCTION

The fetus of a woman with hypertension in pregnancy may be at risk of increased perinatal mortality and morbidity. The goal of antepartum fetal surveillance is to prevent fetal death and avoidance of unnecessary interventions. Several techniques for antepartum fetal surveillance are currently in use. These include fetal movement assessment, nonstress test (NST), CST, fetal biophysical profile (BPP), modified BPP, and Doppler velocimetry.[1]

FETAL MOVEMENT ASSESSMENT

Fetal movement assessment occurs when the mother perceives a diminution in fetal movement. The mother counts fetal "kicks" as a means of antepartum fetal surveillance. Two methods are proposed. (a) Cardiff count 10 formula and (b) daily fetal movement count.

Women with hypertensive disorders of pregnancy should be encouraged to be aware of their baby's movements and to report perceived changes to their healthcare professionals.

CONTRACTION STRESS TEST

The contraction stress test (CST) is based on the response of the fetal heart rate (FHR) to uterine contractions. The CST is interpreted by the presence or absence of late FHR decelerations, which are defined as decelerations that reach their nadir after the peak of the contraction and that usually persist beyond the end of the contraction. The results of the CST are categorized in the ACOG bulletin as follows:

- Negative: No late or significant variable decelerations
- Positive: Late decelerations following 50% or more of contractions (even if the contraction frequency is fewer than three in 10 minutes)
- Equivocal-suspicious: Intermittent late decelerations or significant variable decelerations
- Equivocal-hyperstimulatory: Fetal heart rate decelerations that occur in the presence of contractions that are more frequent than every 2 minutes or last longer than 90 seconds
- Unsatisfactory: Fewer than three contractions in 10 minutes or a tracing that is not interpretable.

NONSTRESS TEST

In the NST a continuous electronic monitoring of FHR along with recording of fetal monitoring is undertaken. Heart rate reactivity is believed to be a good indicator of normal fetal autonomic function.

Results of NSTs are classified as reactive or nonreactive. The NST is considered reactive, or normal, if there are two or more FHR accelerations within a 20-minute period, with or without fetal movement discernible by the woman, according to ACOG. The nonreactive stress test lacks sufficient FHR accelerations over a 40-minute period. The NST of the neurologically healthy preterm fetus is frequently nonreactive—from 24 to 28 weeks of gestation, up to 50% of NSTs may not be reactive, and from 28 to 32 weeks of gestation, 15% of NSTs are not reactive.

BIOPHYSICAL PROFILE

The five components of the BPP are as follows: (1) nonstress test; (2) fetal breathing movements (one or more episodes of rhythmic fetal breathing movements of 30 seconds or more within 30 minutes); (3) fetal movement (three or more discrete body or limb movements within 30 minutes); (4) fetal tone (one or more episodes of extension of a fetal extremity with return to flexion, or opening or closing of a hand; and (5) determination of the amniotic fluid volume (a single vertical pocket of amniotic fluid exceeding 2 cm is considered evidence of adequate amniotic fluid).

Each of the components is given a score of 2 (normal or present as defined previously) or 0 (abnormal, absent or insufficient). A composite score of 8 or 10 is normal, a score of 6 is equivocal and a score of 4 or less is abnormal. In the presence

of oligohydramnios, further evaluation is warranted regardless of the composite score.

MODIFIED BIOPHYSICAL PROFILE

The modified BPP combines the NST with the amniotic fluid index (AFI), which is the sum of measurements of the deepest cord-free amniotic fluid pocket in each of the abdominal quadrants, as an indicator of long-term function of the placenta. The modified BPP is considered normal if the NST is reactive and the amniotic fluid index is greater than 5 cm and abnormal if the NST is nonreactive or the AFI is 5 cm or less.

DOPPLER ULTRASOUND

Doppler investigation identifies the fetal cardiovascular response to progressive hypoxia and acidosis and assists in discriminating small, but constitutionally normal, fetuses from those compromised by placental insufficiency. Doppler flow velocimetry of specific arteries and veins are studied to determine fetal well-being.[2] The common vessels studied are umbilical artery (UA), middle cerebral artery (MCA), ductus venosus, and umbilical vein.

Umbilical artery Doppler

Clinical interpretation: An S/D ratio >3.0 or RI >0.6 at ≥28 weeks of gestation is the best threshold for identifying pregnancies at high risk of adverse outcome. The utility of this technique before 28 weeks for fetal surveillance in high risk pregnancies remains investigational.

A gestational age-specific nomogram may also be used. A Doppler index >95th centile for the gestational age should be considered nonreassuring. An initially high Doppler index may progressively decline with advancing gestation, signifying an improved prognosis. In contrast, a rising UA Doppler index may indicate worsening fetal prognosis.[3]

The most important diagnostic characteristic of the UA Doppler waveform is the state of the end diastolic velocity (EDV). Absent EDV is an ominous finding and should indicate delivery in pregnancies beyond 34 completed weeks. Reversed EDV has an even worse prognosis and should be interpreted as a preterminal finding.

Management with normal Doppler indices: High risk pregnancies (e.g., FGR or preeclampsia) with a Doppler index that remains normal or is not progressively rising should be followed with weekly Doppler evaluation. Either the nonstress test (NST) or biophysical profile BPP can be used as a backup test or simultaneously with the UA Doppler.

Fetal monitoring should be intensified if there is a worsening of the clinical status (e.g., progressive restriction of growth or severity of preeclampsia), and appropriate obstetrical intervention according to the existing standards of practice should be implemented. If the fetal and the maternal evaluations remain reassuring, the pregnancy may continue to 38–40 weeks, at which time delivery should occur.

Management with abnormal Doppler indices: The obstetrical management when the Doppler index is abnormal depends upon the severity of the Doppler abnormality, severity of the underlying obstetrical complication, and the duration of gestation. Fetal malformations and aneuploidy are additional factors; management should be individualized in their presence.

A high or increasing Doppler index in the presence of end-diastolic flow warrants more intensive fetal surveillance, such as weekly umbilical Doppler ultrasound and once or twice per week NST, BPP, or modified BPP, as dictated by the clinical condition. If fetal surveillance tests indicate fetal compromise (e.g., nonreactive NST, poor FHR baseline variability, persistent late decelerations, oligohydramnios, or BPP score <4), delivery should be strongly considered, with the mode of delivery determined by obstetrical factors (e.g., gestational age, presentation, FHR tracing) and maternal factors (e.g., medical complications, cervical status).

Absent end-diastolic velocity (AEDV) or reversed end-diastolic velocity (REDV) is associated with increased likelihood of poor perinatal outcome. Therefore, an urgent clinical response is indicated.

The specific management of severe Doppler index abnormalities depends upon the gestational age. The optimal timing for delivery in early preterm pregnancies with abnormal UA Doppler index remains uncertain.

Middle Cerebral Artery

The MCA is a high resistance vessel. The features of fetal hypoxia demonstrates as an increase in diastolic velocity and a decrease in pulsatility indices (PI) and S/D indices.

Ductus Venosus

Absent or reversed a-wave is an ominous finding for fetal compromise.

Umbilical Vein

Pulsatile flow in umbilical vein is a feature of fetal acidemia.

Fetal Biometry

There is a lack of relevant evidence for the use of biometry in hypertensive disorders. However, because of the recognized risk of intrauterine growth restriction (IUGR) in this group, there is a need for the rational use of biometry within its recommendations.

Liquor Volume

A Cochrane review showed that in women with low- or high-risk pregnancies there is no evidence that one method is superior to the other in the prevention of poor perinatal outcomes including admission to neonatal intensive care unit (NICU), perinatal death, umbilical artery pH <7.1, the presence of meconium, Apgar score <7 at 5 minutes or caesarean section. When the amniotic fluid index was used, statistically significantly more cases of oligohydramnios were diagnosed and more women had induction of labor and caesarean section for fetal distress.

The comparison between methods of amniotic fluid assessment favored the single deepest vertical pocket—the amniotic index resulted in more intervention without any clinical benefit for the fetus.

UTERINE ARTERY DOPPLER VELOCIMETRY IN HIGH-RISK PREGNANCIES

Clinical Effectiveness

Several studies have been done on the use of uterine artery Doppler to predict preeclampsia in high-risk women. Alterations in blood flow velocity in the uterine arteries were interpreted using the following tests: resistance index of the main artery and presence of early diastolic notch in uterine artery.

Using an endpoint of the resistance index (abnormal: >0.58) the results showed a sensitivity of 100% and a specificity of 60%. Unilateral or bilateral notches showed a sensitivity of 100% and a specificity of 66%, while using both bilateral notches showed a sensitivity of 33% and a specificity of 87%.

CONCLUSION

If conservative management of severe gestational hypertension or preeclampsia is planned carry out all the following tests at diagnosis:

- Ultrasound fetal growth and amniotic fluid volume assessment
- Umbilical artery Doppler velocimetry.

If the results of all fetal monitoring are normal in women with severe gestational hypertension or preeclampsia, do not routinely repeat cardiotocography more than weekly.

In women with severe gestational hypertension or pre-eclampsia, repeat cardiotocography if any of the following occur:[4]

- The woman reports a change in fetal movement
- Vaginal bleeding
- Abdominal pain
- Deterioration in maternal condition

Clinical management should integrate the Doppler approach with existing modalities of antepartum fetal monitoring. The most important diagnostic characteristic of the UA Doppler waveform is the state of the EDV.

For pregnancies with suspected fetal growth restriction (FGR), UA Doppler studies should be performed weekly to assess for fetal deterioration

The AEDV is an ominous finding and REDV should be interpreted as a preterminal finding. In pregnancies complicated by FGR or preeclampsia, we recommend prompt delivery rather than expectant management in the setting of AEDV at ≥34 weeks and REDV at ≥30 weeks.

Carry out ultrasound fetal growth and amniotic fluid volume assessment and UA Doppler velocimetry starting at between 28 and 30 weeks (or at least 2 weeks before previous gestational age of onset if earlier than 28 weeks) and repeating 4 weeks later in women with previous:

- Severe preeclampsia
- Preeclampsia that needed birth before 34 weeks
- Preeclampsia with a baby whose birth weight was less than the 10th centile
- Intrauterine death
- Placental abruption.

In women who are at high risk of preeclampsia, only carry out cardiotocography if fetal activity is abnormal.

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4

CHAPTER

Pregnancy and Epilepsy

Vipul D Kapadia

INTRODUCTION

Epilepsy is the most common neurological disorder, with 50 million people affected by it worldwide. Nearly 50% of these affected individuals are women. The burden of epilepsy in women in India is to the tune of 2.73 million, with 52% of them being in the age group of 15–49 years. These women, apart from their neurologically distressing condition, face a great social stigma as compared to men with epilepsy.[1] These social stigmas could be nonacceptance by her in-laws, separation from their husbands and even difficulty in getting married. They may have to face even greater reproductive adversities.

Epilepsy can affect reproductive functions. Reproductive events like menstruation, pregnancy and lactation can also affect epilepsy. If the epileptogenic focus is located in that specific region of functionality, hypothalamo-pituitary axis can get disturbed, leading to ovulatory disturbances and subfertility. Most antiepileptic drugs can interfere with sex hormone metabolism through their action on liver enzymes. In experimental models, estrogen lowers the seizure threshold to electrical shock and can also create new epileptogenic focus when applied topically to cerebral cortex. Intravenous administration of estrogen can enhance epileptiform activity on EEG. Progesterone, through its metabolite, allopregnanolone, a GABA-A receptor modulating neurosteroid, has anticonvolusant property.[2]

There is predilection of seizures at certain phases of menstruation. It is called catamanial epilepsy. Women with ovulatory cycles had higher seizure chances than women with anovulatory cycles (77% vs. 22%). Ovulatory women experience greater incidence of seizures around day 9 to day 14.[3] Late marriage, antiepileptic therapy leading to sexual and reproductive adversities, epilepsy associated endocrinopathies can lead to subfertility. Antiepileptic treatment with multiple drugs (polytherapy) may also be a contributory factor to subfertility.

EFFECT OF PREGNANCY ON EPILEPSY

Effect of pregnancy on epilepsy can be varied. European pregnancy registry showed that 60% of Women with epilepsy (WWE) did not get seizures during pregnancy.

Risk of seizures is maximum during labor and delivery. Fortunately, status epilepticus can occur in <1% of patients. Women with focal epilepsy, women on polytherapy and women who experienced seizures one month prior to the pregnancy are at a higher risk for increased seizures during pregnancy. Women with catamanial epilepsy have absent cyclical hormonal variation during their pregnancy and hence may have decreased seizure activity.[3]

It is of concern that WWE in pregnancy may miss out their antiepileptic drug (AED) doses because of pregnancy nausea and vomiting. They may also fear teratogenicity with AED, and hence may avoid taking the drugs. This may aggravate their condition, leading to seizures.

EFFECT OF EPILEPSY ON PREGNANCY

With seizures, a pregnant woman can have a fall and sustain injuries; she may be errant in taking adequate antenatal care.

However, 90% of WWE have normal course of pregnancy, labor and delivery. Nonetheless, they are at an increased risk of spontaneous abortions, induction of labor, cesarean delivery and even postpartum hemorrhage (PPH). Perinatal complications like preeclampsia, preterm labor, placental abruption, IUGR, neonatal and perinatalmortality, morbidity and even maternal mortality may be increased.

EFFECT OF EPILEPSY AND AED ON FETUS

The fetus in utero in a WWE can be affected by seizures, exposure to AED and the transporters of AED. These adverse effects can be anthropometric and physiological as discussed above, or can even be teratogenic. There may be long-term neurocognitive deficits.

During seizures there is fetal hypoxia due to poor uteroplacental circulation. When circulation is restored, there is increased oxidative stress, which can trigger teratogenesity. Also, exposure to AED is the major teratogen. AED can lead to folate deficiency. Liver metabolism of AED can lead to teratogenic metabolites like arene oxide. Alterations in homeobox genes, retinoic acid signaling pathways, histone deacetylators and polymorphisms involving AED transporters are other teratogenic pathways.[4]

AED induced malformations can affect almost all organs.[5] Such an exposure in 1st trimester with monotherapyhas significant malformation risk: OR 2.6 [95% CI, 08–0.83] which increases with polytherapy: OR 5.1 [95% CI, 1.0–21.1].[6]

All AEDs have teratogenic potential. Valproate and lamotrigine induced malformations are dose dependent. Polytherapy is riskier. It is observed that associated folate deficiency increases the risk and folate supplementation reduces the risks.

EPILEPSY, AED AND NEUROCOGNITIVE EFFECT

Prospective data from Kerala Registry of Epilepsy has shown that 33% of infants of WWE had impaired motor and mental development when assessed at 15 months of age.[7] At a more advanced age of 6 years, they exhibited lower IQ and language performance. Older children of WWE required additional educational assistance.[8]

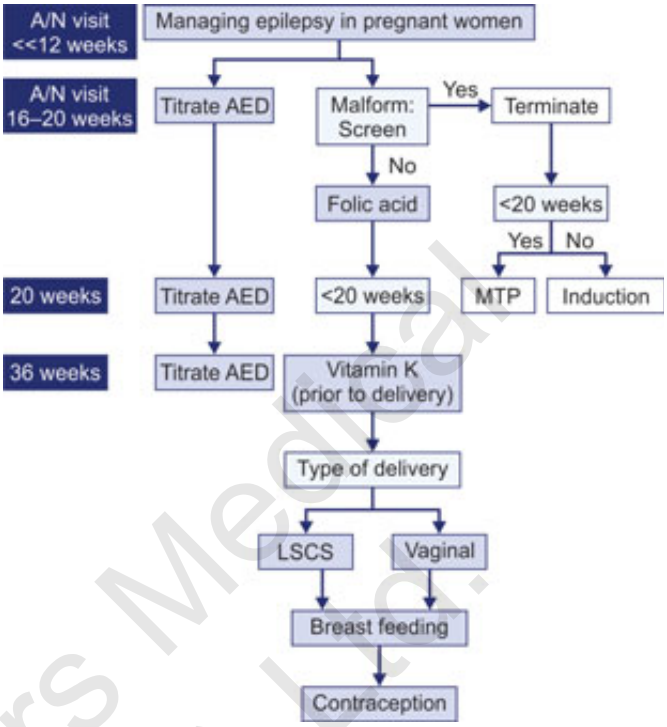
Exposure to polytherapy and Valproate in high doses were associated with increased risks of neurocognitive maldevelopment.

PREPREGNANCY MANAGEMENT IN WWE

The ideal time to start management of WWE is at the time when a couple plans a pregnancy. There should be a joint consultation between the neurologist and obstetrician preconceptionally. The neurologist at such a consultation revises the diagnosis and assesses the need for withdrawal of AED, in case the woman has remission in seizure activity for more than 2 years, AED can be withdrawn. If the AED has to be continued, smallest dose and monotherapy should be the goal. This is the ideal opportunity to change over from valproate to alternate, more acceptable drug. The obstetrician's duty is to start folic acid supplements (5 mg/day) at least 2 months prior to planning the pregnancy. He must reassure the woman that 90% of infants born to WWE on AED are healthy. Only 6–8% have congenital malformations, that too on high dosage and polytherapy. He must also stress the need to continue AED and even warn the patient that it is unsafe to abruptly discontinue or alter dosage of AED. She must be asked to report as soon as the periods are missed.

EPILEPSY MANAGEMENT DURING PREGNANCY

The Indian Epilepsy Society has published its guidelines for management of epilepsy and pregnancy (Flowchart 1). Folic acid supplementation is mandatorily continued. Vigilant imaging and biochemical screening procedures have to be followed at requisite times in the antenatal period to pick up a malformed fetus. The dosage of AED may have to be titrated



Flowchart 1: Algorithm for follow up of women with epilepsy during pregnancy.

and monitored. In olden days, vitamin K was prescribed during pregnancy and delivery to prevent coagulopathy and PPH.

Screening for malformations should include serum AFP levels at 14–16 weeks, and detailed anomaly scan is planned at 16–18 weeks, targeted to detection of neural tube defect (NTD), facial clefts, cardiac anomalies. Nevertheless complete fetal anatomical survey is of great benefit.

Amniocentesis is indicated when serum alpha-fetoprotein (AFP) is raised but the USG anatomical survey is normal. Amniotic fluid AFP + Acetylcholine Esterase levels are estimated. When amniocentesis is added to USG, there is 99% accuracy in NTD detection. Amniotic fluid is also sent for karyotyping.

Pregnancy is associated with hemodilution, altered liver metabolism and altered renal clearance. Gastrointestinal absorption of AED may be erratic and there may be decreased plasma protein binding. Hence the dosage of AED requires adjustments frequently, say at 5–6 weeks, again at 10 weeks, and every trimester thereafter. Total and free drug levels in plasma may be assessed monthly during the pregnancy. Closer monitoring is required for lamotrigine, levetiracetam, oxcarbazepine, phenytoinand topiramate. This intensive monitoring will go a long way in maintaining a seizure free antenatal periodwithout dosge related complications.

The old practice of administration of daily injections of vitamin K 10–20 mg to prevent bleeding in newborns of WWE on AED is not found to be beneficial.[9] Instead, oral vitamin K supplements in the dose of 10–20 mg/day may be offered. Injection vitamin K, 1 mg, is given to the neonate on day 1.

WWE: MANAGEMENT DURING DELIVERY

Most women have normal vaginal delivery. Cesarean section is required on obstetric indications. Frequent seizures in the

3rd trimester or a history of status epilepticus during stressful situations is also an indication for a cesarean delivery.

One to two percent of WWE may have tonic-clonic seizures during labor. 1–2% have postpartum seizures within 24 hours of delivery. Efforts should be made to maintain antiseizure dose even during labor. If there are seizures during labor or delivery, injection of lorazepam or injection of midazolam may be given. Seizures have to be differentiated from eclampsia, because $MgSO_4$ therapy is not appropriate in epilepsy. Nasal oxygen should be offered to prevent maternal and fetal hypoxia. Continuous electronic fetal monitoring is essential during labor.

WWE: MANAGEMENT DURING POSTPARTUM PERIOD

The attending obstetrician must stress on continuation of AED after delivery. Adequate sleep and rest is required, so a helping hand of a close family member during infant feeding, cleaning, etc. will be of great help. While rooming in, the infant should not be allowed by the side of the patient; a separate cradle for the infant should be encouraged. If the dose of the AED was increased during pregnancy, it should be incrementally decreased on days 3, 7, 10. Dosage adjustment for sleep deprivation may be done on the neurologist's advice. The parturient must be informed that breastfeeding is not contraindicated even though most AEDs are secreted in breast milk.

Studies show that there was no difference between the infants who were exposed to AEDs through breast milk and those who were not, with regard to the IQ at 3 years of age.[10]

Nursing the babies first and consuming the AED immediately after will allow only small levels of AED to pass into the breast milk and then on to the infant. At night, the baby can be fed by an attendant with the mother's expressed breast milk. This will allow the parturient with epilepsy to have uninterrupted sleep, and prevent an episode of break through seizure.

APPROACH TO A FIRST SEIZURE DURING PREGNANCY

The diagnostic approach to a pregnant woman with seizure is the same as approach to a nonpregnant woman. However, one must rule out eclampsia and cerebrovenous thrombosis. Neuroimaging procedures should not be withheld for fear of ionizing radiation to the fetus, albeit after evaluating safety concerns. Even in the first trimester, if the risk-benefit ratio allows, MRI can be advised. In pharmacotherapeutics of first seizure due to epilepsy, valproate may be avoided. All efforts must be made to avoid repeated seizures and status epilepticus.

CONTRACEPTION IN WWE

The WHO suggests that women using enzyme-inducing AED should use a method other than hormonal pills, patch or ring contraceptives (Curtis et al., MMWR Recomm Rep 2016). Progestogen-only pill (POP) and Progesterone implants also have high failure rates. Copper or levonorgestrel-only intrauterine system (LNG-IUS) are effective and carry very little potential for drug to drug interaction. If oral contraceptive pills are preferred for whatever reason, a pill containing 50 μg EE should be started. Using extended cycle regimens with shorter pill free interval may also help.

PREGNANCY AND STATUS EPILEPTICUS

Status epilepticus in pregnancy is characterized by more than 30 minutes of recurrent seizure activity without full recovery of consciousness between the seizures. It is a grave medical emergency leading to adverse maternal and fetal effects. Routine resuscitation measures are started immediately.

Control of seizures may be achieved with IV diazepam (5–10 mg), lorazepam (2 mg) or midazolam (0.2 mg/kg). Phenytoin drip is started with a loading dose of 18 mg/kg in 100 mL normal saline over 30 minutes. Continued fall in SpO_2 will necessitate intubation, oxygenation, and ventilator support.

Immediate termination of pregnancy with cesarean may be seriously considered.

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5

CHAPTER

Hypothyroid Complicating Pregnancy Steps to Manage

Jayam Kannan, Dasari Paapa

INTRODUCTION

The relevance of the topic in the current day practice is justified by the fact that there is a lot of controversy regarding thyroid care during pregnancy. The spectrum of thyroid dysfunction in asymptomatic pregnant women varied from subclinical to clinical hypothyroidism to hyperthyroidism and the total prevalence of thyroid dysfunction was reported to be 27%[1] to 31%[2] in recent studies from India. The other reason for screening would be the effect of thyroid disorders on pregnancy outcome as we know there is adverse pregnancy outcome among women suffering from thyroid dysfunction. The last but not the least is the progression of the disease from asymptomatic status to overt status in later life. All these need to be translated in to evidence based medicine before recommendations are made to screen or not to screen.

Various studies, authorities and guidelines from various bodies especially from the West have reported against the routine screening for thyroid disease during pregnancy.[3] They recommended screening for high risk pregnant women, viz., family history thyroid dysfunction, past history of thyroid dysfunction or thyroid disease, age more than 30 years, symptoms of thyroid dysfunction or presence of goiter, thyroid peroxidase (TPO) antibody positive women, type I diabetes and other autoimmune disorders, history of miscarriage or preterm delivery, history of infertility, history of head and neck radiation, obesity (BMI >40), use of amiodarone or lithium, recent administration of iodinated radiologic contrast and residing in an area of moderate to severe iodine deficiency. The controversy regarding universal screening exists as some studies have taken the end point of outcome as only neurocognitive affects and not the pregnancy loss, intrauterine death, preeclampsia and preterm labor, etc., which are more common in women with thyroid dysfunction. Diagnosing thyroid dysfunction is not uniform as various studies have adopted different cut-off levels and used different methods of estimation of thyroid hormones.

DIAGNOSIS OF THYROID DYSFUNCTION

It is essential to understand the thyroid hormone levels during pregnancy and their alterations in correctly interpreting the results and diagnosing thyroid dysfunction. During pregnancy, the raising human chorionic gonadotropin (hCG) acts on the thyroid-stimulating hormone (TSH) receptor and results in increased secretion of T4 and serum TSH drops as hCG acts like TSH agonist. This is called gestational hyperthyroidism or hCG induced thyrotoxicosis which is more evident in cases of multiple pregnancy and hydatidiform mole.[4] The raise in T4 level during normal pregnancy (subclinical hyperthyroidism) should be considered as a normal physiological event. During normal gestation as the hCG peaks between 7–11 weeks, the TSH may be undetectable or very low. Hence there is need to decrease the thresh hold of TSH level to diagnose hypothyroidism from nonpregnant level. The nonpregnant values should not be applied during pregnancy as with raised estrogen levels the thyroid binding globulin (TBG) increases by twofold and there is decreased clearance of TBG. As a result of increased TBG there is a raise in total T4 and T3. TBG normally accounts for about 75% of the bound hormones. About 0.03% of the total serum T4 and 0.3% of the total serum T3 are free. Only free T4 and T3 are metabolically active but the levels of free T4 and free T3 are not affected. The free thyroxine is not much affected by changes in concentrations of binding proteins. Physiologic changes associated with pregnancy require an increased availability of thyroid hormones by 40–100% to meet the needs of mother and fetus during pregnancy.[3,5]

Later in pregnancy hCG secretion declines, serum T4 and T3 concentrations decrease and TSH level raises slightly. Hence pregnancy trimester specific thyroid hormone levels are to be used in diagnosing thyroid dysfunction. Diagnosis is to be made early and therapy needs to initiated early as possible because of the adverse effects of untreated dysfunction on pregnancy outcome (abortions, preterm labor, intrauterine death, hypertension, diabetes, postpartum thyroiditis, thyrotixic heart

disease) and outcome of children (impaired neurocognitive affects). The fetus is totally dependent on maternal thyroxine supply during the first trimester of gestation and up to mid-gestation for normal neurologic development and nervous system maturation. Because the progression of pregnancy and fetal, neonatal and child health are dependent on adequate thyroid hormone supplementation throughout pregnancy, trimester specific reference intervals for thyroid functions are crucial. In the absence of gestational specific TSH values, the cutoff value of TSH level during first trimester ranges from 0.1 (lower limit) to 2.5 mIU/L (upper limit). The reference values during second trimester and third trimester are 0.2–3 mIU/L and 0.3–3 mIU/L, respectively.[2,3,5,6]

Overt-hypothyroidism is diagnosed when TSH level is ≥10 mIU/L irrespective of FT4 and also when FT4 is decreased with TSH level of ≥2.5 mIU/L. It is important to realize pregnant women with overt hypothyroidism are also asymptomatic. Subclinical hypothyroidism is diagnosed when TSH is between 2.5 and 10 mIU/L and FT4 is normal. Isolated hypothyroxinemia is diagnosed when TSH is in normal but FT4 concentrations are below 5th or 10th percentile. The reference intervals for FT4 are 0.26–1.92 ng/dL for the first trimester, 0.59–1.56 ng/dL for the second trimester, 0.65–1.25 ng/dL for the third trimester. The values also vary with the method used to determine the FT4. The TSH level which decreases during the first trimester was greater in twin pregnancies when compared to singleton pregnancies. Hence normograms that adjust for the method of determination of T4, fetal number and gestational age may also be necessary to arrive at accurate diagnosis.[6]

THYROID DYSFUNCTION AND MATERNAL AND FETAL AFFECTS

To meet the increased demand of thyroid hormones during pregnancy, the iodine intake has to be increased. The other reason is the increased renal clearance of iodine that occurs during pregnancy because of increased glomerular filtration rate (GFR) which results in decreased plasma iodine. During later stages of pregnancy, the maternal iodine is being taken up by the fetal thyroid for the synthesis of thyroid hormones. There is no deficiency among normal women in areas of iodine sufficiency as this is met in the diet but in geographic areas where there is iodine deficiency the dietary supplementation of pregnant women has to be undertaken. To prevent iodine deficiency, and thus development of thyroid dysfunction, supplementation of 150 μg per day is needed during pregnancy in iodine deficient areas.[4] Fortification of common salt with iodide salts is undertaken in some countries to ameliorate the deficiency. In endemic iodine deficient areas women may be deficient of iodine even before pregnancy and hence the incidence of hypothyroidism during first trimester of pregnancy can be high which is detrimental for fetal thyroid development and function as well as neurocognitive development. The fetus can synthesize thyroid hormones only after 12 weeks of pregnancy and the placenta actively transfers the maternal thyroid hormones to the fetus.[5] This calls for screening such women even prior to pregnancy. The Thyroid dysfunction needs to be optimized before attempting Pregnancy. In women who are positive for TPO antibodies the incidence of hypothyroidism is high during pregnancy and they may be euthyroid during early pregnancy but as the gestation proceeds hypothyroidism occurs. Hence, the need for repeated testing of TSH in these group of women. It has been shown that the risk of miscarriage increases before 20 weeks if a woman has TPO positivity along with subclinical hypothyroidism.[3] Subclinical hypothyroidism is the most common thyroid dysfunction and the commonest cause for this condition is autoimmune thyroid disease. The thyroid antibodies can cross the placenta and cause immune attack of the fetal thyroid gland. Isolated/congenital fetal hypothyroidism can occur due to failure of fetal thyroid gland to produce adequate amount of thyroid hormones. These neonates are normal at birth as maternal thyroid hormones cross the placenta if mother's thyroid function is normal. However, soon after delivery the infants show features of thyroid hormone deficiency and if not recognized it will result in mental retardation and all other features of cretinism. In iodine deficient areas where the mother is hypothyroid, the fetus develops hypothyroidism, cretinism, deaf mutism with spasticity if the deficiency is not corrected on time with iodine supplementation. The thyroid hormones have the most important function in fetal brain differentiation like synaptogenesis, axonal and dendrtic growth, myelination and neuronal migration. The iodine deficient mother can be treated if screened early and iodine supplementation if given in first and second trimesters one can prevent the neurocognitive developmental defects in fetus. Treatment during third trimester and after birth cannot undo the damage that has already occurred. Women who are known to be hypothyroidism prior to pregnancy require a raise in dose by as much as 30% in first trimester of pregnancy itself.[5,7] The European guidelines state that the current data on subclinical hypothyroidism show increased pregnancy loss, gestational diabetes, gestational hypertension, preeclampsia and preterm delivery but the association with neuropsychological development of children is inconsistent.[8] Maternal hypothyroxinemia is also a common thyroid dysfunction and it was found to be associated with impaired neuropsychological development of the offspring and hence levothyroxine therapy should be initiated in the first trimester for such women.[9] The TABLET trial is being under taken in UK in 48 sites to assess the maternal and neonatal outcomes in women with TPO antibodies supplemented with 50 μg levothyroxine compared to those of unsupplemented.[10] The Chinese prospective large population based study found overt hypothyroidism to be associated with increased fetal loss and congenital cardiovascular malformations and subclinical hypothyroidism in addition to adverse pregnancy outcomes and congenital malformations, it was reported to be associated with neurodevelopmental delay. They found hyperthyroidism also adversely affects neonatal outcome.[7]

The Danish General Suburban Population Study (GESUS) in Danish population showed that subclinical hypothyroidism was associated with infertility. This stresses the need for screening infertile population and pregnant women who achieve pregnancy after a period of infertility. In women with gestational diabetes mellitus (GDM) there is an increased incidence of hypothyroidism when compared to women without GDM.[11] The incidence of GDM in India is as high as 21%. The other risk factor for thyroid dysfunction investigated recently was overweight of pregnant women. A BMI of ≥24 was found

to be associated with hypothyroxinemia and hypothyroidism.[12] A study which measured the FT4, FT3, TSH, and thyroid antibodies during first trimester of pregnancy found that the combination of high TSH and TPO antibody positivity resulted in a four-fold increase in the incidence of GDM and a three-fold increase in low birth weight babies.[13] The FaSTER (first and second trimester evaluation of risk) trial found high maternal weight to be associated with low T4 and higher GDM rate in second trimester.[14]

Gestational hyperthyroidism is transient and accounts for 1–3% and the incidence of hypertensive disorders were reported to be high among those with who showed biochemical hyperthyroidism during early pregnancy.[15] Thyrotoxicosis during pregnancy if undiagnosed and untreated results in heart failure, thyrotxic storm, preterm delivery and maternal and neonatal morbidity and mortality.[16,17]

VIEWS ON SCREENING

As the obstetricians are the primary care givers for the pregnant women and the opinion of endocrinologists is sought to optimize the outcome, there has been a lot of confrontation and controversy regarding screening of all pregnant women for thyroid dysfunction and also subsequent treatment of subclinical hypothyroidism and hypothyroxinemia. The Western guidelines as of now do not recommend universal screening for thyroid dysfunction during pregnancy as they state that the evidence (level 1) is not in favor of the same. The US preventive services task force,[18] American Thyroid Association (ATA)[6] and the ACOG[19] are of this opinion and the main reason was focused on neurodevelopmental outcomes of children. A randomized controlled trial (RCT) on antenatal screening and treatment of women for thyroid dysfunction which only tested the primary outcome of children at 3 years of age did not analyze the pregnancy outcome and pregnancy complications.[20] This study has been taken in to account by all the guideline development groups. The American Endocrine Society recommends identifying the risk factors in pregnant population and screening them. However, this approach was found to miss more than one-third of pregnant women with hypothyroidism.[21] The American Association of Clinical Endocrinologists have recommended universal screening for thyroid dysfunction in the preconceptional period or during first trimester of pregnancy.[22] The recent studies from India support universal screening of pregnant women for thyroid dysfunction as the prevalence and impact of this condition on maternal and fetal health is high in our country.[1,2] The Indian Thyroid Society (ITS) recommends screening of all pregnant women at their first antenatal visit or at preconceptional visit.[23,24] A study from Bangladesh recommends routine antenatal thyroid hormone screening to prevent maternal and fetal morbidity and improve the outcomes.[25] The Spanish Endocrine Society favors screening of all pregnant women for thyroid dysfunction.[26]

The Cochrane review 2015, which analyzed the available literature regarding universal screening versus targeted screening and subsequent treatment of women during pre-conceptional period and during pregnancy found high quality evidence (Grade A) in the primary outcomes in diagnosing more number of women with hypothyroidism and moderate quality evidence (Grade B) in diagnosing hyperthyroidism. Significantly more number of women received pharmacotherapy for thyroid disorders among the universal screen group. There was no difference in other secondary outcomes like pregnancy complications and other fetal, neonatal and intellectual outcomes of children. This is because all the diagnosed women with thyroid dysfunction received therapy. They concluded that well powered studies need to be conducted to see the difference in outcomes.[27] An Asian survey conducted by Fereidoun Azizi to find out the practices of physicians in screening and managing pregnant women with thyroid dysfunction revealed that 21% followed universal screening, 66% performed targeted screening and 13% did not do any screening and majority of them treated the thyroid dysfunction and aimed to keep the hormonal level with in the trimester specific range.[28] An European survey found 42% of physicians performing universal screening of all pregnant women.[8] In 2013, the ATA meeting abstracts revealed 74% advocating universal screening.[29] A recent study which compared the cost effectiveness of universal screening with screening of high risk pregnant women during the first trimester analyzed various outcomes and concluded that universal screening is cost-saving in the scenario of untreated maternal hypothyroidism resulting in decreased child intelligence, with levothyroxine therapy being preventive. The cost effectiveness was found to be well below the accepted threshold for cost-effectiveness of $50,000 per QALY.[30]

The guidelines (ATA, TES, and ITS) on thyroid dysfunction during pregnancy were critically analyzed by Sanjay Karla et al. They brought out the supportive recommendations for screening of pregnant women for thyroid dysfunction from ATA and TES (The Endocrine Society) which also support some of the recommendations of ITS . They recommended that ITS though given the recommendations for universal screening of pregnant women, it should work to frame guidelines for interpreting FT4 values and standardize the techniques for our population and also address the issue of monitoring euthyroid pregnant women without antibody testing and euthyroid women who are negative for antibody testing.[24] Even though the ATA, TES, and European guidelines do not recommend universal screening, from the surveys published it is evident that universal screening is done by most of the physicians in US and Europe.

From the existing literature, it is clear that thyroid dysfunction significantly and adversely affects the maternal and fetal outcomes in any part of the World but the guidelines of various bodies differ only in agreeing regarding the benefits of universally screening all pregnant women. The disagreement is due to lack of uniformity in studies conducted regarding the primary outcomes and secondary outcomes that are essential to arrive at evidence-based recommendations. More RCTs which aim to study similar objectives on this issue are required at the international level using standardized methodology.

CONCLUSION

Taking in to account the asymptomatic (nonspecific symptoms in early stages) nature of the condition, the significant maternal and fetal morbidity and the high prevalence of the dysfunction in our country and the supportive recommendations of our ITS all obstetricians gynecologists and reproductive medicine

specialists should practice universal screening of pre-conceptional and pregnant women for thyroid dysfunction as each woman and each baby's health counts.

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6

CHAPTER

Pyrexia with Pregnancy

Charu Mittal

INTRODUCTION

Febrile illness during pregnancy is of concern to the managing obstetrician due to its potential for critical fetomaternal outcomes. Early diagnosis and initiation of care as well as prompt management of the causative factor form the mainstay for ensuring a favorable outcome for both mother and baby. This chapter covers the overview of common causes of pyrexia with pregnancy and the principles of their management.

PHYSIOLOGICAL CONSIDERATIONS IN PREGNANCY

Various physiologic changes in pregnancy increase blood flow leading to 20% increase in body metabolism, thus creating more body heat. The core body temperature of a pregnant woman rises slightly, up to 37.8°C, while it is 37°C in nonpregnant state. The increased severity of fever during pregnancy is thought to be related to the various physiologic changes during pregnancy such as:

- Decreased cell-mediated immunity
- Increased maternal heart rate and oxygen consumption
- Decreased lung capacity
- Embryonic and fetal susceptibility to elevated maternal body temperature
- Diagnostic difficulties can arise due to first trimester nausea and vomiting
- In second and third trimester physiological hypervolemia, low hematocrit, generalized vasodilatation, high pulse rate and low blood pressure can also present difficulty in assessing severity of the disease.

DEFINITION

Maternal pyrexia is defined as oral temperature >38°C or 100.4°F.

CAUSES

Common as well as few uncommon causes need to be considered while dealing with a pregnant patient with pyrexia. Infections are the most common cause of fever and those which affect a nonpregnant woman or man can similarly affect a pregnant woman. Since tropical diseases are more common in India, these need to be considered early in the differential diagnosis. Some of the causative factors for pyrexia with pregnancy may be:

- Malaria
- Typhoid
- Urinary tract infection (UTI) (acute pyelonephritis)
- Influenza: Seasonal common cold, swine flu (H1N1)
- Dengue
- Chikungunya
- Measles, mumps, rubella, varicella
- Bacillary dysentery
- Intra amniotic infection/chorioamnionitis
- Tuberculosis
- Heat stroke.

DIAGNOSIS

The diagnosis of infections during pregnancy should be made clinically because it is essential to start prompt treatment to reduce the risk of adverse outcomes. Investigations can be sent while simultaneously initiating treatment for control of pyrexia on the basis of clinical judgment. Further line of treatment can be decided once reports of investigations are available.

CLINICAL FEATURES

Eliciting the history meticulously can provide important information about the cause. Detailed general and systemic examination gives additional clues and aids in proper assessment of maternal and fetal condition.

Symptoms

Fever—low grade/high grade, timing, pattern of fever, whether accompanied by chills/rigors, duration of fever, any associated rash and its type/pattern of distribution.

- Perception of fetal movements (after second trimester), any vaginal discharge or bleeding
- Respiratory symptoms like distress, cough, cold, expectoration, and wheezing
- Urinary disturbance like frequency, dysuria, and high colored urine
- Abdominal pain, its location, characteristics (constant, spasmodic, acute, and dull)
- Gastrointestinal disturbances like nausea, anorexia, vomiting, and diarrhea
- Malaise, headache, arthralgia/myalgia
- Bruising/bleeding tendency
- History of recent exposure to any infected individual.

Signs

- Vital signs: Temperature may be mild to moderately elevated, pulse rate: tachycardia is common, however relative bradycardia may be observed with typhoid fever), respiratory rate: normal/tachypnea/respiratory distress, blood pressure: normal/hypotension in dehydration/sepsis
- General examination: Pallor: +/-, cyanosis +/-, edema: +/-, rash +/-, s/o dehydration
- Respiratory system: Look for rhonchi/crepitations/features of pulmonary edema
- CVS: Tachycardia, usually no other significant findings
- CNS: Disorientation in c/o cerebral malaria
- Obstetric assessment: Uterine size, uterine tenderness, any contractions/signs of labor, fetal growth, FHS, liquor, NST, Doppler.

INVESTIGATIONS

Complete blood count with platelet count, ESR, bleeding time, clotting time, malarial parasite [thick and thin film, fluorescent microscopy, antigen testing by polymerase chain reaction (PCR)], peripheral smear for toxic granules/parasites, S. Widal, blood culture, serum electrolytes, urine routine and microscopic examination, urine culture and sensitivity, high vaginal swab, ultrasound for embryonic/fetal well-being, amniotic fluid, cervical length.

Special tests may be needed with high index of clinical suspicion for specific infections. Like RT-PCR or virus isolation in culture from nasopharynx and throat swabs (for H1N1 virus), Virus isolation or PCR/ELISA IgG IgM chikungunya antibody (for chikungunya), NS1Ag for dengue (day 1–5) or IgG and IgM seroconversion after day 5. Sputum for AFB/culture for *Mycobacterium tuberculosis*.

PRINCIPLES OF MANAGEMENT

Supportive Treatment

High grade fever requires prompt treatment especially during first trimester due to risk of embryonic loss and association with neural tube defects and other birth defects while there is risk of abortion, preterm labor and intrauterine fetal death in more advanced pregnancy.

Treatment decisions, especially for initiating empiric therapy, should be based on knowledge of prevalent infections in the community at any given point of time as well as possible drug sensitivity. Seasonal outbreaks of illnesses like malaria, influenza, dengue, chikungunya, etc. should be kept in mind while treating a pregnant woman with pyrexia.

- Tepid sponging, cold compresses, cool environment, appropriate clothing can also aid in reducing maternal temperature effectively. Heat stroke/hyperpyrexia to be corrected promptly by appropriate cooling interventions
- Paracetamol is the antipyretic of choice for controling pyrexia. 500 mg every 6 hours may be administered
- Symptomatic treatment with antacids, antiemetics as required
- Hospitalization in obstetric intensive care unit for morbid cases with complications
- Hydration and maintenance of electrolyte balance: Orally with fluids, ORS/parenterally with isotonic IV fluids, i.e., crystalloids like Ringer's lactate, normal saline
- Monitoring of input and output, electrolytes, blood gases in severe infection
- Oxygen therapy for respiratory distress
- Adequate nutritional intake, correction of hypoglycemia
- Second and third trimester: Monitoring of fetal heart sounds by intermittent auscultation or fetal Doppler
- Blood transfusion: Packed cells, fresh-frozen plasma (FFP), platelet transfusion may be required as per the clinical and hematological parameters
- Close monitoring for signs suggesting onset of maternal or fetal complications.

Specific Treatment

Specific treatment depends on the cause. Most of the drugs used for treatment of infections are FDA category B like ampicillin, amoxicillin, penicillin with beta lactamase inhibitors, clindamycin, metronidazole, sulfonamides, nitrofurantoin, erythromycin, azithromycin, cephalosporins. Chloramphenicol, trimethoprim, aminoglycosides belong to category C and tetracycline are category D which are usually avoided during pregnancy unless maternal benefits clearly outweigh the risks.

- Malaria: Antimalarials like chloroquine (first choice in susceptible areas), quinine, clindamycin, artemesinin derivatives. Complicated cases/falciparum malaria: parenteral artemesinin/quinine. Primaquine is contraindicated in pregnancy
- Typhoid: Cephalosporins
- UTI: Amoxicillin, cephalosporins, nitrofurantoin
- Influenza: H1N1 (swine flu): Oseltamivir (75 mg twice daily for 5 days)
- Dengue, chikungunya, measles, mumps, rubella have no specific treatment and are usually self-limiting
- Intra-amniotic infection: Broad spectrum antibiotic therapy with cephalosporins, clindamycin, metronidazole, gentamicin
- Tuberculosis: Antitubercular therapy can be administered safely in pregnancy. Streptomycin should be avoided. Benefits outweigh the risks.

Obstetric Management

This depends on the duration of pregnancy, onset of labor and fetal status. Unless preterm labor intervenes and cannot be arrested, most infectious causes of fever in pregnancy do not per se require delivery for improvement of maternal status. Morbid women with category C H1N1 virus infection may however require delivery to improve maternal pulmonary function and outcome. Preterm labor should be managed with antenatal corticosteroid therapy for fetal lung maturation. During phase of thrombocytopenia in dengue fever, delivery should be avoided unless antepartum hemorrhage (APH) occurs. Acute febrile illness in term pregnancy carries risk of neonatal infection with causative organism.

Maternal Complications

These can be immediate or delayed. Complications can range from dehydration, preterm labor, anemia, acute pulmonary edema, acute respiratory disease syndrome (ARDS), bronchitis, sinusitis, hypoglycemia, electrolyte imbalance, sepsis, renal failure, shock, bleeding, neuropsychiatric problems up to maternal mortality.

Fetal Complications

Abortions, birth defects, prematurity, low birth weight, neonatal sepsis, congenital/perinatal infection, intrauterine death, neonatal seizures, cerebral palsy, encephalopathy, early neonatal death, cognitive impairment in later years.

PREVENTION

- Protection from bites by vectors like mosquitoes
- Chemoprophylaxis for malaria in endemic areas (chloroquine/mefloquine)
- Influenza vaccine administration
- Avoid exposure to infected individuals during outbreaks as far as practically possible
- Avoiding contaminated water/food items
- Avoiding repeated vaginal examinations.

CONCLUSION

Early access to medical care is essential in pregnant women with pyrexia. Prompt correction of fever and initiating specific treatment for the particular condition causing pyrexia can result in favorable fetomaternal outcome in most of such febrile cases. Though there are currently no specific guidelines for obstetric management in febrile pregnant women, the duration of gestation as well as fetal surveillance tests can help to decide management in individual cases.

7

CHAPTER

Deep Vein Thrombosis in Pregnancy

Dolly Mehra

INTRODUCTION

Deep vein thrombosis (DVT) and its complications are a major cause of maternal morbidity. Pregnancy and puerperium are well established risk factor. The overlap with symptoms of pregnancy may impair clinical physician making diagnosis challenging. Venous thromboembolism (VTE) can manifest during pregnancy as isolated DVT or some times as pulmonary embolism (PE) which is seventh leading cause of maternal mortality. Thus, detecting DVT during pregnancy is critical in preventing deaths from PE.

Studies have shown increasing incidence of VTE in Asian population. Incidence of postoperative DVT is higher in Indian population than western also rate of PE is higher in Indian population with symptomatic DVT.

Identification of risk factors, initiation of prophylactic anticoagulation, early recognition of S/S and prompt treatment can help to reduce morbidity and mortality due to DVT.

INCIDENCE

- Absolute risk of VTE in pregnancy is 0.025–0.1%
- Eighty-five percent of VTE is DVT
- Sixty-five percent of DVT occur antenatally
- Half of antenatal DVT occur prior to 15 weeks
- More than half occur in ileofeomral vein
- Rate of VTE is greatest in puerperial period, which is more on left side.

PATHOPHYSIOLOGY

Rudolf Virchow (1856), a German pathologist postulated the Virchow's triad for thrombosis.

Hypercoagulability

Pregnancy is a hypercoagulable state. Factors I, VII, VIII, X and plasminogen activator inhibitor increase. There is relative resistance to action of anticoagulants protein C and S.

Stasis

Gravid uterus causes compression of pelvic and lower limb veins resulting in slowing of venous flow. Prolonged bed rest, immobilization, labor, and postpartum especially after lower segment cesarean section (LSCS) predispose to stagnation.

Endothelial Injury

Commonly occurring at the time of delivery, exposes highly thrombogenic subendothelial surface and precipitates thrombus formation.

RISK FACTORS

Identification of preexisting or new onset risk factors is very important.

Preexisting Risk Factors

Previous history of VTE, obesity, smoking, parity more than 3, are more than 35 years, oral contraceptive pill, hormone replacement therapy, sickle cell anemia, renal disease, calcium bone, ovary, lyphoma, chemotherapy, autoimmune disease systemic lupus erythematosus (SLE), infection HIV, thrombophilia both acquired and inherited, individuals with non O blood group, gross varicose veins (symptomatic, above knee or with associated with phlebitis).

New Onset Risk Factors

Dehydration, hyperemesis, ovarian hyperstimulation syndrome (OHSS), excessive blood loss like incomplete abortion, ruptured ectopic, antepartum hemorrhage (APH), postpartum hemorrhage (PPH), preeclampsia, surgical procedure like LSCS, systemic infection like P sepsis, pneumonia, multiple pregnancy, prolonged labor, midcavity rotational operative delivery, prolonged immobilization, prolonged travel.

Risk Factor Groups

It is important in whom to give thromboprophylaxsis, what to use, when to start, how long to be given. Identification of risk factors to be done antenatally. The RCOG greentop guidelines classify patients with high risk factors in various groups.

Very high risk group:

- History of VTE on warfarin
- History of VTE with antiphospholipid antibodies (APLAs)
- Antithrombin deficiency.

High risk group:

- History of previous recurrent or unprovoked VTE
- Estrogen or pill provoked VTE
- Thrombophilia with previous VTE
- Asymptomatic high risk thrombophilia (combined defect or homozygous factor V leiden defect).

Intermediate risk group:

- History of previous single VTE with transient factor which no longer exists, no thrombophilia, no family history
- Asymptomatic thrombophilia other than those in high or very high risk group.

Presence of three or more preexisting risk factors require thromboprophylaxis antenatally. Risk assessment is recommended even in postpartum period.

METHODS OF THOMBOPROPHYLAXSIS

Noninvasive and Mechanical Method

- Early mobilization
- Adequate hydration
- Calf exercises
- Graduated elastic compression stockings.

Graduated Elastic Compression Stockings

Recommended in the following group of patients:

- Hospitalized patients with contraindication to low molecular weight heparin (LMWH)
- Post LSCS hospitalized patients with high risk of VTE along with LMWH
- Patients with previous VTE managed on OPD basis
- Prolonged travel (>4 h).

Thigh length stockings preferred which can maintain ankle pressure gradient of 30–40 mmHg.

DRUGS FOR THROMBOPROPHYLAXIS

- Unfractionated heparin (UFH)
- Low molecular weight heparin
- Heparinoids
- Direct thrombin inhibitors
- Factor Xa inhibitors.

Aspirin is not recommended for thromboprophylaxis, it may be used to improve fetal outcome.

Unfractionated Heparin

- Safe in pregnancy, does not cross placental barrier, hence no fetal toxicity
- Dose dependent on body weight and activated partial prothrombin time (aPTT) value
- Standard prophylactic dose (50–90 kg body weight) is 5,000 IU 12 hourly
- Therapeutic dose to achieve target aPTT value 2–2.5 times of INR
- Side effects are bleeding, skin necrosis, thrombocytopenia, osteoporosis
- Heparin induced thrombocytopenia (HIT) early or late onset. Early onset occurs in 48 hours of initiation of therapy, self-limited, no treatment required, resolves in 5 days. Late onset HIT manifests between 5 and 14 days of therapy, platelet count fall to <50% of baseline, can cause bleeding paradoxical venous and arterial thrombosis. Heparin has to be stopped
- Effect of heparin reversed with protamine sulfate 1 mg for 100 units of heparin.

Low Molecular Weight Heparin

- LMWH like enoxaparin, dalteparin, tinzaparin are used
- Antenatal and postnatal prophylactic dose if weight <50 kg = 20 mg enoxaparin, 2,500 units dalteparin, 3,500 units tinzaparin if weight 50–90 kg = 40 mg enoxaparin, 5,000 units dalteparin, 4,500 units tinzaparin daily
- Safe in pregnancy, does not cross placenta, complications like bleeding, HIT, osteoporosis much less
- Osteopenia may occur
- Enoxaparin (40 mg daily) preferred for prophylaxsis. Dose to be modified in obesity and renal failure
- Action of LMWH not completely reversed with protamine
- Disadvantage are higher cost, longer half-life so management in labor is difficult.

Other Drugs

- Heparinoid danoparoid anti-II and anti-Xa activity. No adverse fetal outcome. Used in c/o HIT or intolerance to heparin
- Fondaparinux anti Xa inhibitor. Safest newer anticoagulant as alternative to heparin
- Newer oral anticoagulant like dabigatran, rivaroxaban not approved for use in pregnancy.

Contraindication to Heparin Therapy

- Active APH, PPH
- History of stroke in last 4 weeks
- Thrombocytopenia (75,000/cmm), hemophilia, Von Wilibrand's disease
- Severe renal and hepatic disease.

Duration of Thromboprophylaxis

- Very high risk group—antenatal LMWH and postpartum LMWH or warfarin for a period of 6 weeks
- High risk group—antenatal and postnatal (6 weeks) LMWH
- Intermediate risk group—antenatal LMWH may be considered but not recommended. Strict antenatal surveillance needed. If three or more risk factors develop in course of pregnancy LMWH considered

- Patient with asymptomatic thrombophilia—postnatal prophylaxis recommended for 7 days.

Thromboprophylaxis in Peripartum Period

- Anticoagulation to be stopped before elective LSCS and labor. UFH to be stopped 12 hours prior, LMWH 24 hours prior
- Platelet count should be done with UFH therapy
- For epidural analgesia last dose of prophylactic LMWH should not be earlier than 12 hours and 6 hours for UFH
- UFH has shorter half-life, hence managing in labor is easier. So some people stop LMWH at 36 weeks and convert on UFH
- Anticoagulation to be restarted 4–6 hours after normal delivery, 6–12 hours after LSCS
- All patients on anticoagulations should be warned regarding vaginal bleeding. Baseline a PTT and platelet count should be done. Protamine sulfate should be ready. Fresh frozen plasma should be ready. PPH should be avoided.

CLINICAL FEATURES OF DVT IN PREGNANCY

Signs and symptoms are nonspecific, the two most common symptoms are pain and swelling in lower limbs, sometimes rise in skin temperature. Mose's sign (calf tenderness on squeezing calf muscles) and HOMAN's sign (pain in calf on dorsiflexion of ankle) may be present. A severe uncommon form of DVT is phlegmasia cerulean dolens, where there is complete venous occlusion of lower limb outflow. The leg is cyanosed and edematous.

CLINICAL ASSESSMENT FOR DVT DONE BY WELL'S SCORE

- Calf swelling ≥3 cm compared to symptomatic calf (measured 10 cm below tibial tuberosity) +1 point
- Active cancer (treatment within last 6 months or palliation) +1 point
- Swollen unilateral superficial veins (nonvaricose in symptomatic leg) +1 point
- Unilateral pitting edema in symptomatic leg +1 point
- Localized tenderness along the deep venous system +1 point
- Previous documented DVT +1 point
- Swelling in entire leg +1 point
- Paralysis or paresis or recent cast immobilization of lower extremity +1 point
- Recently bedridden for more than 3 days, or major surgery requiring regional or general anesthesia in past 12 weeks +1 point
- Any other alternative diagnosis at least likely -2 points.

Clinical Probability for DVT Depends on the Score

- <0—low
- 1–2—intermediate
- >3—high.

Utility of Well's scoring system in pregnancy is not fully certain at present.

DIAGNOSIS

- Clinical prediction score
- D-dimer test in patients with low probability for DVT or PE, D-dimer test is a good option if negative it indicates very low likelihood. It has a very high false positive rate but a good negative predictive value
- Ultrasound is recommended in patients with intermediate to high probability for DVT. Compression duplex ultrasound is the primary diagnostic test for DVT.

Diagnostic criteria for DVT are:

- Soft tissue mass within the venous lumen
- Noncompressibility of vein
- Decrease or absent flow in the vessel

Sometimes if the first ultrasound is negative but the index of suspicion is very high, anticoagulation may be continued till performance of the second test. If on repeat testing DVT is negative treatment is stopped.

- Impedance plethysmography
- CT and MRI venography mainly useful in pelvic vein thrombosis.
- Routine test like platelet count, aPTT, RFT, LFT should be done prior to starting anticoagulation
- Thrombophilia screening has to be done, but can be delayed in acute episode, as there would be no change in immediate management
- Radioactive fibrinogen test, not recommended in pregnancy and lactation due to risk of radiation exposure.

Fetal Surveillance in Patients with DVT

Patients with thrombophilia or other risk factors for VTE are at a risk of placental thrombosis, uteroplacental insufficiency, IUGR, sudden fetal death, abruption, and hence poor perinatal fetal outcome.

Patients who were receiving anticoagulation in the periconceptional period with warfarin are at a risk of congenital fetal anomalies. Thus, fetal surveillance should be done.

- Detailed anomaly scan at 18–20 weeks
- Doppler study at 24–28 weeks for placental insufficiency
- Ultrasonography assessment at regular interval in third trimester for growth assessment
- After confirming fetal well-being on term delivery should be planned and appropriate measures taken.

TREATMENT

On confirmation of DVT, the following treatment is started:

- Admission and monitoring in intensive care unit
- Supportive treatment in form of hydration, analgesics and antibiotics
- High quality graduated elastic compression stockings. Randomized controlled trials have shown that early ambulation with leg compression does not increase risk of PE, does not increase thrombus propagation, pain and swelling improved faster compared to those patients who had their mobility restricted. This also prevents development of post thrombotic syndrome

- Fetal surveillance as mentioned earlier
- Anticoagulation. UFH or LMWH can be used. Therapeutic dose -1 mg/kg enoxaparin BD or 100 IU/kg dalteparin BD or 175 IU/kg tinzaparin daily
- Activated PTT is kept 1.5–2.5 times for effective and safe anticoagulation
- Anti-Xa levels are used to monitor treatment with LMWH which should be 0.4–1 U/mL provided patient has normal renal function. Routine testing of anti-Xa level is not recommended except in women less than 50 kg and more than 90 kg weight or associated renal impairment
- Women who are on long-term anticoagulation, higher therapeutic dose of LMWH may be appropriate
- Platelet count are not routinely monitored until patient is on UFH or patient is on LMWH after first receiving UFH of patient received UFH in past
- Patient on therapeutic anticoagulation must continue it till delivery, during labor temporarily stopped and restarted. In postpartum period heparin is continued depending on individual cases. Heparin can be overlapped with oral warfarin then it can be stopped, further anticoagulation done with warfarin (5 mg daily) to maintain PT/INR 2–3 times the control. Postpartum warfarin should be avoided until at least the 5th day and for longer in woman at increased risk of PPH
- Woman should be offered a choice of LMWH or warfarin for postnatal therapy after discussion about need for regular blood tests for monitoring warfarin therapy. If the woman chooses LMWH postnatally, then dosage schedule that were employed antenatally should be continued. If she chooses warfarin postnatally daily INR testing done during transfer from LMWH to warfarin to avoid over coagulation. On warfarin INR should be checked on day two of treatment and subsequent warfarin doses titrated
- In patients receiving therapeutic doses of LMWH, wound drain (abdominal and rectus sheath) should be considered at LSCS and the skin incision should be closed with interrupted sutures to allow drainage of any hematoma
- Anticoagulation therapy should be continued until 6 weeks postpartum. Before discontinuing treatment the risk of thrombosis should be assessed
- Neither heparin nor warfarin is contraindicated in breast-feeding
- Inferior vena cava filters considered in cases of recurrent VTE and where anticoagulation is contraindicated
- Venous thrombectomy needed on case of massive illeofemoral vein thrombosis.

Postnatal Follow Up

- Before discontinuing treatment asses the risk of thrombosis including personal and family history of VTE and thrombophilia screen results
- Assess post-thrombotic venous drainage
- Advise need for thromboprophylaxis in any future pregnancy and at other time of increased risk
- Discuss contraception. Combined oral contraceptive pills, combined injectable contraceptive, combined patches/vaginal ring contraceptive should be avoided. Acceptable forms of contraception for these patients include Cu T, progestin only pill, progestin (lenonorgestrel) releasing IUD, progestin only implant, progestin only injections using depot medroxyprogestrone acetate/norethisterone enanthate. Barrier methods can be used
- Prevention of post-thrombotic leg syndrome, graduated elastic stockings help in this.

CONCLUSION

Pregnancy increases the overall risk of VTE by 4–5 times. Risk factors of VTE could be preexisting or transient. Risk identification and classification is important. LMWH is drug of choice for thromboprophylaxis. Management of VTE in pregnancy needs a collaborative effort of obstetrician and hematologist.

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8

CHAPTER

Malaria in Pregnancy

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INTRODUCTION

Malaria, a parasitic infection transmitted by mosquitoes, is one of the most devastating infectious diseases, killing more than 1 million people annually. Pregnant women, children, and immunocompromised individuals have the highest morbidity and mortality. Malaria and pregnancy are mutually aggravating conditions. The physiological and the pathological changes due to malaria have a synergistic effect on the patient which makes life difficult for the mother, the child and the treating physician.

According to the World Health Organization (WHO), malaria accounts for over 10,000 maternal and 200,000 neonatal deaths per year.

Malaria and six other diseases, viz., diarrhea, HIV/AIDS, tuberculosis, measles, hepatitis B and pneumonia account for 85% of global infectious disease burden.[1]

Forty percent of the world's population remains at risk of infection and over 400,000 people die every year. In India, over 90% of the population live in malaria transmission areas, with two-thirds of infections caused by *Plasmodium falciparum* and one-third by *Plasmodium vivax*.[2]

EPIDEMIOLOGY

Malaria is a parasitic infection caused by the 4 species of Plasmodium that infect humans:

- *Plasmodium vivax*
- *Plasmodium ovale*
- *Plasmodium malariae*
- *Plasmodium falciparum.*

Plasmodium knowlesii is a monkey malarial parasite which is noticed to be infecting humans in South East Asian countries. Plasmodium falciparum is the most deadly of all of these. Malaria is transmitted by the female anopheles mosquito. There are six recognized primary vectors of malaria in India viz., *Anopheles culicifacies*, *An. stephensi, An. dirus, An. fluviatilis, An. minimus* and *An. sundai*

According to the World Malaria Report, released in November 2017, there were 216 million cases of malaria in 2016, 5 million more cases than in 2015. The estimated number of malaria deaths stood at 445 000 in 2016, a similar number to the previous year (446 000).

In India the pattern of malaria transmission is called unstable transmission. Transmission is seasonal and highest in the rainy season. Most of the population has not attained adequate immunity to malaria, this means majority of the people are at a risk of malaria infection irrespective of age whereas in Africa, most of the population is immune and malaria infections are seen in childhood only.

PATHOPHYSIOLOGY

Malaria is transmitted when an infected mosquito takes a human blood meal and the *Plasmodium sporozoites* are transferred from the saliva of the mosquito into the capillary bed of the host. Within hours, the parasite will migrate to the liver, where it undergoes further cycling and replication before being released back into the host's bloodstream in the merozoite form (Fig. 1). The merozoite then invades erythrocytes, leading to phagocytosis of infected blood cells by the spleen.[3]

Malarial symptoms are caused mainly by the red blood cell (RBC) invasion and the body's inflammatory response.[4] The ability of *P. falciparum* to cause cytoadherence of erythrocytes to vascular walls leads to sequestration of infected cells in small blood vessels, causing end organ damage via hemorrhage or infarction (severe malaria). The incubation period is typically 7–30 days. Symptoms include fever, headache, nausea, vomiting, and myalgias. Due to the cycling parasitemia in the bloodstream, patients will often experience symptoms every 2–3 days, depending on the type of *Plasmodium* with which they are infected.

SCENARIO IN PREGNANCY

Pregnant women are exquisitely sensitive to malaria due to an altered immune status during pregnancy and the unique ability of a subset of *Plasmodium falciparum* to sequester in the placental sinuses and avoid being cleared by maternal spleen.

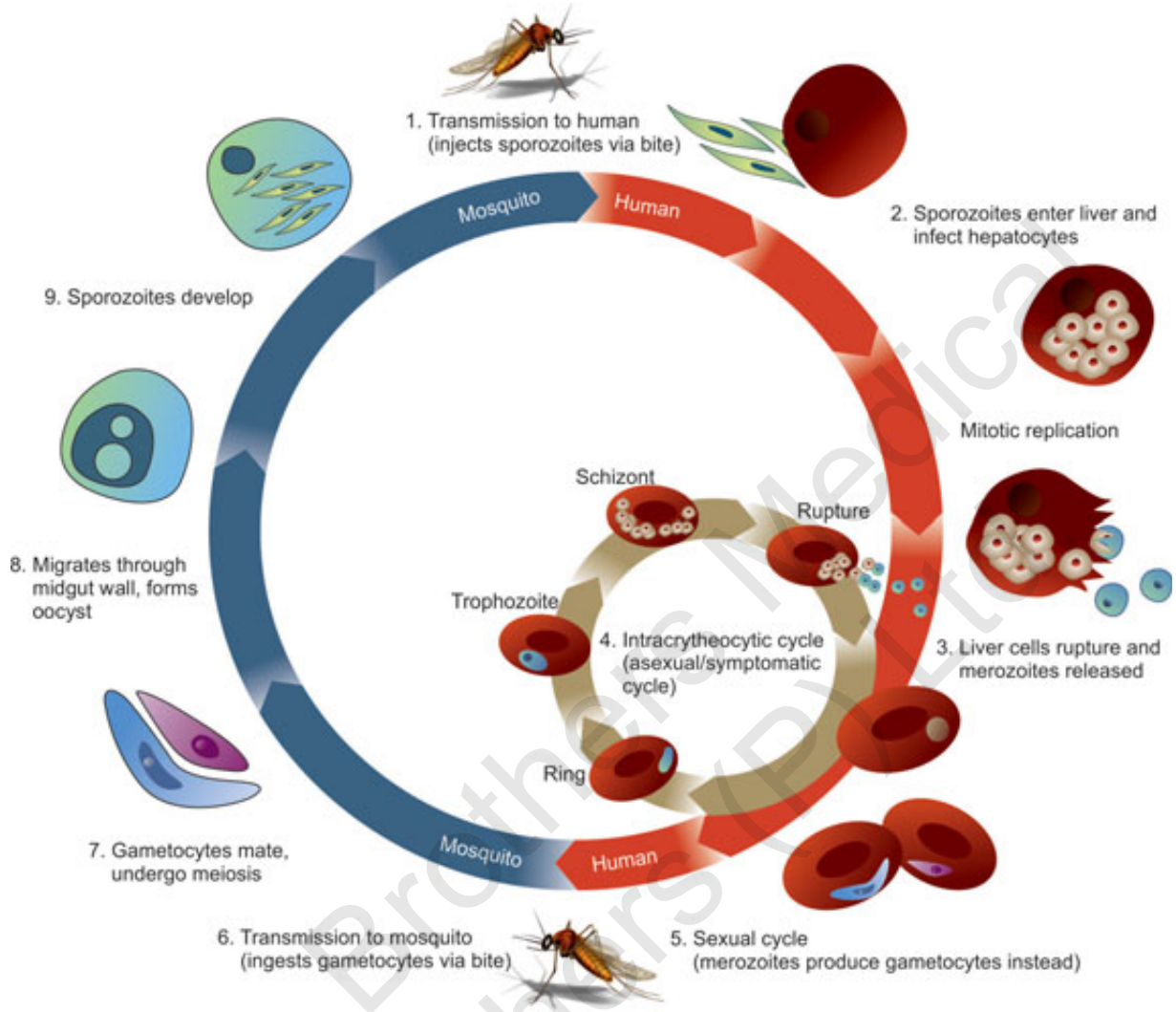


Figure 1: Life cycle of malaria infection.

In areas endemic for malaria at least 25% of pregnant women are infected with malaria. The second trimester appears to bring the highest rate of infection.

Pregnant women are three times more likely to suffer from severe disease as a result of malarial infection compared with their nonpregnant counterparts and have a mortality rate of 50% from severe disease.

Adults in malaria-endemic regions generally have some acquired immunity to malaria infection as a result of immunoglobulin production during prior infections in childhood. This immunity diminishes significantly in pregnancy, particularly in primigravidas causing a high incidence of malaria in these patients, in but subsequent pregnancies the incidence is low. On the contrary all women living in non endemic areas are equally susceptible to malaria irrespective of parity and the severity of the disease and complications are serious and life threatening.

EFFECTS OF THE PREGNANCY ON MALARIA

Anemia due to malaria is more common in between 16 and 29 weeks of gestation. The cause of anemia is hemolysis of parasitized blood, increased demand of blood during pregnancy, and sequestration of malaria infected erythrocytes occurs in the placenta.[5] Anemia in turn increases perinatal mortality and morbidity and increases the risk of postpartum hemorrhage.

Hypoglycemia

It is one of the complications of malaria that is more common in pregnant women because of the increased glucose demand due to the hypercatabolic state and infecting parasites. Increased response of pancreatic islet a secretory stimuli is also another cause.

EFFECTS OF MALARIA ON THE PREGNANCY

Splenic sequestration of malaria infected erythrocytes causes disruption of nutrient exchange between mother and child leading to intrauterine growth restriction (IUGR). Fetal complications also result from placental inflammation, and maternal anemia, and manifest as stillbirth, IUGR, and low-birth-weight neonates. Low-birth-weight neonates, in turn,

are at higher risk for neonatal and newborn death. Congenital malaria is a relatively rare complication in areas with endemic malaria; however, newborn parasitemia may present 2–3 months after delivery when maternal antibodies wear off.

MALARIA IN THE RETROPOSITIVE MOTHER

As a result of the impaired immune status, HIV infection increases the pregnant woman's susceptibility to malaria and the morbidity associated with malaria HIV infection impairs a pregnant woman's ability to control *P. falciparum* infection. Women with HIV infection are more likely to have symptomatic malaria infection and to have an increased risk of an adverse birth outcome due to malaria.

CLINICAL FEATURES

Fever is a nonspecific symptom accompanied with shaking chills and rigor in most of the patients occurring periodically and associated with headache, myalgia, nausea, and vomiting.

THE MALARIAL PAROXYSM

The patient develops symptoms episodically characterized by the following three stages in sequence.

- Cold stage: Characterized by shivering and a feeling of cold lasting 15–60 minutes
- Hot stage: Fever, sometimes reaching 41°C, flushed, dry skin, and often headache, nausea, and vomiting lasting 2–6 hours
- Sweating stage: During which the fever drops rapidly and the patient sweats. This lasts for 2–4 hours.

Each episode occurs every 2-3 days depending on the type of species of *Plasmodium* as follows:

- *P. falciparum, P. ovale, P. vivax:* every 2 days (Tertian fever)
- *P malariae:* every 3 days (Quartan fever)
- *P. knowlesii:* every day (Quotidian fever).

However, the classic features and periodicity of the paroxysms may not be seen early in the infection and so an absence of such a picture doesn't rule out malaria. This is especially true of *P. falciparum* infection which may occur every 2 days, but is notorious for its lack of periodicity.

SEVERE MALARIA

Definition of severe malaria by the working group of WHO.

One or more of the following criteria and the presence of asexual parasitemia defines severe malaria:[6]

1. Cerebral malaria/unarousable coma: Not attributable to any other Coma should persist for at least 30 minutes after a generalized convulsion
2. Convulsion: Repeated generalized convulsions >2 within 24 hours, despite cooling
3. Pulmonary edema/adult respiratory distress syndrome (ARDS)
4. Renal failure: Urine output of <400 mL/24 hours, No improvement with rehydration and a serum creatinine level >3 mg/dL
5. Macroscopic hemoglobinuria: Not associated with effect of oxidant drugs and RBC enzyme defects (such as G6PD deficiency)
6. Severe anemia: Normocytic normochromic anemia with hematocrit <15% or hemoglobin <5 g/dL in the presence of parasitemia >1,000/microl
7. Bleeding/disseminated intravascular coagulation (DIC): Significant bleeding from gums, nose, and GIT and evidence of DIC
8. Hypoglycemia: <40 mg/dL
9. Hypotension/shock: SBP <80 mmHg, with cold, clammy skin, or core/skin temperature difference of ≥10°C
10. Acidosis/acidemia: Arterial pH <7.25 or plasma bicarbonate level of <15 mmol/L. venous lactate level of >15 mol/L.

Severe malaria is seen in *P. falciparum* infections, due to its ability to cause RBCs to adhere to each other causing end organ damage and requires immediate treatment.

DIAGNOSIS

In patients with a clinical picture suggestive of malaria the following tests can be helpful in making a diagnosis.

Blood Smears

Both thick and thin films stained with Geimsa stain to identify the asexual stages of the parasite. This is the gold standard as it can show the parasite even at a low concentration and also identify the species. But it is time consuming (takes about 60 min) and requires laboratory and trained personnel.

In a febrile patient, three negative malaria smears 12–24 hours apart rules out the diagnosis of malaria.

Quantitative Buffy Coat

Diagnosis of malaria made by the acridine orange staining of centrifuged infected RBCs in the buffy layer in microhematocrit tubes and examined under UV light source. This can be performed in 15 minutes.

Rapid Diagnostic Tests

Immunochromatographic dipstick assays that act similar to a home pregnancy test and detect circulating parasite antigens like histidine-rich protein-2 (HRP-2; specific to *P. falciparum*), *Plasmodium* lactate dehydrogenase (pLDH; available against all malaria species 'pan-malaria' or against specific species) and aldolase (common to four major malaria infecting species).[7] Rapid diagnostic tests (RDTs) are mostly monovalent i.e., can identify only one species but now bivalent test kits available for both *P. vivax* and *P. falciparum* The test is simple to perform and easy-to-interpret results are available within 10–20 minutes. RDTs report sensitivities above 90% for detection of malaria, with increasing sensitivity as the level of parasitemia increases. Since RDTs detect circulating antigens, they may detect infection with *P. falciparum* even when the parasites are sequestered deep in the vascular compartment and thus undetectable by microscopic examination of a peripheral blood smear. Effective in symptomatic patients with high parasitemia but not useful as

a screening tool. High sensitivity RDTs will soon be available. It has to be noted though that RDT for *P. falciparum* may continue to be positive upto 3 weeks after successful treatment and clearance of parasites. Correlation with clinical picture and microscopy can help here.[8]

Polymerase Chain Reaction

It is highly sensitive, with quantitative polymerase chain reaction (PCR) being able to detect very low density malaria infection. This needs specially trained staff and lab setting. There are two types nested PCR and real-time PCR both are equally sensitive and can detect <1 parasite/microliter PCR is labor intensive, time consuming and too expensive for routine clinical use in malaria endemic countries it has place in research settings.

Loop-mediated Isothermal Amplification

Loop-mediated isothermal amplification (LAMP), which amplifies sequences from double-stranded DNA of the parasite under isothermal conditions. A positive reaction, due to amplification of the DNA results in the accumulation of a precipitate, making the reaction appear turbid. LAMP is less sensitive than PCR.[9]

Placental Histologic Study

Histological examination of placental tissue at delivery is a sensitive tool for detection of active or past malaria infection. Past infection is detected as the malaria pigment, hemozoin, most commonly in fibrin deposits. Active infection can be accompanied by leukocytes infiltrates, principally monocytes, termed intervillositis, particularly in first-time mothers with little pregnancy-associated malaria immunity.

The PCR, LAMP and placental histology do not have a role in the clinical management of malaria, but are of academic and scientific importance. In patients with clinical suspicion of malaria it is recommended to order thick and thin film microscopy, if results can be prompt and treat accordingly, in scenarios where the slides have to be sent to another place for reporting it is advisable to also do a RDT, start therapy and review when microscopy results are obtained.

TREATMENT OF MALARIA

Malaria in pregnancy can cause sudden and dramatic complications. Therefore it is essential to look for any complications by regular monitoring of the patients treatment of malaria in pregnancy is a balance between potential fetal adverse effects from drug toxicity and improved clinical status with complete clearance of the parasite.

UNCOMPLICATED FALCIPARUM INFECTION

First Trimester

- Drug of choice is quinine 10 mg/kg q8h for 7 days along with clindamycin 10 mg/kg q12h for 7 days
- Quinine monotherapy in case of nonavailability of clindamycin is an alternative
- WHO studies have found ACT (artemisinin-based combination therapy) to be safe and effective in first trimester and can be used as an alternative in patients unable to tolerate oral quinine
- Combination with sulfadoxine-pyrimethamine (SP) should be avoided in first trimester
- Indian guidelines still recommend only quinine in first trimester, however, it carries a risk of hypoglycemia hence blood sugar monitoring during therapy is must.

Second and Third Trimester

Large trials have proved ACT to be more than 95% effective in this scenario.

The ACT comprises of the following combinations all safe in pregnancy as shown in table 1:

TABLE 1: Artemisinin-based combination therapy

Artemisinin combination therapy	*Dose*		
	Day 1	*Day 2*	*Day 3*
Artesunate (4 mg/kg/day) + SP (25 mg/kg and 1.25 mg/kg)	200 mg 500 mg + 25 mg/tab 3 tabs	200 mg –	200 mg –
Attemether (AM) + lumefantrine (1.7 mg and 12 mg/kg/dose)	80 mg + 480 mg/tab 1 tab twice daily	1 tab twice daily	1 tab twice daily
Artesunate (4 mg/kg/day) + amodiaquine, (AQ) (10 mg/kg/day)	2 tabs 100 mg AS + 270 mg AQ/tab	2 tabs	2 tabs
Artesunate (4 mg/kg/day) + mefloquine (MQ) (15 mg/kg on 2nd day and 10 mg/kg on 3rd day)	200 mg	200 mg 3 tabs or MQ 250 mg MQ/tab	200 mg 2 tabs of MQ 250 mg MQ/tab
Dihydroartemisinin (OHA) + piperaquine (PPQ)	4 mg/kg 18 mg/kg Once daily 40 mg DHA + 320 mg PPQ/tab	4 mg/kg 18 mg/kg Once daily	4 mg/kg 18 mg/kg Once daily
Arterolane maleate (ALM) + PPQ	1 tab ALM (150 mg) + PPQ 750 mg/kg	1 tab	1 tab

- Artemether-lumefantrine (AL) 80 mg/480 mg
- Artesunate-mefloquine (AM) 200 mg/440 mg
- Artesunate-amodiaquine (AA) 200 mg/540 mg can cause severe neutropenia in HIV patients on ZVD or Co-trimoxazole hence use with caution
- Dihydroartemisinin-piperaquine (DHA-PQ) dose is weight dependent and piperaquine has to be used with caution in patients with cardiac diseases as it prolongs QT interval
- Artesunate-sulfadoxine-pyrimethamine (A-SP) 200 mg/1,500 mg/75 mg (safe in second and third trimester)

Of all of the above AL has the least side effects and DHA-PQ has the longest post-treatment prophylactic effect.

Rationale behind ACT

The artemisinin derivatives are short-acting drugs and substantially reduce parasitemia in first 3 days of therapy whereas the long-acting partners eliminate the residual parasites and prevent recrudescence. Three days of artemisinin therapy eliminates parasites from two asexual cycles and the residual parasitemia is eliminated by the partner drug.

Quinine treatment in second and third trimester carries an increased risk of hypoglycemia and should be used only if there is no alternative available.

PLASMODIUM VIVAX INFECTION

Chloroquine remains the standard of care for malaria in pregnancy in all trimesters in areas with low chloroquine resistance.

Chloroquine 10 mg/kg (600 mg) on day-1 and day-2 and 300 mg on day-3 is the standard and effective treatment for vivax malaria and can be used throughout pregnancy.

In Chloroquine Resistant Cases

The ACTs except A-SP can be prescribed in the first trimester. In fact ACTs are being recommended for all uncomplicated malaria types. Quinine, chloroquine, clindamycin and proguanil can used safely in first trimester of pregnancy. Uterine contractions are related to pyrexia and parasitemia and not the side effects of drugs used.

Drugs Contraindicated in Pregnancy

Primaquine, used to prevent relapses, is contraindicated in pregnancy due to the possibility of severe hemolysis in a G6PD deficient patient. Doxycycline, tetracycline, and halofantrine are also contraindicated.

Pregnant women living in endemic areas should be given suppressive treatment with chloroquine weekly till delivery and lactation is complete to prevent relapse, after lactation ceases she can take primaquine only if the neonate has been screened and found negative for G6PD deficiency.

SEVERE MALARIA

In cases meeting the criteria for severe malaria as described above, definitive treatment in pregnancy comprises of:

- Treatment of malaria
- Management of complications
- Management of labor.

TREATMENT OF THE INFECTION

Women in second and third trimester are more likely to have severe malaria than other adults and the mortality is 50% higher in pregnant than nonpregnant women.

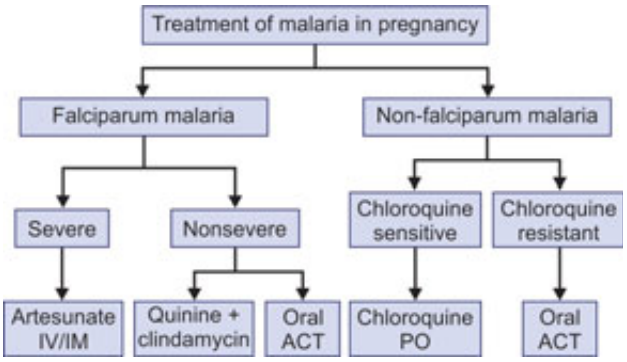
The WHO currently recommends treatment of choice as intravenous or intramuscular artesunate as 2.4 mg/kg stat, repeat 12 hourly till 2 doses then once a day until able to tolerate oral medication and then complete 3 days therapy with an act.

If artesunate is unavailable then intramuscular artemether as 3.2 mg/kg initially and 1.6 mg/kg once a day for 4 days, should be given. Intravenous quinine should be avoided in the second and third trimesters as it is associated with recurrent hypoglycemia, however parenteral quinine can be started immediately if it is the only available drug and given till artesunate is procured. Quinine can be given as 20 mg/kg initial dose as IV infusion in 5% dextrose or normal saline over 4 hours and followed with 10 mg/kg every 8th hourly till orally accepted.[11] Quinine should never be given as intravenous bolus.

Once the patient is able to take orally any ACT can be given for 3 days. In the case of unavailability of ACT, artesunate–clindamycin, artesunate–quinine or quinine–clindamycin can be given. For a quick overview of the treatment refer to flowchart 1.

MANAGEMENT OF COMPLICATIONS

- Hypoglycemia:
  - 25–50% Dextrose 50–100 mL intravenously followed by 10% dextrose infusion can be considered. But fluid overload to be assessed and monitoring is essential
  - Blood sugar to be monitored every 4–6 hours in case of recurrent hypoglycemia
- Anemia: Packed cell should be transfused if hemoglobin is <7 g/dL
- Septicemic shock: Secondary bacterial infections is common in pregnancy associated with malaria. Third generation cephalosporin is useful in this situation
- ARDS:
  - Monitoring of vital parameters



Flowchart 1: Treatment of malaria in pregnancy.

- Careful fluid management
- Oxygen supply and ventilatory support
- Diuretics if needed are essential according to patients clinical and laboratory parameters

- Renal failure: Renal failure could be prerenal due to unrecognized dehydration, heavy parasitemia. Diuretics, careful fluid management and dialysis is the main treatment.

MANAGEMENT OF LABOR

Falciparum malaria induces uterine contractions, resulting in premature labor. Uterine contractions appear to be related to the height of the fever. Therefore, all efforts should be made to rapidly control the body temperature by cold sponging and antipyretics like paracetamol.

Careful monitoring of maternal and fetal parameters. Induction of labor may have to be considered. Fetal or maternal distress may indicate the need to shorten the second stage of labor.

TREATMENT IN HIV POSITIVE PREGNANT WOMEN

- HIV positive women on cotrimoxazole to prevent opportunistic infections should not be given intermittent prophylactic treatment as they have a high risk of Steven Johnson syndrome like skin reactions[12]
- Mefloquine decreases parasite prevalence in HIV infected women but appeared to increase the risk of mother-to-child transmission of HIV[12]
- Avoid artesunate-amodiaquine in women on zidovudine.

Prevention.

WHO recommends a three prong approach for the treatment of malaria:

- Insecticide treated nets (ITNs)
- Intermittent preventive therapy in pregnancy (IPTp)
- Definitive treatment of the disease and its complications.

Insecticide Treated Nets

Mosquito nets sprayed with insecticides have been encouraged in African countries and has been found to be associated with decreased incidence of malaria in pregnant women. This is a cheap easily accepted and used method to reduce the disease.

Preventive Therapy in Pregnancy

Currently being practiced in Africa it consists of 2 or more doses of SP (sulfadoxine and pyrimethamine) after 20 weeks of pregnancy SP has a good safety profile in pregnancy. IPT ensures that the placenta is cleared of parasites at the time of rapid foetal growth.[10] Maximum benefit is derived from 2–3 doses of IPT, although even a single dose is beneficial. However, the Government of India does not recommend the use of IPTp as the epidemiology of the infection in India is different from that in Africa and Northeastern states have resistance to SP-IPTp. Moreover it lacks evidence in use against *P. vivax*.

Another option is IST (intermittent screening and treatment) wherein at each antenatal visit a rapid diagnostic test is performed and if positive full treatment is given.

VACCINE FOR MALARIA

A Malaria Vaccine Technology Roadmap, developed by more than 230 experts representing 100 organizations from 35 countries, has set out a strategic goal to develop a malaria vaccine by 2025 that would have a protective efficacy of more than 80% against clinical disease and would provide protection for more than 4 years.[13]

RTS, S/AS01 is a recombinant protein-based vaccine, the use of which has been recommended by WHO-SAGE (Strategic Advisory Group of Experts) and MPAC (Malaria Policy Advisory Committee) as a pilot programme in three African countries starting in 2018.

BIOMARKERS FOR MALARIA

Biomarkers are indicators that can be objectively measured to provide information on a biological state. Biomarkers can be parasite-derived or host-derived.

- Parasite derived markers are used in RDTs (pfHRP2, pLDH and aldolase)
- Host derived markers There are a number of proteins which can serve as markers like TNF, soluble TNF receptor (sTNFR1and 2), ferritin, leptin, and soluble endoglin.

Levels of sTNFR2 were significantly elevated in occult placental malaria and in submicroscopic malaria and returned to baseline following resolution of infection. These results suggest that sTNFR2 may be a biologic indicator of infection, even when parasites are undetectable peripherally, and could provide a means to measure treatment response in future.

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9

CHAPTER

Thalassemia and Pregnancy: An Update

Archana Verma, Shehla Jamal

INTRODUCTION

Hemoglobinopathies are amongst the most common inherited hematological diseases; a quoted of 7% of the global population is a carrier, and 300,000–500,000 children are born with a severe hemoglobin disorder annually.[1]

Hemoglobinopathies are classified according to the impaired globin chains and whether this disorder leads to reduced production of a normal chain or an abnormal tertiary structure of globin chains. In adulthood, hemoglobin consists of approximately 98% HbA ($\alpha_2\beta_2$), <3% HbA_2 ($\alpha_2\delta_2$), and traces of HbF ($\alpha_2\gamma_2$).[2-4]

Pregnancy with thalassemia poses a higher risk to both mother and fetus and warrants multidisciplinary approach and involvement of hematologist, geneticist, neonatologist and of course a dedicated obstetrician (Flowchart 1).

GENETIC BASIS OF THALASSEMIA

Various types and subtypes have been described based on the globin chain synthesis defect involved. Apha (α-) thalassemia characterized by reduced or suppressed production of α-globin chain. Alpha-globin chain synthesis begins in fetal life and the genes responsible for its production are—four in total—situated in two genetic loci on chromosome 16. Gene deletion or less commonly mutation results in α-thalassemia. When all four genes are affected (-/-|-/-) in homozygous α-thalassemia, fetal synthesis of α-chains is impossible, leading to an excess of γ-chains and forming the unstable Bart's hemoglobin (γ_4),which is incapable of oxygen exchange. The affected fetus results in having severe anemia, cardiomegaly, and hydrops fetalis, and ultimately intrauterine or neonatal death. When three genes are affected (α0/0/0), α-chain synthesis is restricted to a minimum. Therefore, β-chains that exist in excess form the unstable HbH (β_4). HbH disease has a phenotypic variability based on mutation type, ranging from mild anemia (deletions on chromosome 16) to a transfusion-dependent one.[5]

Beta-thalassemia is extremely heterogeneous in terms both of genotype and phenotype, depending on the nature of β-gene mutation and the extent of IMP, inheritance of two defective β-globin genes results in a wide phenotype spectrum, ranging from transfusion-dependent thalassemia major (TM) to mild or moderate anemia (thalassemia intermedia [TI]). β0 refers to the complete absence of production of β-globin on the affected allele, β0 refers to alleles with some residual production of β-globin, and β+ to a very mild reduction in β-globin chain production. β-TM or Cooley's anemia (β0/β0 or β0/β+) is characterized by severe hypochromic microcytic anemia, which becomes symptomatic at infancy or early childhood and is apparently transfusion-dependent.[6] The globin chain-synthesis reduction leads to an unbalanced β/α-globin chain production, where the chains in abundance precipitate, forming erythrocyte inclusions. Pathophysiology is characterized by damaged red blood cells, hemolysis, and erythroid-precursor release in the peripheral circulation, due to ineffective erythropoiesis. The phenotype includes anemia, bone marrow expansion, skeletal deformities, growth restriction, and late sexual maturity.

Hemoglobin electrophoresis remains the gold standard for the diagnosis and classification of thalassemia.[7,8]

Where both parents are carriers of the same trait (α–α or β–β couple), genetic counseling should be performed so as to achieve prenatal diagnosis.

PRENATAL GENETIC COUNSELING/TESTING

Identification of high risk group for thalassemia is the revolutionary step for decreasing the incidence. High risk ethnic groups, patients having affected offspring should be offered with various screening options available. Differential hematocrit analysis, Mentzer's index, NESTROFT test are some of the screening tools, but hemoglobin electrophoresis and high-pressure liquid chromatography remains the GOLD STANDARD for diagnosing. Carriers may demonstrate higher values of HbA2.

If both the partners are detected to be carriers, genetic counseling has to be offered. Diagnosis can be confirmed by chorionic villi sampling (11th week) and amniocentesis (after

16 weeks). The risk of miscarriage for both the procedures is small and same, i.e., <1%.

If the partner of a homozygous parent is heterozygous, preimplantation genetic diagnosis can be offered by way of IVF/ICSI, embryo biopsy, either in eight cell or blastocyst stage.

ANTENATAL CARE

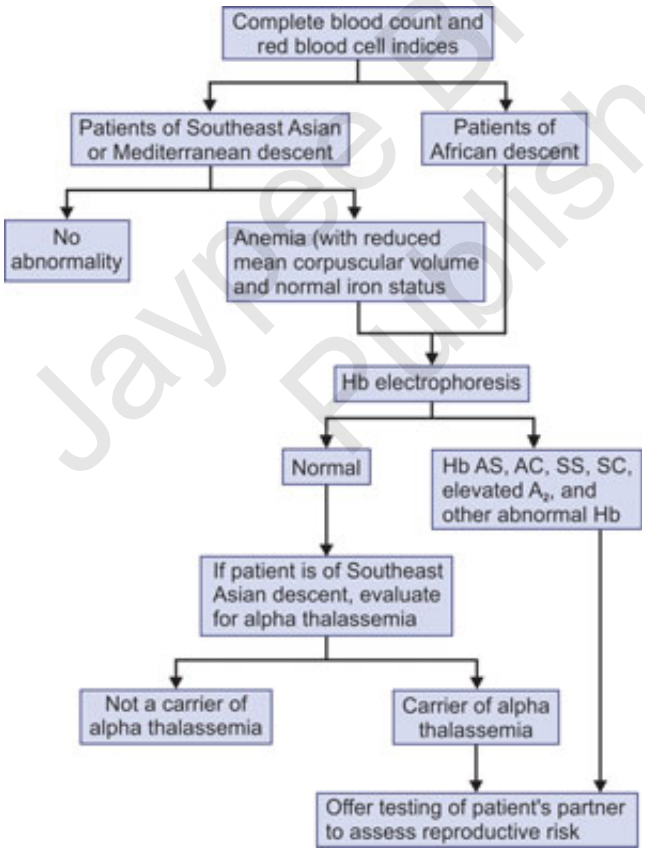
Highest form of antenatal care has to be imparted to the diagnosed cases.

Cardiac Assessment

Cardiac complications remain the leading cause of death for the thalassemic population due to cardiac iron overload as a result of regular blood transfusions and delayed or inadequate chelation therapy.[9-10] Cardiac magnetic resonance imaging (MRI) has been proven of high value with regard to preconception cardiac assessment. The target is T_2* $20 ms, however, if T_2* lev10 ms suggest a high risk of developing heart failure.[11] Therefore, all women planning a pregnancy should be assessed by a thalassemia-specialist cardiologist by ECG, cardiac echo study, 24-hour Holter monitoring of rhythm, and mainly by MRI T_2* measurement.[12]

Infections

During gestation estrogen levels are elevated, leading to reduction of total immune function and an augmented infection risk. Therefore, clinical as well as silent infections have higher prevalence during pregnancy. All women should be tested for hepatitis B virus (HBV), HCV, HIV, cytomegalovirus, and human parvovirus B19, splenectomized women should take penicillin prophylaxis.[13]



Flowchart 1: Work up of anemia in pregnancy.

Liver Function

Thalassemic women are prone to cholelithiasis, cholecystitis, impaired liver function. Preconception liver and biliary tract ultrasound assessment should be performed to detect liver cirrhosis, fibrosis, and cholelithiasis, and cholecystectomy should be considered before impregnation[14] MRI provide quantitation of liver iron concentration in thalassemia.[15] A target liver iron concentration of less than 7 mg/g dry weight is recommended prior to conception, and in cases of target excess, intensive preconception chelation should be proposed.[16]

Endocrinopathies

Diabetes is often encountered owing to pancreatic damage and genetic factors.

Their target fructosamine should be kept below 300 nmol/L, thyroid function should be optimized. Bone deformities can manifest due to parathyroid dysfunction. Women on oral chelators desferfirox (DFX), or deferiprone should be switched to desferrioxamine preconceptionally.

Anemia in Pregnancy

Thalassemia in combination with gestational anemia (secondary to increased fluid compartment of the body) account partly for different complications of the thalassemic pregnancy, such as fetal intrauterine growth restriction (IUGR) and preterm labor.[17] Aim is to maintain hemoglobin at the preconception goal (10 g/dL) to ensure appropriate fetal growth.[15,18,22] Despite following this approach, IUGR may be present, suggesting the role of other fetoplacental and maternal factors, while transfusion-acquired red-cell antibodies should be checked prior to pregnancy (Table 1).[18]

Chelation therapy will reduce iron overload and help free radical scavenging, reducing the inflammatory process,[19] but DFO fetotoxicity has not yet been definitely assessed. According

TABLE 1: Causative etiology of anemia in pregnancy

Incidence of common hematologic problems in pregnancy	
Iron deficiency anemia	-10%
B12 deficiency	5%
Folate deficiency	5%
Hemoglobinopathies and thalassemias	5%
Sickle cell	4%
Alpha thalassemia	0.8–5%
Beta thalassemia	0.25–10%
Thrombocytopenia	
<150	6.6%
<100	1.2% %
Von Willebrand's hemophilia	1%

to studies, DFO should be avoided during the first trimester, but subcutaneous administration may be considered in the second and third trimesters for indicated.[20] DFX use is contraindicated in pregnant women. During pregnancy, chelation should be restricted for cases where the potential benefit outweighs the potential fetal risk.

Thrombosis in Pregnancy

Thalassemic women have an increased risk for thrombosis, as the disease entity is a chronic hypercoagulable states.[21-22] According to studies, low-dose aspirin administered to splenectomized β-thalassemia patients seems to be effective in preventing preeclampsia, preterm labor.[23] Thus, splenectomized women or those with a serum platelet count above 600×10^9/L should begin or continue taking aspirin at a dose of 75 mg/day.

ANTEPARTUM MANGEMENT

Fetal Monitoring

Obstetric complications like diabetes, abruption, etc. should be anticipated.

The first ultrasound scan should be performed at the 7th–9th week of gestation, as these women have a high risk of miscarriage and multiple gestations. In addition to first-trimester (11th–14th weeks) and second trimester (18th–21st weeks) scans, serial fetal biometry scans should be performed monthly after the 24th gestational week, focusing on possible IUGR.

Women should be advised to modify their lifestyle and diet, avoid smoking and alcohol, and start taking supplements of folic acid, calcium, and vitamin D.

Folate demand in pregnancy is normally increased, and all thalassemic women are advised to receive folic acid supplementation at a dose of 5 mg/day to prevent fetal neural tube defects.

INTRAPARTUM MANAGEMENT

Time and mode of delivery should be individualized for thalassemia as an uncomplicated disease course and thalassemia itself should not be considered a proper indication for Cesarean section (CS). In case of CS, epidural anesthesia is preferable compared to general anesthesia, as severe maxillofacial deformity in TM patients, especially the older ones, may augment difficulties of intubation.[24]

If vaginal delivery is decided, active management of the third stage of delivery is recommended, as this intervention is supposed to reduce blood loss. Fetal hypoxia is common during labor, and thus continuous electronic fetal monitoring is recommended.

POSTPARTUM MANAGEMENT

During the postpartum stage, there is a high risk of venous thromboembolism for women with thalassemia, and low-molecular-weight heparin prophylaxis should be administered in hospital, followed by a 7-day postdischarge regimen after vaginal delivery or a 6-week regimen after CS.[25]

Chelation therapy with oral agents using DFO seems to be safe, as DFO is not orally absorbed. Calcium and vitamin D supplements should be continued during breast-feeding, but bisphosphonates should be resumed after cessation of breast-feeding.

CONTRACEPTION

Oral contraceptive pills are generally considered safe, and all form of contraception should be provided according to WHO MEC.

FUTURE

Transfusions, chelations, infections in these patients burdens the family, clinicians and economy at large. Future preventive strategies include stem cell, gene therapy, etc. nonetheless, prevention is always more fruitful.

National prevention program is the cry of the hour, and intensive efforts for creating awareness should be implemented.

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CHAPTER

Refractory Anemia in Pregnancy

Mausumi D Banerjee

INTRODUCTION

Anemia is defined as quantitative and qualitative diminution of red blood cell (RBC) and/or hemoglobin (Hb) concentration in relation to standard age and sex.

- According to WHO (World Health Organisation) definition,[1] a pregnant women suffers from anemia when her hemoglobin <11 g/dL.
- According to CDC (Centres for Disease Control and Prevention),[2] hemoglobin <11 g/dL in first and third trimester and below 10.5 g/dL in second trimester.
- In developing countries like India, due to high prevalence of anemia (Hb) <10 g/dL is considered as anemia in pregnancy.

CLINICAL GRADES OF ANEMIA

According to the laboratory findings of Hb%.

- Mild: 9.1–10.9 g/dL
- Moderate: 7–9 g/dL
- Severe: <7 g/dL
- Very severe: <4 g/dL.

COMMON CAUSES OF ANEMIA

Hemorrhagic, Hemolytic

- Hereditary—hemoglobinopathies, thalassemia, sickle-cell anemia, spherocytosis, etc.
- Acquired—malaria.

Nutritional Deficiency

Iron (commonest), folic acid, vitamin B12 deficiency, protein deficiency.

Miscellaneous

- Bone marrow insufficiency, neoplasm, chronic infection, chronic renal disease, tuberculosis.

Refractory anemia is defined as a group of anemic conditions not associated with any other disease and is marked by persistent, frequently advancing anemia that only can be successfully treated through parenteral iron or blood transfusions.

Suspicion of refractory anemia in pregnancy is based on exclusion of the different types of anemia, gastrointestinal disorders and proved refractoriness to oral hematinics. (<1 g/dL Hb rise after 4 weeks of oral iron therapy provided patient compliance is adequate and acquired forms of GI disorders are ruled out).[3]

It is said that an etiological relation exists between low serum zinc concentration and refractory anemia of pregnancy resulting in increased intramedullary cell destruction aggravated by iron deficiency.[4]

HISTORY OF REFRACTORY ANEMIA

- 1981: Buchan and Sheehan first found 3 siblings presented with iron deficiency anemia despite adequate nutritional intake of iron and no visible GI loss, responded only partially to parenteral iron
- 1996: Hartman and Barker highlighted iron malabsorption as the cause of anemia
- 2008: Finberg et al. classified these presentations as IRIDA and defined key abnormality along with mutations in TMPRSS6 gene.

PATHOPHYSIOLOGY

- Iron refractory iron deficiency anemia (IRIDA) is a hereditary autosomal recessive disorder due to a defect in TMPRSS6 gene located on chromosome 22 encoding matriptase-2, a transmembrane serine protease, that plays an essential role in down-regulating hepcidin, the key regulator of iron homeostasis secreted by the liver by cleaving hemojuvilin a surface co-receptor in BMP-6-SMAD signaling pathway[5]
- Hepcidin acts on the ferroportin channels at the basal enterocytes in the duodenum blocking iron absorption. The gene has 18 exons and encodes 802 amino acid proteins that has 4 domains aSEA, 2CUB, 3LDR and C-terminal serine protease domain and a transmembrane region.[6]

- Hence it is imperative to screen and sequence all 18 exons including exon-intron boundaries to identify deleterious mutation to qualify for a confirmed diagnosis of IRIDA.

OTHER RARE REFRACTORY ANEMIA

Hypotransferrinemia, DMT-1 mutations, STEAP3, aceruloplasmia, X-linked sideroblastic anemias, AR sideroblastic anemias.

Types

- Type 1: Level of blasts <10%
- Type 2: Level of blasts—10–20%, this condition may progress to AML occurs in 1/3 type 2 cases.[7]

The World Health Organization classified as:

- Refractory cytopenia with unilineage dysplasia—RCUD
- Refractory anemia with ring sideroblasts—RARS
- Refractory cytopenia with multilineage dysplasia—RCMD
- Refractory anemia with excess blasts—RAEB-1 and RAEB-2
- Refractory myelodysplastic syndrome associated with isolated del (5q).

HOW TO INVESTIGATE?

History/Examination

- Presence of mild to moderate anemia in infancy/early childhood
- Family history of anemia of siblings without improvement with oral iron
- Absence of organomegaly/minimally evident stigmata of classical iron deficiency anemia like hair changes, koilonychias, angular cheilitis.

Symptoms

Lethargy, weakness, shortness of breath, palpitation, syncopal attacks, headache, tinnitus, sleeping difficulty, loss of appetite, poor weight gain.

Signs

Pallor, ankle edema, oral ulcers, hemic murmurs.

Routine investigations in a case of anemia

- Purpose: To determine the severity of anemia and etiology of anemia so that proper therapy can be given.
- Investigation parameters:
  - Hemoglobin estimation, total RBC count and packed cell volume (PCV)
  - Blood indices – MCV, MCHC, MCH
  - Peripheral blood smear – RBC morphology, reticulocytes, malaria parasite
  - Serum values – Serum iron concentration, sickle cell preparation serum ferritin level, TIBC.
  - Urine analysis
  - Stool examination
  - Bone marrow examination-rarely needed
  - Investigations for abnormal hemoglobin
  - Electrophoresis HPLC (high performance liquid chromate).

Laboratory Findings Leading to Differential Diagnosis

- Iron deficiency anemia: Low—MCV, MCH, TSAT, serum ferritin), high-TIBC
- Beta/alpha thalassemia: Low—MCV, high—RBC count, RDW/red cell distribution width, if PBF contain target cells then HbA2 and HbF advised.

IRIDA–usually the refractoriness to oral iron becomes evident from 20 weeks of gestation or earlier-Low-(MCV, MCH, TSAT), low/normal serum ferritin, high-serum/urine hepcidin level, thrombocytopenia.

Bone marrow usually has normoblastic hypoplasia or may be hyperplastic.

Case Presentation-rare Case of Primary Refractory Anemia with Pregnancy[8]

- 21 years primigravida presents at 12 weeks with h/o no previous illness or regular drug intake in prepregnant state. No family h/o anemia
- O/E-Pale, obese, young woman with numerous petechial hemorrhagic spots and ecchymosis
- No palatal, buccal, faucial ulceration or enlargement of liver, spleen, lymph nodes
- No evidence of renal disease
- Hb—7.1 g/dL, at 12 weeks. Oral iron supplementation given., 4 weeks later her Hb was 5.6 g/dL; WBC—39,000/cumm with 26% neutrophil polymorphs and platelet count <10,000/cumm. RBC—normocytic, normochromic
- Bone marrow aspirates from sternum/iliac crests shows a few islands of stromal cells and occasional plasma cells, severe hypoplasia.

Management

- Additional to oral iron folic acid-10 mg twice daily, prednisolone 60 mg/day, pyridoxin 100 mg/day added. Blood transfusion was done in 5 occasions
- There were episodes of epistaxis and UTI, treated conservatively
- Patient developed PET at 35 weeks with gross IUGR and undergone spontaneously normal delivery with approx. blood loss of 200 mL.

Effects on Mother

- Antenatal: Infections,[6] pregnancy induced hypertension, abruptio placentae, heart failure, preterm labor
- Intranatal: Postpartum hemorrhage, heart failure, cerebral hypoxia, and collapse
- Puerperium: Puerperal sepsis, subinvolution, venous thrombosis, pulmonary embolism, lactational failure.

High maternal morbidity and mortality.

Effects on Fetus

- Fetal growth restriction/small for gestational age
- Intrauterine death
- Preterm delivery
- Fetal malformation
- Fetal heart failure

- Fetal hydrops
- High perinatal morbidity and mortality.

Others Causes of Treatment Failure of Oral Iron Therapy?

- Gastrointestinal disease—Crohn's disease, ulcerative colitis, celiac disease
- Poor compliance
- Dimorphic or β-thalassemia
- Blood loss, e.g., bleeding piles, hookworm infestations
- Presence of any infection like unrinary tract infection
- Other dietary deficiency
- Drugs that inhibit erythropoiesis (like immunosuppressants, cytotoxic agents).

Management

Initially we start with the standard recommendations

- The WHO recommends 60 mg elemental iron and 250 μg of folic acid
- Government of India recommends 100 mg of elemental iron and 500 μg of folic acid daily for 100 days during pregnancy starting from 14–16 weeks of gestation. This should be followed by the same dose for 100 days in the postpartum period
- When the patient is diagnosed to be refractory to oral iron therapy then parenteral therapy recommended but response may be partial.

TABLE 1: Injectable forms of iron for parental therapy

Preparation	*Composition*
Iron dextran	50 mg elemental iron/mL, IM/IV
Ferric gluconate	12.5 mg iron/mL, IV only
Iron sucrose	20 mg iron/mL, IV only
Iron-sorbitol-citric acid complex	50 mg elemental iron/mL, intramuscular only

Dosage of Parenteral Iron Therapy[9]

- Total iron requirement in mg = Weight in kg × (ideal Hb – actual Hb) × 2.21 + 1,000 ideal Hb is considered as 14 g/dL
- Alternate method is—250 mg elemental iron × Hb/dL deficit.
- Ferrous sucrose complex, is preferred
- Ferrous sucrose is safer than iron dextran with rare anaphylactic reaction
- Ferric carboxymaltose by rapid intravenous infusions (15 min) and reduces the need for repeated infusions and potentially may be an ideal agent but considered unsafe in the first trimester of pregnancy.

Role of Blood Transfusion (Valid Consent to Be Taken)

- When the patient needs to be delivered shortly
- Emergency operative procedure required
- Partial response to parenteral iron therapy
- Maternal Hb <6 g/dL
- Fresh frozen plasma (FFP) at a dose of 12–15 mL/kg should be administered for every 6 units of RBC during major obstetric hemorrhage. PT and APTT ratio need to be well maintained.

Fetal Anemia

- Intrauterine fetal transfusion may be considered[10]
- Doppler measurement of peak velocity of systolic blood flow in MCA can sometimes safely replace invasive testing.[11]

Special Steps for Management of Labor

First stage:

- Moist oxygen, strict asepsis, adequate sedation, close Hb and ECG monitoring

Second stage:

- Cut short second stage of labor
- Injection of lasix in severely anemic women to prevent heart failure
- AMTSL-active management of third stage of labor.

Third stage:

- Oxytocics, to prevent PPH.

Fourth stage:

- Close observation.

Management of Puerperium

Antibiotics, hygiene, and balanced diet maintained.

Role of Stem Cell Transplantation

Pregnancy in a woman with polycystic ovarian syndrome and myelodysplastic syndrome (in the form of refractory anemia) treated with allogenic hemopoietic stem cell transplantation (allo-HSCT).[12]

Management of Neonates

- Hemoglobin and bilirubin levels
- Breastfeeding and guard against dehydration as this increases chance of jaundice[11]
- Phototherapy/exchange transfusion when required.

CONCLUSION

Refractory anemia is a relatively new disease entity, which needs more research. Very few cases are in literature till date and the disease is underdiagnosed.

FUTURE RESEARCH

Required in the following fields:

- Developing more antihepcidin antibodies; e.g., anticalins which are genetically modified lipocalins
- Other methods of manipulation of hepcidin pathway with aim of suppressing it.

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CHAPTER

Prediction and Monitoring in Pregnancy-induced Hypertension

Kiran Pandey, Pavika Lal

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) is a global health problem with multisystem affection that is distinct to human pregnancy. It is known to increase the risk of maternal and perinatal morbidity and mortality especially in middle and low income countries.[1,2]

Preeclampsia complicates 2–8% of all pregnancies, contributes to 15% of preterm deliveries, and between 9% and 26% of maternal deaths worldwide.[3] Case fatality rate of HDP is highest in the world (ranged from 0 to 1.8% in developed countries and 17.7% in India in 2014) and delay in seeking healthcare as well as delay in initiation of treatment contributes majority to maternal mortality.[4,5]

RISK FACTORS

The incidence of preeclampsia is increasing with the global increase in risk factors, and therefore early identification of preeclampsia is the core principle of adequate management and timely, and proper referral.

There are many conditions and high-risk behaviors that predispose to HDP.

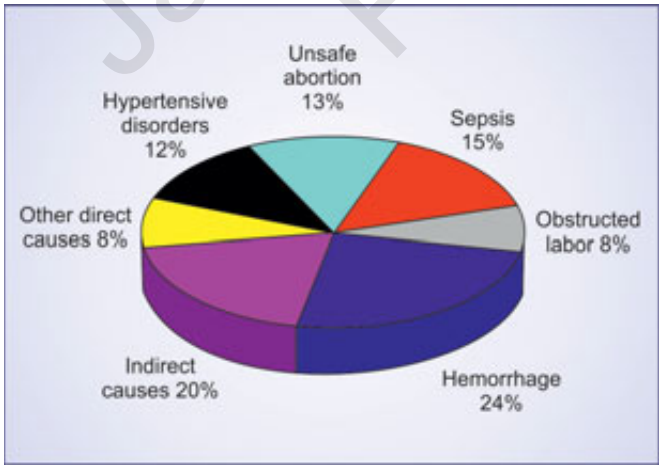


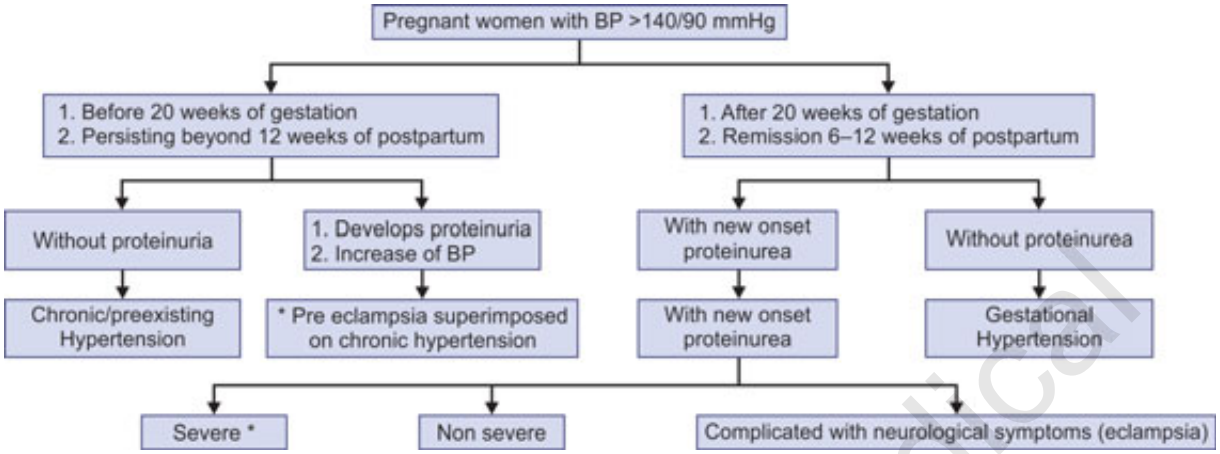
Figure 1: Global cause of maternal mortality.

BOX 1 Recognized maternal risk factors[6-9]

- Previous preeclampsia
- Previous early onset preeclampsia and preterm delivery at <34 weeks' gestation
- Preeclampsia in more than one prior pregnancy
- Chronic kidney disease
- Autoimmune disease such as systemic lupus erythematosis or antiphospholipid syndrome
- Heritable thrombophilias
- Type 1 or type 2 diabetes
- Chronic hypertension
- First pregnancy
- Pregnancy interval of more than 10 years
- New partner
- Reproductive technologies
- Family history of preeclampsia (mother or sister)
- Excessive weight gain in pregnancy
- Infection during pregnancy
- Gestational trophoblastic disease
- Multiple pregnancies
- Age 40 years or older
- Ethnicity: Nordic, Black, South Asian, or Pacific Island
- Body mass index of 35 kg/m^2 or more at first visit
- Booking systolic blood pressure >130 mmHg or diastolic blood pressure >80 mmHg
- Increased prepregnancy triglycerides
- Family history of early onset cardiovascular disease
- Lower socioeconomic status
- Cocaine and methamphetamine use
- Nonsmoking

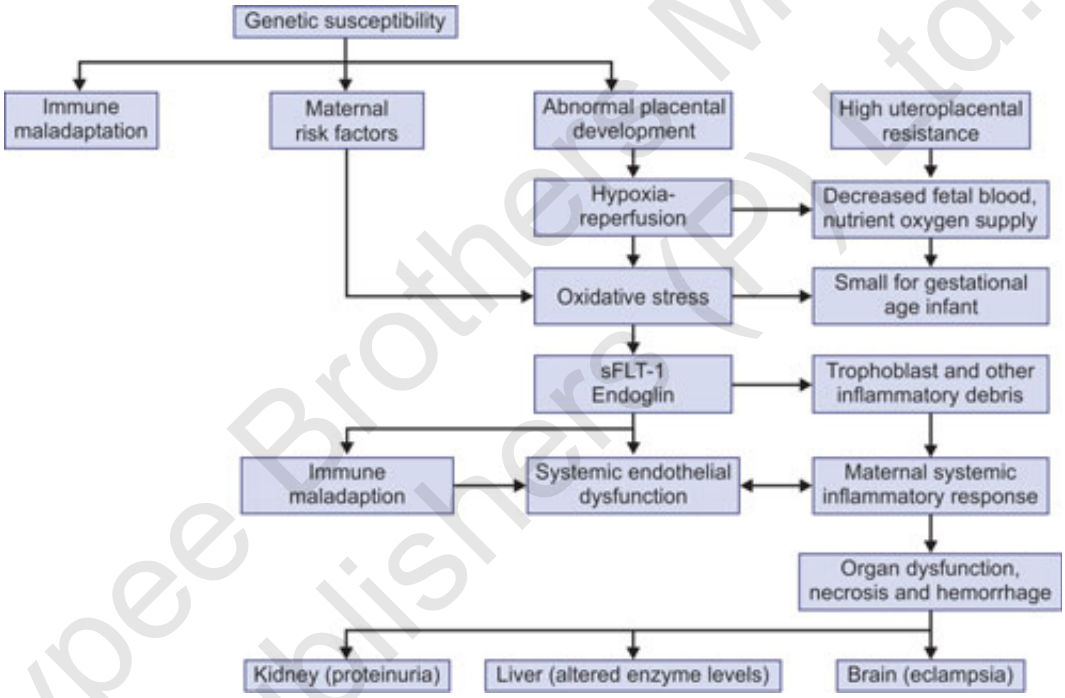
ACOG CLASSIFICATION OF HYPERTENSIVE DISORDERS IN PREGNANCY (2013)

- Sudden exacerbation of hypertension
- Sudden increase of liver enzymes to abnormal level



*Features of severe PET/PET super imposed on chronic hypertension.

Flowchart 1: Classification of hypertensive disorders in pregnancy (ACOG 2013).



Flowchart 2: Depicting pathogenesis of hypertensive disorders of pregnancy.

- Platelet count <100,000/mL
- Manifest symptoms, e.g., right upper quadrant pain and severe headaches
- Develop renal insufficiency
- Develop pulmonary congestion or edema
- Sudden, substantial, and sustained increase in protein excretion.

PATHOLOGICAL PROGRESSION OF PREECLAMPSIA

Hypertensive disorder in pregnancy is a complex disease and its clinical evolution varies and can result in wide varieties of unpredictable clinical features as well as adverse outcomes both for mother and fetus.

Impaired trophoblastic differentiation and invasion in early pregnancy compounded by maternal risk factors, fetal genetic composition, and environmental factors trigger sustained oxidative stress and systemic inflammatory response syndrome (SIRS).

Systemic inflammatory response syndrome plays an important role in development of this disorder as evidenced by:[10,11]

- Exaggerated leukocytosis
- Extensive platelet activation
- Enhanced compliment activation.

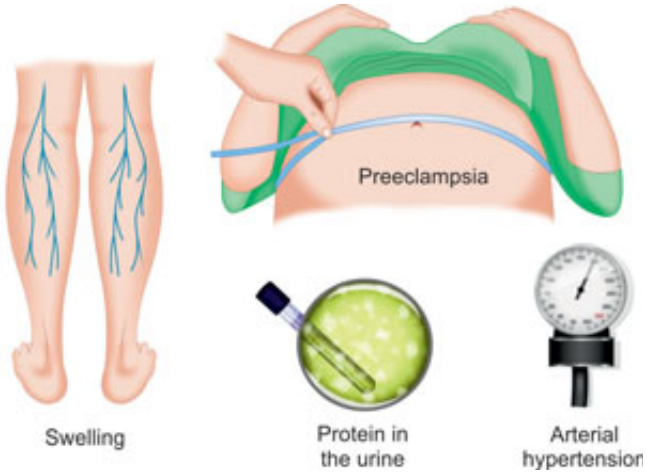


Figure 2: Manifestation of an eclamptic patient.

PREDICTION OF HYPERTENSIVE DISORDERS OF PREGNANCY

Despite recent advances in the understanding of pathophysiology of this heterogeneous disorder, there is a lack of predictive markers which would diagnose HDP with high sensitivity and specificity.

- Preeclampsia can be subdivided into:
  - Early onset (<34 weeks)
  - Late onset (>34 weeks).

As early onset preeclampsia is associated with increased incidence of adverse outcome, therefore, the herculean task in modern obstetric is to identify these subgroup of females that would allow referral for more intensive surveillance or application of preventive therapies as well as to reduce the prevalence of disease.

SREENING BY MATERNAL HISTORY

Multivariate screening with maternal risk factors has evolved into a new approach in which the gestation at the time of delivery for preeclampsia is treated as a continuous rather than a categorical variable, based on survival time model assuming that all women would develop preeclampsia if pregnancy was to continue indefinitely as explained in the figure 3.[12]

SCREENING BY MATERNAL BIOPHYSICAL MARKERS

Uterine Artery Doppler

- The most promising screening test for preeclampsia is uterine artery Doppler velocimetry
- Defective trophoblastic differentiation with impaired invasion of the maternal spiral arteries and failure of these vessels to transform into low resistance vessels:
  - Increased placental perfusion, which is reflected in increased uterine artery pulsatility index (UAPI)
- First trimester UAPI is affected by:
  - Gestational age at screening
  - Maternal weight

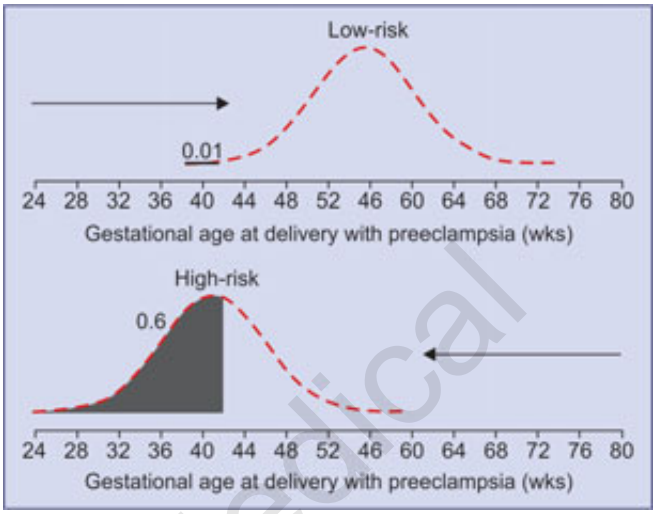


Figure 3: Distribution of gestational age at delivery for preeclampsia. In pregnancies at low-risk for preeclampsia the gestational age distribution is shifted to the right and in most pregnancies delivery will occur before the development of preeclampsia. In pregnancies at high-risk for preeclampsia the distribution is shifted to the left. The risk of preeclampsia occurring at or before a specified gestational age is given by the area under the distribution curve (black). In the low-risk group the risk of preeclampsia at or before 34 weeks' gestation is 0.01 or 1% and in the high-risk group the risk is 0.6 or 60%.

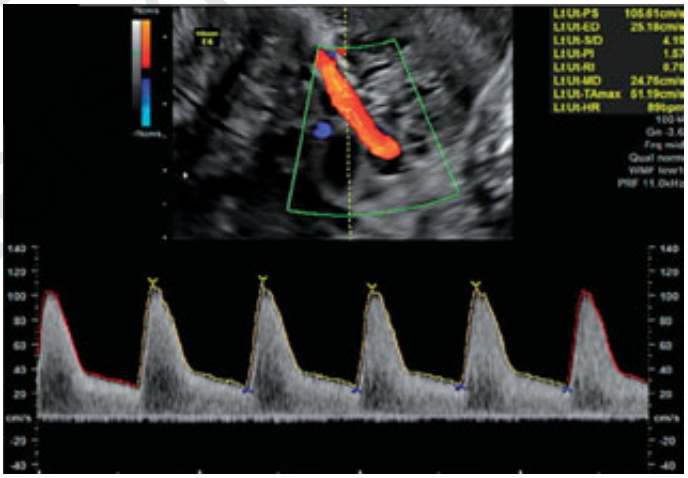


Figure 4: Uterine artery Doppler depicting increased pulsatility index.

  - Racial origin
  - History of preexisting diabetes mellitus and, therefore, expressed as multiple of median (MoM) after adjustments for these factors
- The MoM value of UAPI is significantly increased at 11–13 weeks, gestation in females who later develop preeclampsia and there is a significant negative linear correlation between UAPI MoM and with gestational age at delivery.[12]

Blood Pressure

- Although hypertension is only a secondary sign of preeclampsia, it is an important sign as it is an early indicator

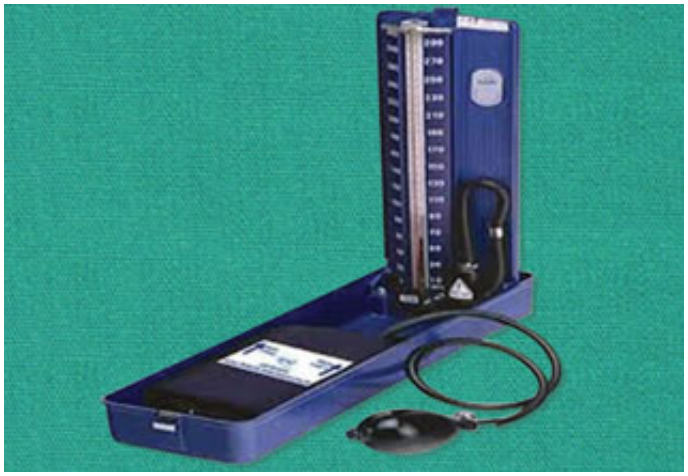


Figure 5: Mercury sphygmomanometer.

of the disease which highlights the importance of accurate blood pressure measurement during antenatal care

- Use of mercury sphygmomanometer remains the gold standard for noninvasive BP monitoring, and it is recommended that a series of BP measurements should be made until a prespecified level of stability is achieved
- Mean arterial pressure (MAP) should be measured by validated automated devices, with women in sitting position with back supported and legs uncrossed, that two measurements should be taken from each arm simultaneously with each arm supported at the level of the heart, and that the average of the four measurements should be used.[13,14]
- A systematic review concluded that MAP is significantly better than systolic or diastolic blood pressure in predicting preeclampsia.[15]
- First-trimester MAP is affected by maternal weight, height, age, racial origin, cigarette smoking, family/prior history of preeclampsia, and history of chronic hypertension, and therefore it should be expressed as MoM after adjustment for these factors.

Screening by Maternal Biochemical Markers

Although there are innumerable number of biochemical markers that have been investigated for prediction of preeclampsia, two novel markers have shown promising results.

TABLE 1: Two novel biomakers

Pregnancy associated plasma proteins (PAPP-A)	*Placenta growth factor (PIGF)*
• PAPP-A • Syncytiotrophoblast-derived metalloproteinase • Increases the mitogenic function of the insulin-like growth factors • Play important role in placental growth and development[16,17]	• PlGF • A glycosylated dimeric glycoprotein, is a member of the VGEF subfamily • Synthesized in villous and extravillous cytotrophoblast • Contribute a change in angiogenesis from branching to nonbranching phenotype controlling the expansion of capillary network[18,19]

In chromosomally normal pregnancies, low maternal serum pregnancy associated plasma proteins (PAPP-A) and placenta growth factor (PIGF) in both first and second trimester increased incidence of preeclampsia.[20,21]

Since the first trimester maternal serum concentration of both the biochemical markers are affected by certain maternal and pregnancy characteristics therefore expressed as MoM.

FETAL MEDICINE FOUNDATION[22]

- A software has been developed by which allows estimation of risks of early preeclampsia (at <32 weeks' gestation), preterm-PE (<37 weeks), and term-preeclampsia (>37 weeks) by a combination of maternal factors and results of various biophysical and biochemical measurements made at different stages in pregnancies
- Useful markers in the first trimester (11–14 weeks) are MAP, UTPI, PIGF, and PAPP-A
- Useful markers in the second trimester (19–24 weeks) and third trimesters are MAP, UAPI, PIGF, and sFLT-1
- MoM values for biochemical markers depend on the equipments and reagents used at a specific laboratory apart from maternal characteristics
- Use of this method advocated by Fetal Medicine Foundation (FMF) is superior to those recommended by NICE and ACOG guidelines in identifying the group of pregnancies that could benefit from early intervention.

According to ACOG and NICE guidelines:

- The current predictive tests for preeclampsia may harm more women than they benefit due to their low PPV and cost effectiveness
- Such strategies should quantify the adverse effects of identifying women as high risk of preeclampsia.

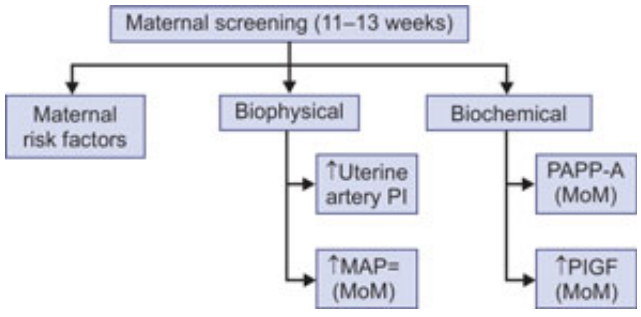
The best and the only recommended approach is to obtain an appropriate and detailed medical history for evaluation of risk factors (ACOG 2013).

In second trimester (19–24 weeks) PAPP-A is replaced by sFLT-1 according to the software developed by FMF.

PREVENTION

Goals of Preconceptional Counseling

- To optimize maternal health conditions prior to conception
- Detect potential adverse outcomes
- To achieve optimal perinatal outcomes in subsequent pregnancy



Flowchart 3: Strategy devised by fetal medicine foundation.

- For women of childbearing age with chronic hypertension ACE inhibitors and ARB be stopped within 2 days of notification of pregnancy and offered an alternative antihypertensive treatment as there is increased risk of congenital malformations
- Assessment for end-organ damage (ventricular hypertrophy, retinopathy, and renal disease) should be done
- Optimize BP control
- AIM for BP control target during pregnancy:
  - <150/100 for uncomplicated HTN
  - <140/90 for HTN with end organ damage.

PRIMARY PREVENTION

NICE (2015) and ACOG (2013) guidelines states:

- Lifestyle modifications
  - Reduce obesity
    - Regular exercise has been hypothesized to prevent preeclampsia by improving vascular function
    - In women who are not pregnant, moderate exercise has been shown to reduce hypertension and cardiovascular diseases
    - Thirty minutes of moderate exercise on most days is currently recommended during normal pregnancy
  - Encourage women to have children at younger age (>18 years)
  - Cessation of smoking
- Nutritional interventions and antioxidant supplementation
  - Do not recommend magnesium, folic acid, antioxidant (vitamin C and E), fish oil or garlic for the purpose of preventing hypertensive disorder in pregnancy
  - A recent Cochrane systematic review (2015) of 15 randomized controlled trials that used vitamin C and vitamin E for the prevention of preeclampsia found no benefit
  - Dietary salt should not be restricted during pregnancy for the prevention of preeclampsia
  - Calcium supplementation (1.5–2 g) may be considered in pregnant women from populations with low baseline calcium intake (<600 mg/dL)
  - Vitamin D deficiency has been suggested as a factor contributing to preeclampsia; however, whether supplementation with vitamin D is helpful, is unknown
  - Protein and calorie restriction for obese pregnant women shows no reduction in the risk of preeclampsia or gestational hypertension and may increase the risk of intrauterine growth restriction and should be avoided
  - It is suggested that bed rest or the restriction of other physical activity not be used for the primary prevention of preeclampsia and its complications.

SECONDARY PREVENTION

Antiplatelet agents:

- Low dose aspirin (81 mg or less), an anti-inflammatory agent blocks the production of thromboxanes and thus inhibits the alterations in systemic prostacyclins-thromboxane balance, which is responsible for preeclampsia
- Advice women with one high risk factor or two or more moderate risk factors to take 75 mg aspirin daily from 12 weeks until the baby is born (NICE).

Do not use the following to prevent hypertensive disorders during pregnancy:

- Nitric oxide donors
- Progesterone
- Diuretics
- Low molecular weight heparin.

MONITORING IN PREGNANCY-INDUCED HYPERTENSION

The basic AIM for HDP include:

- To decrease the maternal and perinatal morbidity and mortality
- To identify at the earliest the complications to avoid major sequelae.

Decision for expectant versus termination depends on:

- Type
- Severity
  - Mild: 140/90–149/99

TABLE 2: Maternal monitoring in gestational hypertension

Degree of hypertension	*Mild*	*Moderate*	*Severe*
Admit	No	No	Yes (until blood pressure is 159/109 mmHg or lower)
Measure blood pressure	Once a week	At least twice/week	At least 4 times/day
Test for proteinuria	At each visit using automated reagent-strip reading device or urinary protein: creatinine ratio	-do-	-do-
Blood test	Routine antenatal tests	CBC (platelet count), LFT, RFT, serum electrolytes Do not carry out further blood tests if no proteinuria at subsequent visits	Test at presentation and then monitor weekly: CBC (Platelet count), LFT, RFT, serum electrolytes
Weight	Weekly	-do-	-do-
Warning signs and symptoms	Evaluated at each visit	-do-	-do-
Treat	No	Yes	Yes

- Moderate: 150/100–159/109
- Severe: >160/100

- Gestational age
- Presence of any complicating features (HELLP, pulmonary edema, eclampsia, etc.).

FETAL MONITORING IN GESTATIONAL HYPERTENSION

Indication for Termination of Pregnancy

- 37 weeks or more of gestation
- Suspected abruption placentae
- 34 weeks or more of gestation, plus any of the following:
  - Progressive labor or ROM (rupture of membranes)
  - Ultrasonographic estimate of fetal weight <5th percentile
  - Oligohydramnios (persistent amniotic fluid index <5 cm).
  - Persistent BPP 6/10 or < (normal 8/10–10/10).

If the patient is in labor, monitor the following every 8 hours to look for abruption placentae:

- Presence of contractions
- Rupture of membranes
- Bleeding per vaginum.

Fetal Monitoring in Preeclampsia

Since it is a known risk factor for perinatal death, it is a common indication for antenatal fetal surveillance.

In the absence of intrauterine growth retardation (IUGR), there are no clear guidelines regarding when to start fetal monitoring.

In the presence of intrauterine growth restriction, the following conditions are vigilantly monitored during expectant management as these are the contraindications for expectant management.

Maternal conditions:

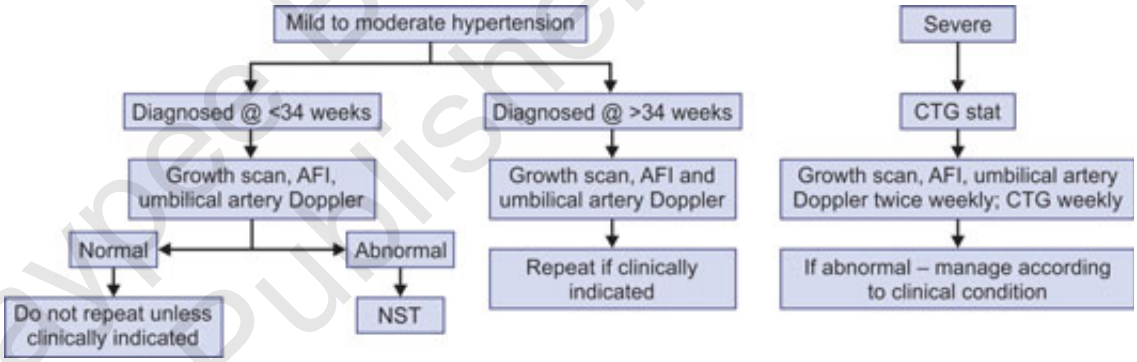
- Recurrent severe hypertension
- Recurrent warning signs of severe PET
- Progressive renal insufficiency (serum creatinine >1.1 mg/dL or doubling serum creatinine levels in the absence of any other renal disease)
- Persistent thrombocytopenia or HELLP syndrome
- Pulmonary edema
- Eclampsia
- Suspected abruptio placenta.

Fetal conditions:

- Severe IUGR (<5th percentile)
- Persistent oligohydramnios (largest vertical pocket <2 cm)
- BPP ≤4/10 on more than 2 occasions 6 hours apart
- Reversed end diastolic flow on umbilical artery Doppler
- Recurrent variable or late decelerations in NST
- Fetal demise.

Intrapartum monitoring:

- During labor, measure blood pressure:
  - Hourly in women with mild or moderate hypertension
  - Continually in women with severe hypertension
- Continue use of antenatal antihypertensive treatment
- Continually monitor fetal heart rate by using electronic CTG
- Do not routinely limit the duration of the second stage of labor:
  - In women with stable mild or moderate hypertension or

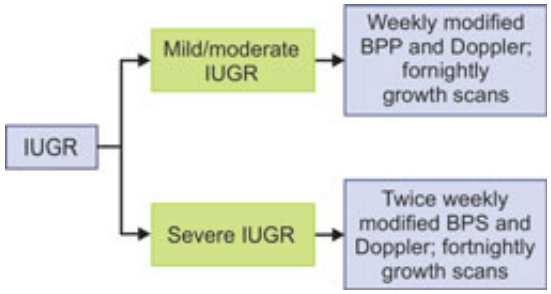


Flowchart 4: Fetal monitoring in gestational hypertension.

TABLE 3: Maternal monitoring in preeclampsia during expectant management

Degree of hypertension	*Mild*	*Moderate*	*Severe*
Admit to hospital	Yes	Yes	Yes
BP monitoring	At least 4 times/day	At least 4 times/day	>4 times/day depends on clinical condition
Input and output charting	Monitor every 8th hour	Monitor every 8th hour	Monitor every 8th hour
Weight monitoring	Once weekly	Once weekly	Once weekly
Warning signs and symptoms*	Reported daily	Reported daily	Reported daily
Blood tests (CBC, LFTs, KFTs)	Repeat twice a week	Repeat thrice a week	Repeat daily*
Test for proteinuria	Do not repeat	Repeat daily	Repeat daily
Treat	No	No	Yes

*Headache, visual changes, retrosternal/epigastric pain, nausea, and vomiting.



IUGR, intrauterine growth retardation; BPP, biophysical profile; BPS, biophysical score.

Flowchart 5: Fetal monitoring in preeclamsia.

TABLE 4: Postpartum follow up of hypertensive disorders in pregnancy

On AHT during ANC period	*Not on AHT during ANC period*
Four times a day as long as she is inpatient	Four times a day as long as she is inpatient
Once daily for 3–5 days after birth	Every 1–2 days up to 2 weeks
On alternate days until BP is normal and she is off the medications	On alternate days until BP is normal

  - If blood pressure is controlled within target ranges in women with severe hypertension
- Offer instrumental delivery in the second stage of labor for women with severe hypertension whose hypertension has not responded to initial treatment
- Do not preload women who have severe preeclampsia with intravenous fluids.

Postpartum monitoring:

- Postnatal review at 2 weeks and at 6–8 weeks after the birth
- Ask women about warning signs and symptoms each time BP is measured
- In patients with chronic hypertension, restart the antihypertensives which the patient was taking in antenatal period
- In breastfeeding, avoid diuretics as antihypertensives.

CONCLUSION

Hypertensive disorders in pregnancy is a significant contributor of maternal morbidity and mortality. ACOG and NICE guidelines at present: (i) does not recommend screening based on biochemical and biophysical markers, and (ii) a detailed and comprehensive history for evaluation of risk factors is the best and only recommended approach. Monitoring of patients with HDP is critical to identify complications so that they can be treated early and sent for prompt referral at appropriate center. Expectant versus termination of pregnancy is the challenging clinical decision to prevent major sequelae depending upon the type, severity, gestational age and presence of any complicating features.

Research: The FMF has designed a new screening strategy based on maternal risk factors, biochemical and biophysical markers which although effective still needs validation by ACOG and NICE.

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12

CHAPTER

Antihypertensive's in Preeclampsia

Hemant Deshpande

INTRODUCTION

Hypertension is the most common medical problem encountered during pregnancy, complicating 10% of all pregnancies. Eclampsia and preeclampsia account for about half of these cases worldwide.

In the 5th century, Hippocrates noted that headaches, convulsions, and drowsiness were ominous signs associated with pregnancy. In 1619, Varandaeus coined the term eclampsia in a treatise on gynecology.

Preeclampsia/eclampsia produces multiple systemic derangements that can involve a diversity of organ systems including hematologic, hepatic, renal, and cardiovascular systems as well as the central nervous system. The severity of these derangements often correlates with maternal medical (e.g., preexisting renal or vascular pathology) or obstetric factors (e.g., multifetal gestations or molar pregnancy).

DEFINITION OF PREECLAMPSIA AND ECLAMPSIA

The clinical manifestations of maternal preeclampsia are hypertension more than 140/90 mmHg after 20 completed weeks of gestation with or without systemic abnormalities involving the kidneys, liver, blood, headache, vomiting and upper abdominal right quadrant pain.

There is also a fetal manifestation of preeclampsia involving fetal growth restriction, reduced amniotic fluid, and abnormal fetal oxygenation, HELLP syndrome is a severe form of preeclampsia and involves hemolytic anemia, elevated liver function tests, and low platelet count.

Antihypertensive treatment should be started in women with a systolic blood pressure (SBP) over 160 mmHg or a diastolic blood pressure (DBP) over 110 mmHg. In women with other markers of potentially severe disease, treatment can be considered at lower degrees of hypertension 140/100 mmHg.

There is continuing debate concerning women with a blood pressure (BP) between 100 mmHg and 110 mmHg diastolic. Maternal treatment is associated with a reduction of severe hypertensive crises and a reduction in the need for further antihypertensive therapy; however, there appears to be a small reduction in infant birth weight. With treatment a prolongation of pregnancy of an average of 15 days is possible as long as there is no other reason to deliver.

CENTRALLY ACTING α_2-ADRENERGIC AGONISTS

Methyldopa is a centrally acting α_2-adrenergic receptor agonist. It inhibits vasoconstriction via a central mechanism by reducing catecholamine release. It decreases central sympathetic outflow, decreasing systemic vascular resistance without decreasing cardiac output. It reduces peripheral vascular resistance and inhibits renin release also.

The side effects of methyldopa include fatigue, depression, poor sleep and decreased salivation. Dose independent adverse effects include elevated liver enzymes in up to 5% of women and some patients can develop a positive antinuclear antigen or antiglobulin (Coombs') test although a clinical hemolytic anemia is rare.

It has been suggested that methyldopa should be avoided in women with a prior history of depression, because of the possible increased risk of postnatal depression.

Methyldopa has a long history of use in pregnancy and does not appear teratogenic. Methyldopa has a record of safety in pregnancy, as established by follow-up studies in the 1980's of children exposed to the drug in utero. More recent studies indicate that in hypertensive pregnancy disorders, treatment with methyldopa does not affect the maternal uterine artery Doppler pulsatility and resistance indices, suggesting that it does not impair uteroplacental circulation and consequent fetal growth.

The doses of methyldopa recommended in pregnancy are similar to those used in nonpregnant patients.

250–500 mg QID—max 2 g

PERIPHERALLY ACTING ADRENERGIC-RECEPTOR ANTAGONISTS

Labetalol a nonselective β-blocking agent with vascular α_1-receptor blocking capabilities is widely used in pregnancy. Fetal growth restriction and low placental weight in patients (with essential hypertension) have been associated with the use of atenolol during the second trimester, but not with labetalol (an α- and β-blocker), which is used frequently for the treatment of severe acute hypertension during pregnancy, and has shown equivalent efficacy and better tolerability compared to hydralazine.

Side effects include fatigue, lethargy, exercise intolerance, sleep disturbance and bronchoconstriction have been reported. Beta-blockers are not associated with teratogenicity.

It has shown neonatal hypoglycemia, fetal hypoxia and in some cases risk of IUGR.

Labetalol

- Oral 100–200 mg BID—max 1200 mg
- Contraindications are asthma, cardiac disease.

According to FDA labetalol is a class C drug. It may be associated with a risk of fetal bradycardia and neonatal hypoglycemia. According to either the WHO and/or Thomson lactation ratings methyldopa is usually compatible with breast milk.

CALCIUM CHANNEL BLOCKERS

Oral nifedipine is frequently seen as second line agents used for the treatment of hypertension in pregnancy. Calcium channel blockers (CCBs) inhibit the influx of calcium ions to vascular smooth muscle, resulting in arterial vasodilation; nifedipine act predominantly on the vasculature improves renal, uterine, cerebral flow.

Side effects of CCB use in the mother include tachycardia, palpitations, peripheral edema, headaches and facial flushing it may cause parotitis if patient develops eclampsia.

According to FDA nifedipine is class C drugs. With all CCBs, there is a risk of interactions with magnesium, resulting in profound hypotension.

- Nifedepine: Orally only (no sublingual use)
- Dose: 30–60 mg/day—max 120 mg.

Vasodilators

Hydralazine is now predominantly used intravenously for the treatment of severe hypertension in pregnancy. Hydralazine selectively relaxes arteriolar smooth muscle.

Adverse effects include headache, nausea, flushing, and palpitations. It does not appear teratogenic. There have been reports of neonatal thrombocytopenia, rare cases of a pyridoxine-responsive polyneuropathy with chronic use, and drug-induced lupus.

However, there is evidence that intravenous labetalol or oral nifedipine are preferable first-line agents compared to intravenous hydralazine in severe hypertension in pregnancy.

Hydralazine is an FDA class C drug. It is usually compatible with breast-feeding.

Nicardipine Hydrochloride Injection, Calcium Ion Influx Inhibitor/Calcium Channel Blocker

- It decreases in systemic vascular resistance. It is metabolized in liver
- This drug should not be used when liver functions are abnormal
- Nicardepine is contraindicated in aortic stenosis.

Nicardipine Half-life 2–5 Minutes

- Starting dose 1–3 mg/h
- Increase by 0.5–1.0 mg/h to maximum 10 mg/h until the target BP is reached.

MANAGEMENT OF HYPERTENSION POSTPARTUM

In the postpartum period, previously normotensive women have been noted to have a rise in BP, which reaches a maximum on the 5th postpartum day, and in one study 12% of patients had a DBP exceeding 100 mmHg. This is thought to be a consequence of physiological volume expansion and fluid mobilization

TABLE 1: Antihypertensive agents in acute hypertension

Drug	*Mechanism of action*	*Dosage*	*Result*
Hydralazine hydrochloride	Arterial vasodilator	5 mg IV, then 5–10 mg IV/20 min	Must wait 20 minutes for response between IV doses; possible maternal hypotension
Labetalol	Selective alpha- and nonselective beta-antagoist	20 mg IV, then 40–80 mg IV/10 min to 300 mg total dose; IV infusion 1–2 mg/min, titrated	Less reflex tachycardia and hypotension than with hydralazine
Nifedipine	Calcium channel blocker	10 mg by mouth, may repeat after 30 minutes	Oral route only; possible exaggerated effect if used with $MgSO_4$
Nitroglycerin	Relaxation of venous (and arterial) vascular smooth muscle	5 µg/min infusion, double every 5 minutes	Requires arterial line for continuous BP monitoring; potential methemoglobinemia
Sodium nitroprusside	Vasodilator	0.25 µg/kg/min infusion; increase 0.25 µg/kg/min/5 minutes	Requires arterial line for continuous BP monitoring; potential cyanide toxicity

in the postpartum period. The natural history of gestational hypertension and preeclampsia in the postpartum period BP is normalized but in general the agents commonly used in the antepartum period may be continued postpartum till BP returns to normal, however doses requirement may reduce.

ANTIHYPERTENSIVE USE IN BREASTFEEDING

There are no well-designed studies assessing neonatal effects of maternally administered antihypertensive drugs delivered via breast milk. The pharmacokinetic principles that govern drug distribution to milk and ensuing exposure to the infant are well established.

Milk, secreted by alveolar cells, is a suspension of fat globules in a protein-containing aqueous solution with a pH lower than that of maternal plasma.

Factors that favor drug passage into milk are a small maternal volume of distribution, low plasma protein binding, high lipid solubility, and lack of charge at physiological pH. Even when drugs are ingested by nursing infants, exposure depends on volume ingested, intervals between drug administration and nursing, oral bioavailability, and the capacity of the infant to clear the drug. Neonatal exposure to methyldopa via nursing is likely low, and it is generally considered safe.

CONCLUSION

Current recommendations for treatment of most pregnant hypertensive women of 140–150 mmHg systolic, and/or 95–100 mmHg diastolic to prevent worsening hypertension in the mother. Acceptable agents include methyldopa, labetalol, and nifedipine in standard doses.

Control of severe hypertension has been studied in a recent meta-analysis, and this suggests that intravenous labetalol or oral nifedipine is as effective as intravenous hydralazine, with fewer adverse effects.

Many research questions surrounding hypertension in pregnancy and preeclampsia remain unanswered.

13

CHAPTER

Cardiomyopathy and Pregnancy

Pratima Mittal, Jyotsna Suri

INTRODUCTION

Cardiovascular diseases are seen in about 0.5–4% of all pregnant women and are a significant cause of maternal mortality. Cardiac diseases in pregnancy comprise of rheumatic heart disease (RHD), congenital heart disease (CHD), ischemic heart disease and cardiomyopathy.

Cardiomyopathy is defined as "a myocardial disorder in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular disease and CHD sufficient to explain the observed myocardial abnormality." The cardimyopathies are classified as – dilated cardiomyopathy, restrictive cardiomyopathy, hypertrophic cardiomyopathy and unclassified cardiomyopathy.

In young women of childbearing age the most common causes of cardiomyopathy is prior viral infection, HIV infection, drug-induced cardiomyopathy (e.g., cocaine, doxorubicin) and peripartum cardiomyopathy (PPCM).

Since peripartum cardiomyopathy is a condition unique to pregnancy and the other types of cardiomyopathy are uncommon in pregnant women, the rest of the chapter will focus on peripartum cardiomyopathy.

WHAT IS PERIPARTUM CARDIOMYOPATHY?

The 2010 European Society of Cardiology (ESC) working group defined peripartum cardiomyopathy (PPCM) as an idiopathic cardiomyopathy with the following characteristics:

1. Development of heart failure toward the end of pregnancy or within 5 months following delivery.
2. Absence of another identifiable cause for the heart failure.
3. Left ventricular (LV) systolic dysfunction with an LV ejection fraction (LVEF) of <45%. The LV may or may not be dilated.

ETIOLOGY OF PERIPARTUM CARDIOMYOPATHY

The etiology of PPCM is thought to be multifactorial including angiogenic imbalance, altered prolactin processing, genetic, inflammatory, hormonal, hemodynamic, and autoimmune factors.

Recent research on mice models suggests that altered prolactin processing may be central to the pathogenesis of PPCM. An abnormal signally leads to increased cleavage of prolactin into an antiangiogenic and proapoptotic 16 kDa isoform by cathepsin D. The 16 kDa prolactin fragment (16K PRL) also causes endothelial damage and myocardial dysfunction. Endothelial damage may also be a result of defects in the regulation of proangiogenic factors such as VEGF. This common pathogenetic pathway of PPCM and preeclampsia i.e., endothelial dysfunction, can explain the association of the two conditions.

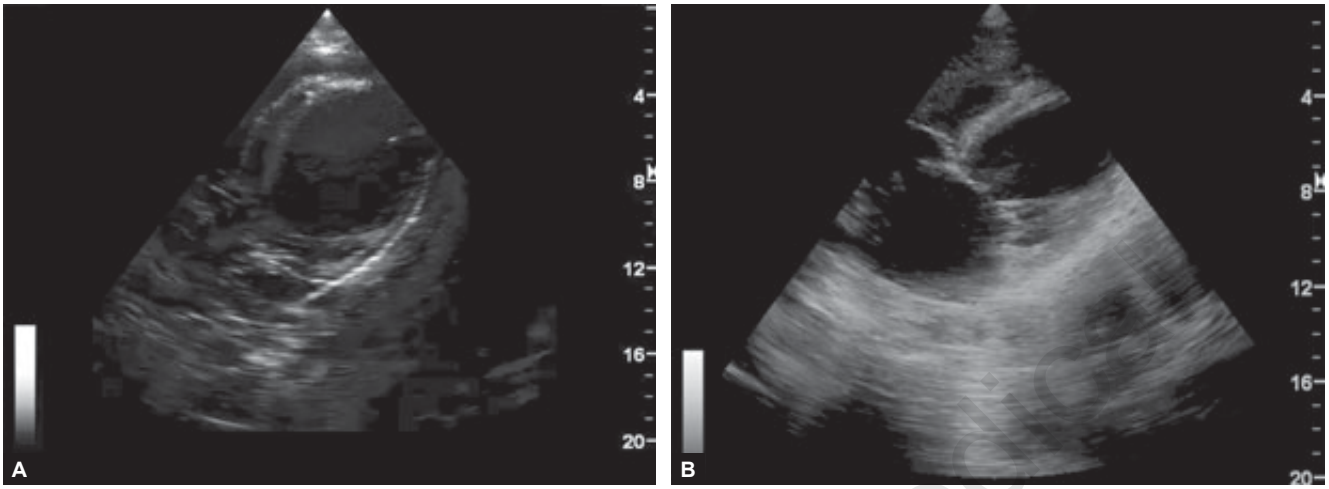
Inflammatory cytokines, tumor necrosis factor (TNF)-alpha and interleukin-6 may also be instrumental in the pathogenesis and progression of cardiomyopathy and heart failure. Genetic factors may also play an important role in the causation of PPCM. It is postulated that pregnancy associated factors like endothelial dysfunction can result in PPCM in women who are genetically susceptible. A familial clustering of PPCM and dilated cardiomyopathy gives concurrence to this hypothesis.

RISK FACTORS FOR PERIPARTUM CARDIOMYOPATHY

Various risk factors have been identified for the development of PPCM. Older women more than 30 years, African descent, multiple pregnancy, preeclampsia/gestational hypertension, long term tocolytic therapy with β2 agonists (terbutaline) and cocaine abuse are some of the important risk factors.

CLINICAL PRESENTATION

The patient typically presents in the later part of pregnancy or in the weeks after delivery with history of shortness of breath of a few days duration (Fig. 1). The presentation differs from that of RHD and CHD as these conditions present much earlier in pregnancy because of the physiological effects of pregnancy on the cardiovascular system (Table 1). The symptoms of any



21 - year -old primigravida, full term normal vaginal delivery, uneventful; discharged home in stable condition. Presented after 2 weeks with complaints of exertional breathlessness, easy fatiguability and bilateral swelling feet. O/E- Afebrile, Pulse – 146/min, RR – 36/min, BP –96/60 mmHg, Spo 2–82% on room air JVP raised, bilateral pitting pedal edema, Chest – Bilateral end inspiratory crepts her ECHO revealed gross LV dilation and poor contractility (LVEF = 25%).

Figure 1: Echocardiography finding of a case with peripartum cardiomyopathy.

TABLE 1: Physiological and Anatomical changes in the cardiovascular system in pregnancy

Parameter	*Change*	*Antenatal period*	*Labor*	*Postpartum*
Plasma volume	Increase 50%	Increases from 6 weeks, peaks 30–32 weeks	Remains same	There is fall due to blood loss
Stroke volume	Increase 20%	Increases from early pregnancy Peaks at 20 weeks, gradually falls	During straining in 2nd stage (Valsalva) there is a fall	Normal in 6 weeks
Heart rate	Increase 15–20 bpm	Rise more in 2nd half	Further rise seen	Prelabor level by 1 hour; normal in 6–12 weeks
Arterial blood pressure*	Decrease 10–15%	Declines by 5–10 mmHg in 2nd T, normal values in 3rd T	Rise by 10-25 % during contractions.	Normal values
Cardiac output**	Increase 40%	Increases from 8 weeks, peaks at 32 weeks	Further increase by 25- 50%	Immediate postpartum rise by 80%**; prelabor level in 1 hour; normal by 6–12 weeks
Uterine blood flow	~ 10% of cardiac output at term	–	–	–
Cardiac anatomy	Heart rotated cephalad and to the left, Increase chamber size, particularly the left atrium	–	–	–

*The reduction in blood pressure in pregnancy is predominantly secondary to a decrease in the diastolic component which in turn is due to reduction in systemic vascular resistance because of progesterone, and the development of the placenta, a low resistance vascular bed.

** The increased cardiac output that develops in pregnancy is further augmented during the third stage of labor as a result of autotransfusion of blood from the uteroplacental to maternal circulation as the uterus contracts.

heart disease in pregnancy may be masked because of these physiological changes which can lead to fatigue, breathlessness and edema even in a normal gravida (Table 2). Hence it is important for the clinician to keep a high index of suspicion when the patient presents with such symptoms so that the diagnosis of any pathological heart condition is not delayed.

The other presenting symptoms may be cough, orthopnea, hemoptysis and paroxysmal nocturnal dyspnea. Some patients may present acutely with systemic or pulmonary thromboembolism as patients with PPCM are prone to thrombus formation in the left ventricle.

TABLE 2: Signs and symptoms of normal pregnancy which can mimic heart disease

Signs and symptoms • Peripheral edema • Jugular venous dilatation • Reduced exercise tolerance • Dyspnea	**Chest X-ray** • Change in heart position and size • Increased vascular markings
Auscultation • S3 gallop • Systolic ejection murmur	**ECG** • Nonspecific ST-T wave changes • Axis deviation • Mild left ventricular hypertrophy

Physical signs which can be seen in PPCM are a raised jugular venous pressure, a displaced apical impulse, a third heart sound, and a murmur of mitral regurgitation.

DIAGNOSIS

The diagnosis of PPCM requires the presence of the three clinical criteria namely development of heart failure toward the end of pregnancy or within 5 months following delivery; absence of another identifiable cause for the heart failure and left ventricular systolic dysfunction with an LVEF of <45%. The LV may or may not be dilated. The most essential investigation to make the diagnosis is hence echocardiography.

Echocardiography

The findings on echo which are generally seen in PPCM are a global reduction in LV function with a LVEF <45%. Other possible echocardiographic findings include left atrial enlargement, LV or left atrial thrombus, dilated right ventricle, right ventricular hypokinesis, mitral and tricuspid regurgitation, and rarely pericardial effusion (Fig. 1).

Echocardiogram

Sinus tachycardia and nonspecific ST and T wave changes may be seen.

Chest X-ray

The cardiac silhouette may be enlarged. There may be features of pulmonary congestion.

Brain Natriuretic Peptide

The brain natriuretic peptide (BNP) or the pro-BNP is significantly elevated and is considered to be a very sensitive marker for heart failure.

DIFFERENTIAL DIAGNOSIS

The PPCM may be confused with normal physiological changes of pregnancy as mentioned above and vice versa. The other important differential diagnosis are preexisting dilated (idiopathic or familial) cardiomyopathy, myopathy due to HIV/AIDS, valvular disorders leading to heart failure such as stenotic or regurgitant lesions of the aortic and mitral valve. However as discussed above, most of these conditions will present earlier in the antenatal period, rather than in the last month of pregnancy or the postnatal period.

MANAGEMENT

The management of PPCM aims at: treating heart failure; arrhythmia management; antithrombotic therapy; mechanical treatment; and experimental therapy like bromocriptine.

Heart Failure

The goals of treatment for heart failure in PPCM are same as for any other heart disease, i.e., relief of symptoms; good oxygenation; optimization of preload; support with ionotropes/vasopressors if required; and chronic long therapies when indicated.

In the nonpregnant patient Angiotensin-converting enzyme (ACE) inhibitors and Angiotensin II receptor blockers (ARBs) are the mainstay of treatment for cardiomyopathy. However, these drugs are category D and hence are not recommended during pregnancy in any trimester and also during lactation. This group of drugs can be replaced by hydralazine (Cat. C) or amlodipine (category C) both being effective vasodilators.

The other drugs which are often used to treat heart failure in PPCM are beta blockers and loop diuretics (both category C). In case PPCM is accompanied by preeclampsia/gestational HT as is often the case, labetolol can be considered. However in decompensated heart failure in the setting of hypertension, nitroglycerine is the drug of choice.

Digoxin is also a Category C drug and can be used in situations where the heart failure does not respond to beta blockers and vasodialators. Digoxin is also used for treatment of maternal tachycardia and atrial fibrillation.

Anticoagulants

Women with PPCM who have a LVEF <35% are prone to thromboembolism. Any patient with ventricular thrombus or atrial fibrillation should be anticoagulated with either unfractionated heparin or low molecular weight heparin. Both are category C drugs and do not cross the placenta. Warfarin is category D and is avoided in the last month of pregnancy; however it is safe during lactation.

Antiarrhythmic Therapy

The insertion of implantable cardioverter defibrillator (ICD) is indicated in some patients who need long term antiarrhythmic therapy, such as the cases whose heart function does not recover even after 6 months of delivery.

Role of Bromocriptine in PPCM

Bromocriptine has an investigational role in the management of PPCM and is not recommended for clinical use as there is lack of good quality evidence favoring its use. However, preliminary evidence is encouraging. A randomized study conducted on 20 African women with PPCM in which 10 were given bromocriptine (2.5 mg twice daily for 2 weeks followed by 2.5 mg daily for 2 weeks) along with standard care whereas 10 were given only standard care found a significant decrease in 6-month mortality and complication rate in the bromocriptine group. Larger well designed trials are required before this can be regularly prescribed in PPCM. Of note is the fact that bromocriptine is known to increase thrombogenic events, and hence should be given along with anticoagulants.

Mechanical Support

Mechanical circulatory support devices are considered in patients with hemodynamic instability and those who are unresponsive to medical therapy with the maximal ionotrope dose. When mechanical circulatory support is required, the

devices that can be used are the intra-aortic balloon counter pulsation, venoarterial extracorporeal membrane oxygenation, and LV assist device.

Cardiac Transplant

This is the ultimate treatment for patients with severe heart failure not responding to any other therapy. World literature shows that the cardiac transplant rate in PPCM varies from 4–23%.

TIMING OF DELIVERY

The decision for delivery is to be taken on case to case basis, considering the obstetric factors, gestational age, cervical status and severity of heart failure. The 2010 ESC working group statement advised that early delivery is not required if the maternal and fetal conditions are stable.

In women with PPCM with advanced heart failure, prompt delivery is indicated for improving maternal cardiovascular status. Planned cesarean delivery is preferred for women with advanced heart failure requiring inotropic therapy or mechanical circulatory support. Women who have stable disease should have cesarean section only for obstetric indications.

LACTATION

With prolactin as an incriminating factor in the pathogenesis of PPCM, it has been postulated by some that lactation may worsen the maternal heart failure. However, there is no evidence for this and one study on 55 patients found that there was no poor outcome in any of the woman who chose to breastfeed her infant. Hence, breastfeeding may be allowed in these patients especially considering its overall benefits.

Levels of ACE inhibitors in breast milk are low and are not expected to cause adverse effects in breastfed infants. The ACE inhibitors like enalapril, quinapril, benzepril and captopril are preferred as they are the most studied drugs in this setting. However caution should be exercised in preterm infants, especially in the first few weeks after delivery where ACE inhibitors may cause neonatal hypotension.

CONTRACEPTION

The patient of PPCM should be counseled about the risk of recurrence in next pregnancy. Effective contraception is hence very important. Sterilization of patient/partner, IUCD and etonogestrel implants are the best options.

PROGNOSIS

Maternal

Complete recovery of the LVEF has been reported in up to 60% patients of PPCM within 6 months of delivery. The recovery rate in other forms of dilated cardiomyopathy is lower. The factors which are predictive of delayed recovery or mortality are:

- NYHA functional class 3/4
- LVEF <25%
- Black race
- Multiparity
- Age >35 years.

The mortality rate in PPCM is around 10% in 2 years.

Fetal

The rate of preterm birth and small for gestational age babies is higher in PPCM as compared to normal pregnancy.

Future Pregnancy

The risk of recurrence and death is higher in women who have not made full recovery and whose LVEF remains <50% on follow up. Even those who make complete recovery may have a recurrence in pregnancy but with lower mortality rates. However all patients of PPCM should be counseled about this and future pregnancy should be avoided.

CONCLUSION

Peripartum cardiomyopathy is defined as the development of systolic heart failure toward the end of pregnancy or in the months following pregnancy with LVEF <45% in the absence of another identifiable cause of heart failure. The etiology of PPCM is not well elucidated. The possible causes are angiogenic imbalance, altered prolactin processing, genetic, inflammatory, hormonal, hemodynamic, and autoimmune factors. The risk factors for PPCM are older age, multiple gestation, African descent, and a history of preeclampsia/eclampsia/postpartum hypertension. The management of heart failure due to peripartum cardiomyopathy is similar to that due to other causes which may occur during pregnancy. The role of bromocriptine in PPCM is controversial. While preliminary data have suggested a benefit from bromocriptine in patients with PPCM, further trials are needed to establish safety and efficacy and hence it should not be used outside of clinical trials. The timing and mode of delivery in PPCM is made depending on the obstetric factors, severity of heart failure, cervical favorability and fetal condition. Multidisciplinary team involving cardiology, obstetrics, anesthesiology, and neonatology services are required for optimum patient management. Prompt delivery is indicated in women with PPCM with advanced heart failure.

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CHAPTER

Pregnancy with Valvular Heart Diseases

Indrani Roy

INTRODUCTION

Heart disease is one of the most common medical disorders of pregnancy and complicates 1–4% of pregnancy in healthy women. Valvular heart disease (VHD) accounts for approximately a quarter of the cardiac disease complicating pregnancy and is an important cause of maternal mortality, posing challenges in management. VHD in pregnant women, whether due to congenital or acquired etiologies, poses a challenge to clinicians and their patients. VHD due to rheumatic heart disease (RHD) has declined, but it remains a prevalent cause of maternal cardiovascular morbidity and mortality in the developing countries. In India, RHD contributes to approximately 69% of cardiac disorders in pregnancy. Given the complexity of VHD in pregnancy, women with congenital and acquired heart disease should be managed with a multidisciplinary approach before and throughout pregnancy.

HEMODYNAMICS IN PREGNANCY

This is associated significant hemodynamic changes in pregnancy which aggravates VHD and increase the risk of thromboembolic events.

The first trimester is characterized by increased cardiac output brought about by increased heart rate and stroke volume induced by onset of an expanded intravascular volume. Human chorionic gonadotrophin, which has some thyroid stimulating factor homology and activity also contributes to rise in cardiac output.

In the second trimester the volume expansion continues and peripheral vasodilation dominates the pregnancy adaptation, leading to a fall in blood pressure. Early in the third trimester, the volume expansion peaks and vascular resistance rises.

Major Cardiovascular Changes in Pregnancy

- Higher cardiac output from 4.5 L/min at the 12th week to 6.8 L/min at 32 weeks (increase of 40–50%)
- Cardiac output is lowest in the sitting or supine position and highest in the right or left lateral or knee chest position
- Systemic vascular resistance (SVR) decrease (–21%) due to smooth muscle relaxing effect of progesterone, NO, prostaglandin (Fig. 1).

Changes in Labor and Delivery

During labor and delivery, maternal hemodynamics are influenced by an array of factors including response to pain, method of delivery and analysis. Cardiac output increases up to 30% in the first stage of labor and up to 80% in the immediate postpartum period. The increase in cardiac output is driven by increased stroke volume, which remains elevated up to 24 hours postpartum. With each uterine contractions, 300–500 mL of blood is "autotransfused" from the placenta to the systemic circulation. Similarly, systolic and diastolic blood pressure increase with each uterine contraction. Epidural and spinal analgesia may result in transient hypotension related to systemic vasodilation. Alterations in maternal hemodynamics change dramatically in the first 24 hours postpartum.

Preload increases with relief of inferior vena cava compression by the uterus, however blood loss can also be significant. Although blood loss is expected with both vaginal and cesarean delivery, shifts in maternal hemodynamics peak within 24–72 hours after delivery. Thus, it is within this period that women are at increased risk for symptomatic heart failure due to underlying valvular disease or ventricular dysfunction. Lastly, pregnancy creates a hypercoagulable state. The risk of thrombosis peaks during the postpartum period. It is highest within the first 6 weeks postpartum but increased risk persist up to 12 weeks after delivery. Meticulous management of anticoagulation in women with prosthetic valve is required during this period given the high risk of thrombosis (Tables 1 and 2).

Risk Stratification

Preconceptual counseling and risk stratification of women with VHD is ideal and recommended based on current guidelines (Box 1). The WHO classification divides women with congenital and acquired heart disease into four classes, ranging from low to high risk (Table 3).

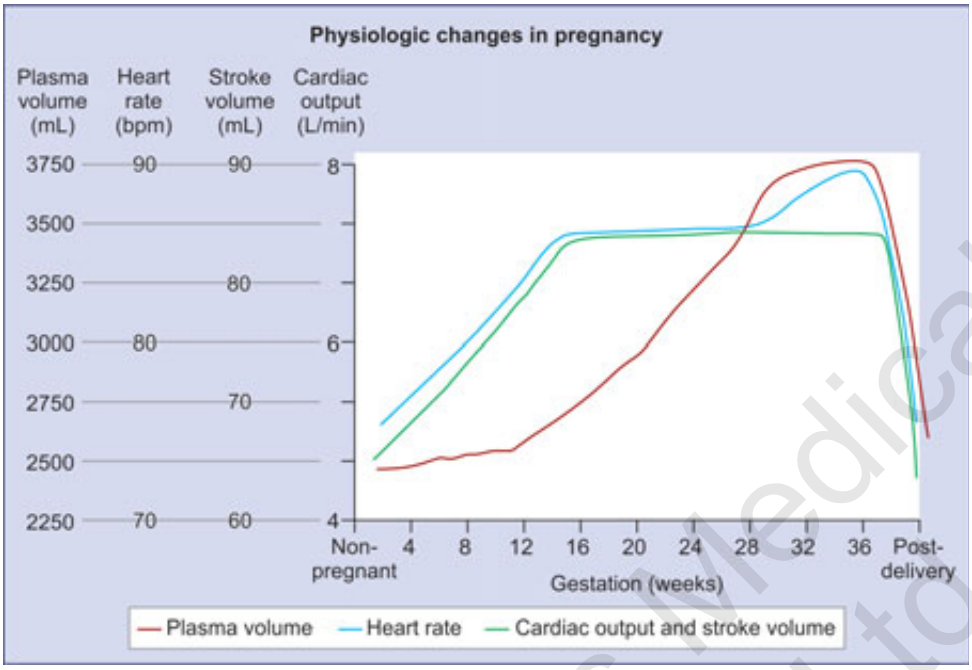

Figure 1: Normal physiological changes in pregnancy.

TABLE 1: Normal physiological changes in labor and delivery

Parameters	*Change*	*Comments*
Blood volume	Increase	300–500 mL
Cardiac output	Increase	30–60%
Heart rate	Increase	
Blood pressure	Increase	SBP/DBP
Peripheral resistance	Unchanged	
O_2 consumption	Increase	100% increase

TABLE 2: Normal physiological changes in postpartum

Parameters	*Change*	*Comments*
Blood volume	Decrease	Blood loss
Cardiac output	Increase	60–80% immediate increase followed by rapid decrease, returns to normal levels after few weeks
Stroke volume	Increase	
Heart rate	Decrease	
Blood pressure	Unchanged	
SVR	Increase	Loss of low resistance

BOX 1 **Preconception evaluation in any women with valvular heart disease planning a pregnancy or assessment in early pregnancy**

- Careful history, family history, and physical examination, including screening for connective tissue disorders
- 12-lead electrocardiogram
- Echocardiogram including assessment of left- and right-ventricular and valve function
- Exercise test to be considered for objective assessment of functional classification
- Careful counseling including maternal risks for complications and mortality, information on choices of therapy (heparin vs. vitamin K), risk of miscarriage, and small for gestational age, and when applicable, risk of fetal congenital defect (inheritance risk).

TABLE 3: Risk classification

Risk class I	In this class, there is a slight increase in the maternal morbidity but there is no increase in maternal mortality
Risk class II	There is a moderate increase in morbidity and also a small increase in maternal mortality
Risk class III	Associated with severe increase in morbidity and significant increase in maternal mortality. In case patients decide upon pregnancy, multidisciplinary approach together with obstetrician and cardiologist required all throughout pregnancy and puerperium
Risk class IV	Both morbidity and maternal mortality extremely increases, hence pregnancy is contraindicated. Also if pregnancy occurs, termination option should be discussed and in case pregnancy continues, extreme caution is required

STENOTIC LESIONS

Mitral Stenosis

It is the most commonly encountered valvular lesion in pregnancy and is caused in almost all cases by RHD.

Given the risk to mother and fetus, women with moderate or severe mitral stenosis should be counseled to undergo vulvular intervention prior to pregnancy when the diagnosis is known prior to conception.

Percutaneous balloon valvuloplasty should be considered in selected patients to obviate the complications of either pros-

thetic or mechanical valve replacement. Given the tachycardia and volume load of pregnancy, women asymptomatic prior to pregnancy may develop heart failure, particularly in the second and third trimester. Heart rate control is essential to help mitigate symptoms. Heart failure should be treated with β1-selective blockers and diuretic therapy when needed for volume overload, with care to avoid over diuresis. Therapeutic anticoagulation is a must in this high risk group of women due to increased risk of thromboembolic events.

Percutaneous mitral valvuloplasty is an option for women refractory to optimal medical therapy, ideally performed after 20 weeks of gestation. As there is increased incidence of fetal demise following maternal cardiopulmonary bypass, maternal cardiac surgery should be performed only when other treatment strategies have been ineffective at stabilizing the mother.

Fetal risks are also high, with maternal mitral stenosis increasing the risk of fetal prematurity (20–30%), intrauterine growth retardation (5–20%) and still birth (1–3%). Most women can be management conservatively and delivered vaginally, but planned cesarean section may be considered in women with severe disease with NHYA class III or IV symptoms, with pulmonary hypertension that persists despite optimal medical and surgical therapy.

AORTIC STENOSIS

Congenital bicuspid aortic valve (BAV) disease is the primary cause of aortic stenosis (AS) in pregnancy though it is a rare condition. When diagnosis is made prior to conception, proper counseling optimization of maternal care, and planning of antenatal care is required transthoracic echocardiogram should be performed for quantification of AS, severity and measurement of aortic diameter. Exercise testing is recommended in asymptomatic patients to confirm asymptomatic status and evaluate exercise tolerance, blood pressure response, arrhythmias, and need for intervention. Features that predict a favorable outcome during pregnancy include absent symptoms, normal ECG, normal exertional blood pressure rise, aortic valve ≥1 cm^2 and normal left ventricular (LV) function.

Pregnancy is usually well tolerated in asymptomatic AS, even when severe, as long as the patient remains asymptomatic during exercise testing and has a normal blood pressure response during exercise. Pregnancy should not be discouraged in asymptomatic patients even with severe AS, when LV size and function as well as the exercise test result are normal.

Cardiac deterioration due to AS may be indicated by worsening breathlessness, syncope, chest pain, deterioration in left ventricular ejection fraction, and/or ischemic ECG changes.

Symptomatic patients with severe AS or asymptomatic patients with impaired LV function or a pathological exercise test should be counseled against pregnancy and valvuloplasty is indicated prior to conception.

Women with AS are at increased risk of heart failure (10%), arrhythmias (up to 25%) and increased risk of preterm delivery, intrauterine growth retardation, and low birth weight. Atrial fibrillation (AF) is to be treated with β-blockers, calcium channel antagonists, or digoxin when necessary. For women refractory to medical therapy, percutaneous balloon valvuloplasty remains an option in the absence of significant calcification or regurgitation and should be performed as late as possible in pregnancy and with measures to reduce fetal radiation exposure. Most women will be able to delivery vaginally, assisted second stage to be considered to shorten the duration of labor. Cesarean delivery should be reserved for obstetric indications in all but the most critically ill women.

PULMONIC STENOSIS

Congenital pulmonary stenosis (PS) is the most common cause of right ventricular outflow tract obstruction in pregnant women.

Patients asymptomatic prior to pregnancy, are likely to tolerate well in pregnancy. Symptomatic women with favorable valve anatomy and without significant pulmonary regurgitation, balloon valvuloplasty may be performed with adequate fetal shielding. Evidence shows increased incidence of preeclampsia and other hypertensive disorders in women with PS, though association is not well understood.

REGURGITANT LESIONS

Regurgitant lesions are better tolerated than stenotic as a result of the decrease in systematic vascular resistance during pregnancy. Rheumatic disease accounts for a large proportion of women with mitral regurgitation in pregnancy, with mitral valve prolapse representing another common etiology.

Common etiologies of aortic regurgitation include BAV, rheumatic disease, endocarditis or aortic annular dilation. With preserved LV function, women with significant regurgitation usually tolerate pregnancy well, though they are at increased risk for the development of arrhythmias. Women with severe regurgitation with LV dysfunction or heart failure are at increased risk for adverse cardiovascular events during pregnancy, and thus women who require repair or replacement should be intervened upon prior to conception.

In patients with moderate to severe regurgitant lesions, symptomatic volume overload may occur during the second and third trimester and during the first 24–72 hours after delivery as cardiac output peaks. Diuretics can be administered, and after load reduction can be initiated with hydralazine and nitrates during pregnancy or enalapril postpartum.

Postpartum, women with regurgitant lesions may be at increased risk for development of heart failure in the content of a normalization of systematic vascular resistance in the face of a continued volume load as compared to the pre pregnancy state, and thus women should be followed closely, and treated with diuretic therapy if needed. As with other cardiac surgical procedures, surgical valve replacement should be avoided in pregnancy because of the high risk of fetal loss with cardiopulmonary bypass.

ANTENATAL MANAGEMENT

Recommendations are serial imaging with echocardiography in addition to close clinical monitoring. Echocardiography, once per trimester is sufficient with the third trimester

echocardiography performed around 32 weeks' gestation at the time of peak hemodynamic load.

Medical management for heart failures related to increased valvular gradients includes up-titration of nodal blocking agents, which may improve valvular gradients via reduction in heart rate. Metoprolol, propranolol, and diltiazem are safe to use for nodal blockade during pregnancy. Diuretics such as furosemide may be used to decrease pulmonary venous congestion, but care should be given to avoid over diuresis.

Aortic or mitral valvuloplasty can also be considered in severely symptomatic patients who are refractory to medical management and with favorable anatomy. If surgical intervention is required during pregnancy, intervention during the second trimester, after organogenesis is completed is recommended to maximize fetal outcomes.

LABOR AND DELIVERY

Multidisciplinary planning is important approach for delivery in women with valvular disease. Regurgitant lesions are usually better tolerated as compared to stenotic lesions. Recommendations are early use of epidural anesthesia with slow up-titration in dosage to achieve adequate analgesia. Intravenous fluids should be used to maintain euvolemia.

Women with mild symptoms and good functional status should be allowed to go into spontaneous labor and vaginal delivery is to be planned, with consideration of an assisted second stage of labor.

In highly symptomatic patients, planned cesarean section with assistance of a cardiac anesthesiologist may be required (Table 4).

CONTRACEPTION

Combined hormonal method of contraception that contains estrogen, including the patch, the pill and the vaginal ring should generally be avoided by women with mechanical valves or AF or flutter. These methods are associated with increased risk of thrombosis. Long acting, reversible methods of contraception, such as the hormonal or copper intrauterine device or etonogestrel subcutaneous implant, offer highly effective (1 year failure rate <1%) and safe protection against unintended pregnancy for all cardiac patients.

PREGNANCY IN WOMEN WITH PROSTHETIC HEART VALVES

A large number of prosthetic heart valves (PHVs) have been developed and are implanted worldwide, many in women of child-bearing age. The two major groups of artificial heart valves, bioprosthesis/tissue valves and mechanical valvular prosthesis have different risk/benefit profiles with regard to need for anticoagulation, valve hemodynamics, incidence of thrombotic events, durability and impact of fetal outcome. Women should be extensively counseled on the risks and benefits during pregnancy of each type of valve, and that prosthetic valves increase the risk of cardiovascular complication.

BIOPROSTHETIC VALVES

Although bioprosthetic valves do not require anticoagulation and have low risk of thrombosis, women should be aware that they have a higher rate of structural valve deterioration

TABLE 4: Type of lesion and severity and associated risk

Type of lesion	*Maternal risk*	*Fetal risk*	*Intervention*	*Delivery*
Mitral stenosis	Mild cases—low risk Moderate cases—up to 3% mortality	Intrauterine growth retardation (5–20%), prematurity (20–30%), stillbirth (1–3%)	Patients to be counseled before pregnancy In pregnancy—medical management/percutaneous mitral commissurotomy	Mild cases—vaginal delivery Moderate to severe cases—cesarean delivery
Aortic stenosis	Heart failure in 10%, arrythmias in 3–25%	Preterm, IUGR, low birth weight up to 25%	Severe AS—counseled against pregnancy, or intervention first followed by pregnancy. Percutaneous valvuloplasty in severely symptomatic patients	Mild to moderate cases—vaginal delivery. Severe cases —cesarean delivery
Mitral regurgitation	Severe cases—risk of heart failure and arrhythmias	No increase in fetal complication	Prepregnancy—surgery Pregnancy—conservative Postdelivery—surgery for intractable heart failure	Vaginal delivery, epidural anesthesia and cut short second stage of labor
Aortic regurgitation	Severe cases risk of heart failure and arrhythmias	No increase in fetal complication	Prepregnancy—surgery Pregnancy—conservative Postdelivery—surgery for intractable heart failure	Vaginal delivery, epidural anesthesia and cut short second stage of labor
Tricuspid regurgitation	Severe cases risk of heart failure	No increase in fetal complication	Prepregnancy—tricuspid valve repair Pregnancy—conservative management	Vaginal delivery

irrespective of pregnancy than do mechanical valves. Thus the decision to place a bioprosthesis in any young patient requires counseling that they require a repeat valve replacement in their lifetime as well as careful periodic monitoring of their valve function.

MECHANICAL VALVES

Mechanical prosthesis have a longer durability than bioprosthetic valves, which renders them the preference in young women who do not wish to become pregnant, but pose a significant challenge regarding management in pregnancy mainly because of their high thrombogenic nature which necessitates uninterrupted anticoagulation (Box 2).

INFECTIVE ENDOCARDITIS PROPHYLAXIS

Risk factors for development of infective endocarditis include valve disease (rheumatic), commonest pathogen being streptococcus viridans. The most commonly involved valve is the mitral valve, followed by aortic and tricuspid valves.

BOX 2 Anticoagulation for women with mechanical valves during pregnancy

Preconception

- Discuss with the patient an anticoagulation strategy for pregnancy including a thorough discussion of the risks/benefits of each strategy and arrive at a preformed plan individualized based on patient preference and risk profile
- Counsel patient to monitor for pregnancy by tracking menstrual cycles and frequent pregnancy tests and contact her cardiologist as soon as pregnancy is known.

Pregnancy: Conception to 12 weeks

- If the warfarin dose is <5 mg, it may be continued
- If the warfarin dose is ≥5 mg or if the patient prefers to avoid warfarin altogether during pregnancy, switch to weight-based LMWH BID and adjust dose based on weekly peak/trough monitoring for goal peak anti-Xa levels of 0.6–1.2 IU/mL 4 hours post-dose. If trough levels are <0.6 IU/mL with therapeutic peaks, dose TID.

Pregnancy: Week 13–35

- All patients can be switched to warfarin.
- For patients who prefer to avoid warfarin during pregnancy, LMWH can be continued with careful weekly monitoring as above.

Pregnancy: Week 36

- Switch patients on warfarin to LMWH or IV UFH. LMWH should be monitored weekly, with a goal peak anti-Xa level of 0.7–1.2 IU/mL 4 hours post dose. If trough levels are <0.6 IU/mL with therapeutic peak, dose TID.

Labor and postpartum

- 36 hours prior to induction or cesarean delivery, all patients should be switched to IV UFH
- 6 hours prior to delivery, IV UFH should be stopped
- Restart IV UFH 4–6 hours after delivery (provided the risk of bleeding is not prohibitive from an obstetric perspective)
- Once safe to start long term anticoagulation from bleeding perspective, bridge with LMWH or IV UFH to warfarin with careful INR monitoring postpartum, especially in breastfeeding patients.

Infective endocarditis is a life-threatening condition; hence intravenous antibiotics, close surveillance and anticipation of valve surgery are mandated. Antibiotics prophylaxis is reasonable during vaginal delivery at the time of membrane rupture in women with prosthetic cardiac valves, presence of prosthetic material used for valve repair.

CONCLUSION

Valvular heart disease in pregnancy is a common cause of adverse complication for both mother and baby. While RHD has become relatively rare in developed countries, it is still quite common in developing countries and is an important cause of VHD. Recommendations are an integrated risk stratification scheme for pregnant patients with VHD, WHO classification and an algorithmic approach to preconception counseling, anticoagulant strategy as well as early referral to cardiologist with expertize in the management of cardiac disease and pregnancy.

KEY POINTS

- Cardiac output increases by 30–50% by the end of first trimester and continues to increase until the second and third trimesters, as a result imposes an additional burden on the cardiac patient especially around labor and immediate puerperium
- The prevalence and distribution of VHD differs depending on the location of the patient's origin
- Preconception risk assessment is essential
- Mitral stenosis, the most common manifestation of RHD remains the most common acquired valvular lesion in pregnant women and the most common cause of maternal death from cardiac causes
- Patients of childbearing age with mechanical prosthetic valves pose unique challenges since there is no optimal anticoagulation agent considered safe at all stages of pregnancy
- Appropriate contraceptive and family planning advice during the postpartum period is mandatory
- Ongoing risk assessment and a tailored multidisciplinary (obstetrician, physician, cardiologist, anesthetists, pediatrician) management approach during pregnancy, labor and delivery in patients with valvular disease are essential to ensure optimal results.

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CHAPTER

Septic Shock

Sasmita Dash

INTRODUCTION

Septic shock is a life-threatening condition caused by a severe localized or system-wide infection that requires immediate medical attention. Sepsis and septic shock increase lactate in a number of exciting ways, many of which have little to do with impaired tissue perfusion (though it does play a role).

Every year 800,000 cases suffer from severe sepsis out of which 400,000 land in septic shock. Death from septic shock happens in more than 200,000 cases. Mortality out of sepsis is around 35–50%.

Sepsis undeniably results in lactic acidosis and this is not a matter for dispute. However, the origin of the extra lactate is still being disputed. There is no doubt a combination of things happening here as follows:

- Microvascular stasis, slowed circulation
- Catecholamine-related increase in the rate of glycolysis, especially in the skeletal muscle.

Decreased mitochondrial pyruvate dehydrogenase activity, due to cytokine activity and bacterial endotoxin.

- Microcirculatory shunting (oxygenated blood never reaches hypoxic tissues)

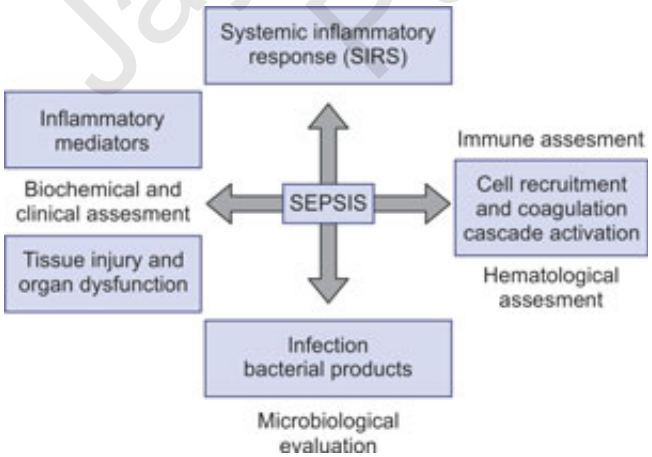

Figure 1: Diagnostic sepsis phases.

Symptoms include low blood pressure, pale and cool arms and legs, chills, difficulty breathing and decreased urine output. Mental confusion and disorientation may also develop quickly.

Emergency treatment may include supplemental oxygen, intravenous fluids, antibiotics and other medications.

Sepsis and septic shock represent the systemic inflammatory response to the presence of infection with a variety of microorganisms. The complex pathophysiology of the inflammatory response has been brought into clearer perspective during recent years, in part, related to the ability to interrupt the inflammatory cascade with the use of specific blockers or inhibitors of the individual potential mediators into the events that trigger and sustain the inflammatory response. Many questions persist and further work is required to fully unravel the complex interrelationships between the various components of this inflammatory cascade. Sepsis, septic shock, and the adverse sequelae of the systemic inflammatory response to infection are now the 13th most common causes of death in the United States and are among the most common causes of death in the noncoronary intensive care unit.

It is estimated that there are approximately 400,000–500,000 septic episodes each year in the United States. These figures appear to be on the rise; however, the numbers are only estimates because there have not been uniformly accepted definitions to allow an exact determination of the true incidence and prevalence.

On the basis of the discharge diagnosis codes for bacteremia and septicemia, the Centers for Disease Control (CDC) reported a dramatic 139% increase in the incidence of sepsis over a recent 10-year interval. In addition to the increase in incidence, there has been an increase in both gram-positive and gram-negative sepsis and a parallel increase in the mortality rate associated with sepsis.

It is important to appreciate that this increase in the sepsis-related mortality rate has occurred despite recent advances in our knowledge concerning the complex pathophysiology of sepsis and the tremendous improvements that have taken place

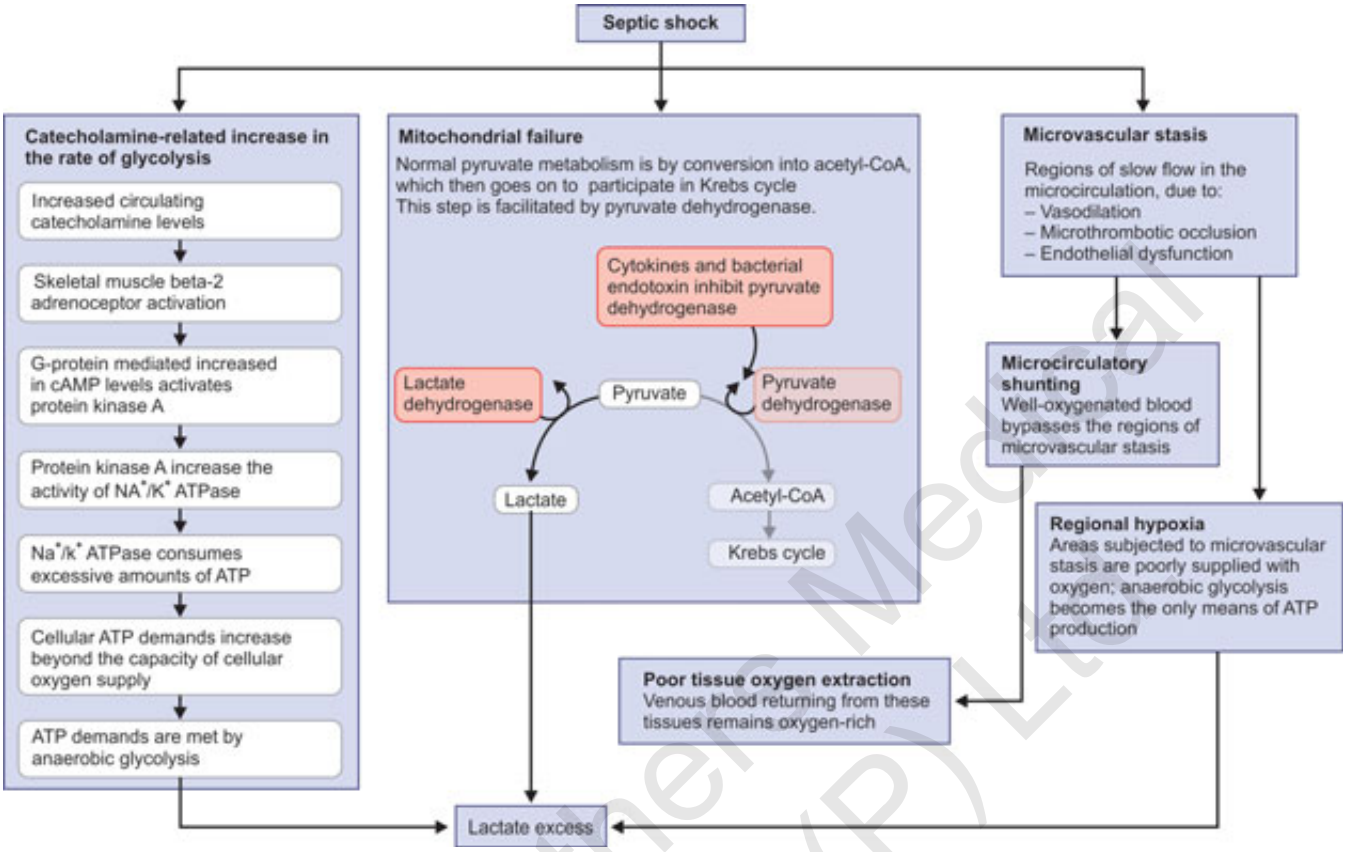

Figure 2: Pathogenesis.

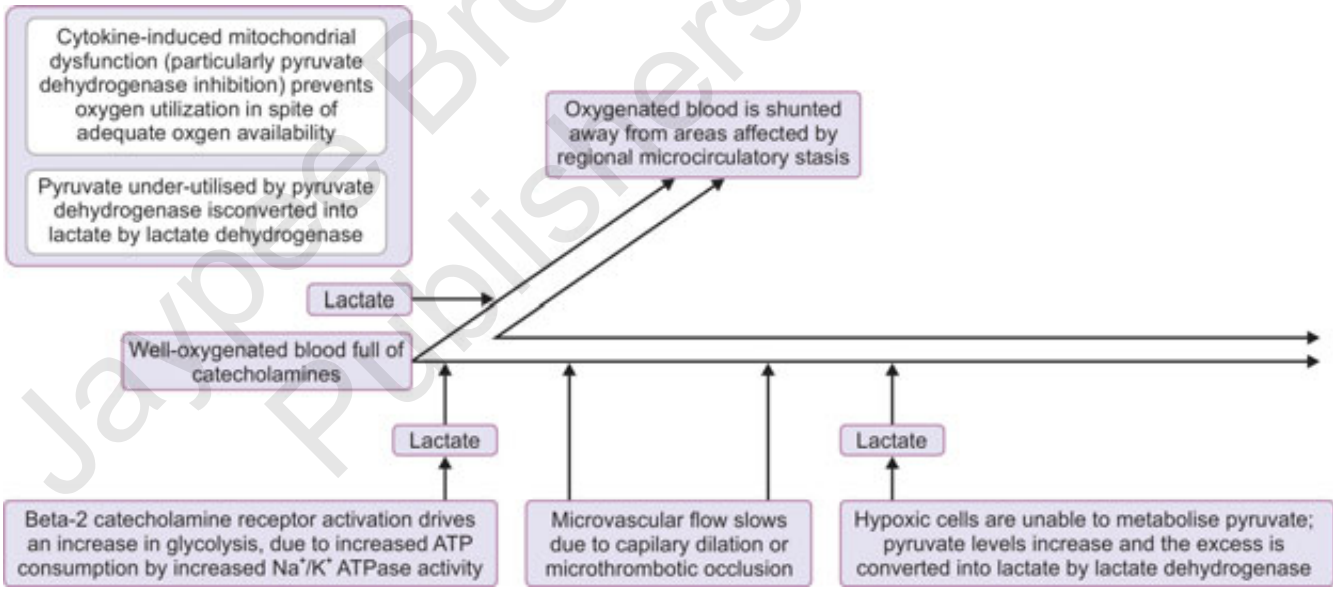

Figure 3: Biochemical change.

in the clinician's ability to monitor and provide technologic supports and treatment for the critically ill patients in today's intensive care units.

Factors that are potentially responsible for the growing incidence of sepsis and septic shock are an increased awareness, sensitivity for the diagnosis, an increased number of patients who have compromised immune status, the increased use of aggressive invasive procedures in patient management and diagnosis, a growing number of resistant microorganisms in clinical settings, and an ever-growing number of elderly patients who are at greater risk for the development of sepsis and septic shock.

DIAGNOSIS

- Temperature >38°C or <36°C
- Heart rate >90 beats/min; respiratory rate >20 breath/min or $PaCO_2$ <32 mmHg; and WBC >12,000/mm^3, <4,000/mm^3, or >10% immature
- Appropriate routine microbiologic cultures (including blood) be obtained before starting of antimicrobial therapy
- Empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage)
- Antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is found
- Systemic antimicrobial prophylaxis is given in patients with severe inflammatory states of noninfectious origin (e.g., severe pancreatitis, burn injury)
- Strategies of antimicrobials be optimized based on accepted pharmacokinetic/pharmacodynamics principles and specific drug properties in patients with sepsis or septic shock
- Empiric combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock
- An antimicrobial treatment duration of 7–10 days is adequate for most serious infections associated with sepsis and septic shock
- Always include at least two sets of blood cultures (aerobic and anaerobic).

INITIAL RESUSCITATION

Delay in first antibiotic administration was associated with increased in-hospital mortality. In addition, there was a linear increase in the risk of mortality for each hour delay in antibiotic administration.

These results underscore the importance of early identification and treatment of septic patients in the hospital setting.

- Sepsis and septic shock are medical emergencies, treatment and resuscitation begin immediately
- Resuscitation from sepsis-induced hypoperfusion, is to be treated at least 30 mL/kg of IV crystalloid fluid be given within the first 3 hours (strong recommendation)
- Frequent reassessment of hemodynamic status
- Assessment of cardiac status
- Vasopressors (strong recommendation) when MAP <65 mmHg
- Normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.

Daily assessment for de-escalation of antimicrobial therapy in patients with sepsis and septic shock.

FLUID THERAPY

Crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock using albumin in addition to crystalloids for initial resuscitation and subsequent intravascular.

VASOACTIVE MEDICATIONS

- Norepinephrine as the first-choice vasopressor
- Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients, patients with low risk of tachyarrhythmias and absolute or relative bradycardia
- Low-dose dopamine for renal protection is used.

Dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents.

CORTICOSTEROID

Intravenous hydrocortisone is used to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are not able to restore hemodynamic stability. (IV hydrocortisone at a dose of 200 mg/day).

BLOOD PRODUCTS

Red blood cell transfusion occur only when hemoglobin concentration decreases to <7.0 g/dL in adults in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, or acute hemorrhage. Prophylactic platelet transfusion when counts are <10,000/mm^3 (10×10^9/L) without bleeding or counts are <20,000/mm^3 (20×10^9/L) if the patient has a significant risk of bleeding. Use of immunoglobulin and dialysis of blood has a doubtful role.

MECHANICAL VENTILATION

Target tidal volume of 6 mL/kg predicted body weight compared with 12 mL/kg in adult patients with sepsis-induced acute respiratory distress syndrome (ARDS). Higher positive end-expiratory pressure (PEEP) over lower PEEP is preferred in adult patients with sepsis-induced moderate to severe ARDS. Prone over supine position is preferred in adult patients with sepsis-induced ARDS and a PaO_2/FIO_2 ratio <150. Mechanically ventilated sepsis patients be maintained with the head of the bed elevated between 30° and 45° to limit aspiration risk and to prevent the development of aspiration pneumonia spontaneous breathing trials in mechanically ventilated patients with sepsis who are ready for weaning to be practiced.

SEDATION AND ANALGESIA

Limiting the use of sedation in critically ill ventilated patients reduces the duration of mechanical ventilation and allows earlier mobilization.

GLUCOSE CONTROL

Insulin dosing when two consecutive blood glucose levels are >180 mg/dL. This approach should target an upper blood

glucose level ≤180 mg/dL rather than an upper target blood glucose level ≤110 mg/dL.

Blood glucose values be monitored every 1–2 hours until glucose values and insulin infusion rates are stable, then every 4 hours thereafter in patients receiving insulin infusions.

Glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution because such measurements may not accurately estimate arterial blood or plasma glucose values (BPS).

Arterial blood rather than capillary blood for point-of-care testing using glucose meters if patients have arterial catheters.

RENAL REPLACEMENT THERAPY

Continuous renal replacement therapy (CRRT) or intermittent RRT be used in patients with sepsis and acute kidney injury. CRRT to facilitate management of fluid balance in hemodynamically unstable septic patients.

BICARBONATE THERAPY

Sodium bicarbonate therapy may be useful in limiting tidal volume in ARDS in some situations of permissive hypercapnia, but no evidence supports the use of sodium bicarbonate therapy in the treatment of hypoperfusion-induced lactic acidemia associated with sepsis.

VENOUS THROMBOEMBOLISM PROPHYLAXIS

Intensive care unit patients are at risk for deep vein thrombosis (DVT) as well as pulmonary embolism (PE). The incidence of DVT acquired in the Intensive care unit may be as high as 10%. The incidence of acquired PE may be 2–4%. Patients with sepsis and septic shock are likely at increased risk for this complication.

A number of studies have also compared use of low-molecular-weight heparins (LMWHs) to unfractionated heparin (UFH) for prevention of venous thromboembolism (VTE) prophylaxis in critically ill patients.

NUTRITION

Critically ill patients are at significant risk for gastrointestinal (GI) dysmotility, which may then predispose them to regurgitation or vomiting, aspiration, and the development of aspiration pneumonia. Use of prokinetic agents in critically ill patients with sepsis or septic shock and feeding intolerance (weak recommendation, low quality of evidence). Early initiation of enteral feeding rather than a complete fast or only IV glucose.

Parenteral nutrition delivery can secure the intended amount of calories. This may represent an advantage over enteral nutrition, especially when patients may be underfed due to GI intolerance, which may be pertinent over the first days of care in the Intensive care unit. However, parenteral delivery is more invasive and has been associated with critically ill patients are at significant risk for GI dysmotility, which may then predispose them to regurgitation or vomiting, aspiration, and the development of aspiration pneumonia. The rationale for measurement of gastric residual volume (GRV) is to reduce the risk for aspiration pneumonia by either ceasing or modifying the enteral feeding strategy based on the detection of excess gastric residuals.

Glutamine levels are also reduced during critical illness. Exogenous supplementation can improve gut mucosal atrophy and permeability, possibly leading to reduced bacterial translocation. Other potential benefits are enhanced immune cell function, decreased proinflammatory cytokine production, and higher levels of glutathione and antioxidative capacity. However, the clinical significance of these findings is not clearly established.

CONCLUSION

Rapid diagnosis is essential in the case of sepsis. Laboratory findings are important and represent a two-sided process.

The first side is responsible for monitoring changes in metabolic homeostasis and patient evaluation; indicating severity of the disease and whether there is involvement of specific organs or entire systems. The second refers to pathogen identification through a microbiological screening of the patient.

Several indicators might be used for this purpose: pro-inflammatory mediators, acute phase indicators, and pathogen metabolites. Lactate levels, serum cytokines, presence of colony stimulating factors, and plasma nitric oxide levels may be early indicators of systemic inflammatory response syndrome (SIRS), but remain restricted to research units.

An ideal test should allow for a fast and precise diagnosis, be reproducible, affordable, and have high sensitivity and specificity. Despite several candidates such as blood culture, serum lactate, and PCT levels, a combination of tests is still compulsory for the diagnosis of sepsis. In a field where speed and accuracy are needed, a gold standard test for sepsis is still searched for. Because health is so precious, knowledge must rise to meet current needs.

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CHAPTER

Human Immunodeficiency Virus in Pregnancy

Laxmi Shrikhande, Bhushan Shrikhande

INTRODUCTION

About 3.2 million children worldwide are living with HIV. Most of these children were infected by their HIV-positive mothers.

MOTHER CHILD TRANSMISSION

Vertical transmission of HIV can occur via:

- *In utero* across placenta or in the amniotic fluid
- During birth process via direct contact with blood, infected maternal cervical and vaginal secretions
- Postnatally via breast milk.

Estimated Mother Child Transmission Rates

Without intervention:

- During pregnancy: 5–10%
- During labor and delivery: 15–20%
- During breastfeeding: 5–15%
- Total: 25–45%.

To tackle the problem, the WHO has suggested a comprehensive four pronged approach:[1]

1. Preventing new HIV infections among women of childbearing age
2. Preventing unintended pregnancies among women living with HIV
3. Preventing HIV transmission from a woman living with HIV to her baby
4. Providing appropriate treatment, care and support to mothers living with HIV and their children and families.

Prevention of Parent to Child Transmission

- The first step to interrupt mother-to-child transmission (MTCT) of HIV is identification of those at risk so that they may be provided with therapy and information to prevent transmission to their infant
- Prevention of parent-to-child transmission (PPTCT) programs provides antiretroviral treatment (ART) to HIV-positive pregnant women to stop their infants from acquiring the virus
- The PPTCT services should also continue after an infant has been born—although this remains a major challenge
- The PPTCT services are provided at the following levels:
  - Antenatal care
  - Intranatal care
  - Postnatal care.

Antenatal Care

Good antenatal care ensures that pregnancy and delivery:

- Is a safe experience for the mother
- Builds the foundation for the delivery of a healthy baby (minimal risk of HIV transmission to the baby).

From the HIV care aspect for pregnant women, the initial assessment follows standard adult ART guidelines including:

- Screen and treat any STIs: any concurrent STIs may increase the risk of HIV transmission from mother-to-child, and may adversely affect the pregnancy
- CD4 cell count (baseline).

Women who do not return for results should be actively traced back and brought to the continuum of care through the help of grass-root level health functionaries i.e., ANMs/ASHAs/Community health workers and initiated adherence counselling as well as breastfeeding counseling.

WHO PPTCT Guidelines 2015[2]

In September 2015, the WHO released new guidelines recommending that all pregnant women living with HIV be immediately provided with lifelong treatment, regardless of CD4 count and WHO stage.
This approach is called option B+.

Choice of ART Regimen for HIV-infected Pregnant Women

The recommended first-line regimen for HIV infected pregnant women is Tenofovir (TDF) (300 mg) + Lamuvidine (3TC) (300 mg) + Efavirenz (EFV) (600 mg) (if there is no prior exposure to NNRTIs (NVP/EFV) at any gestational age.

Safety of Efavirenz in Pregnant Women

Based on evidence available, EFV has been recommended for use in pregnant women in all trimesters of pregnancy including first trimester.[3]

ART Regimen for Pregnant Women having Prior Exposure to NNRTIs for PPTCT

In HIV infected pregnant women who have had previous exposure to NVP (or EFV) for PPTCT prophylaxis in prior pregnancies, an non-nucleoside reverse-transcriptase inhibitor (NNRTI)-based ART regimen such as TDF + 3TC + EFV may not be fully effective due to persistence of archived mutations to NNRTIs. Thus, these women will require a protease-inhibitor based ART regimen, viz., TDF + 3TC + LPV/r (Lopinavir/ritonavir).

The dose will be TDF + 3TC (1 tablet daily) + LPV (200 mg)/r (50 mg) (2 tablets BD)

Pregnant Women Already Receiving ART

Pregnant women who are already receiving ART for their own health, should continue to receive the same regimen throughout pregnancy, labor, breastfeeding period and thereafter life-long. If a woman is on an EFV-based regimen, there is no need to substitute with nevirapine (this was done as per earlier guidelines).

She must continue on whatever regimen she is stabilized on and is responding to adequately.

Pregnant Women with Active TB

The risk of active TB is approximately 10 times higher in HIV-infected pregnant women compared to HIV uninfected women. Active TB in HIV-infected pregnant women can contribute to increased risk of maternal mortality, and is also associated with prematurity, low birth weight, and perinatal tuberculosis.

A recent study in India found that maternal TB increases the risk of HIV transmission from mother-to-child by 2.5 times. HIV-infected pregnant women with active tuberculosis should start ART, irrespective of CD4 cell count. The tuberculosis treatment should be started first, and followed by ART as soon as feasible (usually after 2 weeks).

Drug interactions between rifampicin and some of the antiretroviral drugs, including NVP, complicate simultaneous treatment of the two diseases. EFV is the preferred NNRTI for pregnant women which can also be used in those with concurrent TB treatment.

For those HIV-TB co-infected women not able to tolerate EFV, a NVP-based or a boosted PI regimen can be considered after expert clinical consultation. With the use of a boosted PI regimen, rifampicin should be substituted with rifabutin.

Intrapartum Antiretroviral Therapy

Women on life-long ART should continue to receive ART as per the usual schedule including during labor and delivery.

Pregnant Women in Labor Who are Found Positive in HIV-screening Test

- Initiate ART (TDF + 3 TC + EFV) immediately
- Offer pretest counseling
- Counsel and advice for exclusive breastfeeding for first 6 months.

ARV Prophylaxis for Infants Born to HIV-positive Women Presenting in Active Labor

All infants born to women who present directly-in-labor and are receiving intrapartum ART and regularly thereafter, should be started on daily NVP prophylaxis at birth and continued for a minimum of 6 weeks.

This needs to be extended to 12 weeks as mother has not yet received adequate duration of ART to suppress viral replication. However, EID (early infant diagnosis) should be carried out at 6 weeks as per guidelines.

For Baby-EID Protocol

The HIV exposed baby is initiated on cotrimoxazole prophylaxis at 6 weeks and is tested for HIV DNA PCR at 6 weeks by DBS (dry blood spot) collection. If the DBS sample is positive for HIV DNA PCR, then a repeat DBS sample is tested for HIV DNA PCR. The HIV exposed baby is then initiated on lifelong ART at the earliest if confirmed HIV positive through 2 DNA PCR test.

ARV Prophylaxis for Infants Born to Women Who Did not Receive Any ART (Home Delivery)

Infants should be started on daily syrup NVP prophylaxis at their first contact with health services.

Daily infant NVP prophylaxis can be started even if more than 72 hours have passed since birth.

Daily infant NVP prophylaxis should continue for at least 12 weeks, by which time the mother should be linked to appropriate ART services. The duration of daily infant NVP prophylaxis will depend on whether the mother is to be initiated on life-long ART and infant feeding practices.

Cesarean Section

Cesarean section is not recommended for prevention of MTCT and should be done only if there is an obstetric indication for the same.

Use of ARV Drugs during Cesarean Section

- For planned (elective) cesarean sections, ART should be given prior to the operation.
- In case of an emergency cesarean section in pregnant women who are not on ART, ensure that the women receive ART prior to the procedure and continues thereafter.

All HIV-infected women who undergo cesarean section should receive the standard prophylactic antibiotics. Complications of cesarean section are higher in women with HIV, with the most frequently reported complication being postpartum fever.

Safer Delivery Techniques

- Observe Standard/Universal Work Precautions (UWP)
- Keep membranes intact for as long as possible
- Minimize vaginal examination and use aseptic techniques
- Avoid invasive procedures like fetal blood sampling, fetal scalp electrodes
- Avoid instrumental delivery as much as possible
- If indicated, low-cavity outlet forceps is preferable to ventouse, as it is generally associated with lower rates of fetal trauma than ventouse
- Avoid routine episiotomy as far as possible
- Suctioning the newborn with a nasogastric tube should be avoided unless there is meconium staining of the liquor
- The cord should be clamped as early as possible after delivery
- Use of round-tip blunt needles for cesarean section
- Do not use fingers to hold the needle; use forceps to receive and hold the needle
- Observe good practice when transferring sharps to surgical assistant, e.g., holding container for sharps.

Waste Disposal

For disposal of tissues, placenta and other medical/infectious waste material from the delivery of HIV-infected deliveries, standard waste disposal management guidelines should be followed.

The Postpartum Period

Infants born to HIV-infected mothers should receive NVP prophylaxis immediately after birth.

Infants after delivery should be put on the mother's abdomen for skin contact to be established. This helps in bonding and maintenance of baby's body temperature as well as helps initiation of breast milk within 1 hour of birth.

Exclusive Breastfeeding[4]

If the mother has not made a decision about feeding yet, she should be counseled to give exclusive breastfeeds for the first 6 months which is the preferred option, followed by complementary feeds after 6 months.

Exclusive Replacement Feeding

Mothers known to be HIV-infected, if insist on opting for exclusive replacement feeding which is contrary to the WHO/NACO's guidelines of giving exclusive breastfeeds for first 6 months, are doing so at their own risk.

Mixed feeding should not be done during the first 6 months. Feeding a baby with both breast and replacement feeds in the first 6 months is known as mixed feeding, which leads to mucosal abrasions in the gut of the baby facilitating HIV virus entry.

AFASS Criteria for Replacement Feeding

A—Affordable
F—Feasible
A—Acceptable
S—Sustainable
S—Safe.

Wherever possible, include family counseling (of husband, in-laws, direct family members) to support care of the HIV infected mother and HIV exposed infant. Postpartum depression and psychosis is common in HIV infected women.

Contraception

Insertion of Cu-T for HIV infected mother at 6 weeks if a postpartum IUD (PP-IUD) has already not been inserted within 48 hours in addition to the use of condoms will prevent unwanted pregnancies (dual protection). Encourage male sterilization in the father [no scalpel vasectomy (NSV) between 18 months to 2 years when baby's survival has been ensured].

Postpartum Intrauterine Contraceptive Device

Intrauterine contraceptive device (IUCD) is a good contraceptive method for HIV infected pregnant women. PP-IUD requires specialized training before the healthcare personnel undertake the same.

Condom Use

Condom should be consistently used by all HIV infected males despite following any other family planning method (dual protection).

Postpartum Follow-up and Care

This extends beyond the 6 weeks postpartum period and includes:

- Assessment of maternal healing after delivery and evaluation for postpartum infectious complications
- Continued counseling and information on fertility choices and effective postpartum contraceptive methods as well as condom promotion
- Linking of the baby to the EID program and ART program for mother/child as indicated.

HIV-positive Partners in HIV Serodiscordant Couples

The results of the HPTN052 study strongly support the use of ART to prevent HIV transmission among HIV-sero-discordant couples (96% reduction).

The guidelines, therefore, endorse that the sexual partner with HIV in a serodiscordant couple should be offered ART regardless of CD4 count.

Guidelines for HIV-exposed Infants

If an HIV-exposed infant is given ART within the first 12 weeks of life, they are 75% less likely to die from an AIDS related illness. This is one of the reasons that WHO recommends that infants born to mothers living with HIV are tested between 4–6 weeks old. This is often referred to as "early infant diagnosis."

The WHO further recommends that another HIV test is carried out at 18 months and/or when breastfeeding ends to provide the final infant diagnosis. All infants who test positive for HIV should be immediately initiated on treatment.

The treatment should be linked to the mother's course of ARVs and would vary according to the infant feeding method as follows:

1. Breastfeeding: The infant should receive once-daily nevirapine from birth for six weeks

2. Replacement feeding: The infant should receive once-daily nevirapine (or twice-daily zidovudine) from birth for 4–6 weeks.

Pediatric ART

All babies detected positive less than 2 years of age are given pediatric ART irrespective of CD4%.

Barriers to the Uptake of PPTCT Programs

A number of studies have identified the link between knowledge of HIV, MTCT and PPTCT, and uptake of PPTCT services. Knowledge of HIV status is vital in order for pregnant to women access the appropriate treatment and care for themselves and their infants.

Barriers to the uptake of PPTCT programs:

- Confusion over exclusive breastfeeding: The fact that formula feeding can be difficult to achieve in resource poor settings, coupled with breastfeeding's recorded benefits for preventing malnutrition and serious infectious diseases, has resulted in exclusive breastfeeding being recommended by WHO for women living with HIV in resource poor settings provided they have access to ART. Formula feeding is recommended for women living with HIV in countries in high resource settings
- HIV stigma, discrimination and PPTCT: HIV-related stigma and discrimination affect a pregnant woman's decision to enroll on PPTCT programs and interrupt adherence to treatment and retention in care. It has been estimated that over 50% of vertical HIV transmissions from mother-to-child globally can be attributed to the cumulative effect of stigma
- Stigma in healthcare settings: For women living with HIV, experiences of stigma, discrimination, and abuse often occur when they seek maternal healthcare. This can take many forms including physical abuse, nonconsented clinical care, nonconfidential care, nondignified care, abandonment or denial of care, and detention in facilities
- Country and clinic resources: In resource-poor settings, shortages of PMTCT staff, interruptions in treatment and supplies of medical equipment, as well as a shortfall in counseling services, all act as barriers to PMTCT services. Poor monitoring of PMTCT services by healthcare workers also leads to poor retention in care
- Considerations for co-infection of tuberculosis and HIV: HIV-TB co-infection is one of the most challenging issues in the effort to scale up ART since more than 60% of PLHIV develop TB. Active TB is the commonest OI among HIV infected individuals and is also the leading cause of death in PLHIV
- Delays in early infant diagnosis: One barrier to successful early infant diagnosis is the waiting time for test results. The fact that in many places HIV treatment for mothers and babies is followed up separately, rather than as a pair, presents another barrier to successful early infant diagnosis. Moreover, healthcare workers must know the protocols for providing the service, and have the drugs and supplies in place to do so
- Cultural beliefs and gender dynamics: In many communities, pregnancy is viewed as a 'woman's affair', with a man's role primarily to provide financial support. Even where men view accompanying their partner to antenatal clinics or PMTCT services as good practice, many still feel their main role is to provide financing for registration and delivery fees
- Low male involvement: Health workers' friendliness toward male partners was significantly associated with male involvement in PMTCT. The study found that those men who were made to feel needed and an important part of the pregnancy by health workers when they accompanied their wives for ANC were more likely to become involved in PMTCT
- Option B+ challenges: Women who started treatment in the context of B+ are five times more likely to be lost to follow-up compared to those who started treatment for their own health.

INDIAN DATA

As on 31st August 2016 in India there are 20,756 Integrated Counselling and Testing Centres (ICTC), most of these in government hospitals, which offer PPTCT services to pregnant women.

The NACO Technical Estimate Report (2015) estimated that out of 29 million annual pregnancies in India, 35,255 occur in HIV-positive pregnant women. In the absence of any intervention, an estimated (2015) cohort of 10,361 infected babies will be born annually.

The PPTCT services cover about 47% annual estimated pregnancies in the country. In the year 2015–16, 12.7 million pregnant women accessed this service. Of these, 11,918 pregnant women were HIV positive. In order to provide universal access to these services further scale up is planned up to the level of community health centers.

CONCLUSION

- The PPTCT services, where implemented, are effective
- Around 1.6 million new HIV infections among children have been prevented as a result of these programs since 1995. Of these, 1.3 million are estimated to have been averted in the 5 years, between 2010 and 2015
- Despite this significant progress, in 2015, 23% of pregnant women living with HIV did not have access to ART and 150,000 children (400 children a day) became infected with HIV[5]
- Global PPTCT targets: Reducing the number of new HIV infections among children to fewer than 40,000 by 2018 and fewer than 20,000 by 2020. There is also a commitment to ensure that 95% of pregnant women living with HIV are receiving lifelong HIV treatment by 2018.

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CHAPTER

Screening for Gestational Diabetes: An Update

Venus Bansal

WHY SCREENING IS REQUIRED FOR GESTATIONAL DIABETES?

India today is recognized as the Diabetic capital of the world. The prevalence of GDM in India varies from 9.9% in rural population to 17.8% in urban areas.[1] Women of Asian origin and especially Ethnic Indians, are at a higher risk of developing GDM and subsequent type 2 diabetes. Lifestyle of today's urban population has made them more prone to lifestyle diseases like Obesity, PCOD and Gestational Diabetes. As per the recent data, obesity is present in 30%, 50%, 27% and 20% of women of Mumbai, Delhi, Chennai and Kerala respectively. Keeping all these facts in mind, there is no doubt that universal screening, instead of selective, is ideal for our population.

WHAT CAN BE THE RISK FACTORS FOR GESTATIONAL DIABETES?

In India, being a high prevalence area "universal screening at earliest" is recommended. At the same time we need to triage the ones who are even at more risk. Risk factors for Gestational Diabetes are overweight, moderate to severe obesity, prior Gestational Diabetes, prior macrosomic infant, greater maternal age, multiple gestation, South East Asians, Hispanic, PCOD, parent or sibling with diabetes. Periodontal disease and low maternal birth weight and high consumption of sugar sweetened colas are recently published associations.

WHAT ARE THE HEALTH RISKS OF GESTATIONAL DIABETES?

Health risks of gestational diabetes are given in table 1.

WHEN SHOULD AN INDIAN WOMAN SCREENED FOR GESTATIONAL DIABETES MELLITUS?

Insulin is detectable in fetal pancreas as early as 9 weeks after conception. An increase in pancreatic beta cell mass and insulin secretion in the fetus occurs by the 16th week of gestation, in response to maternal hyperglycemia. The priming of fetal beta cells may account for the persistence of fetal hyperinsulinemia throughout pregnancy and the risk of accelerated fetal growth. This necessitates performing the test procedures to diagnose GDM in the first trimester itself.

WHICH TEST AND HOW OFTEN SHOULD WE SCREEN?

The controversy concerning optimal strategy still continues for the detection and diagnosis of GDM. DIPSI (Diabetes in

TABLE 1: Health risks of gestational diabetes

Mother	*Fetus*	*Newborn*	*Child/adult*
• Birth trauma • Increased cesarean delivery • Preeclampsia/gestational hypertension • Type 2 diabetes • Metabolic syndrome	• Hyperinsulinemia • Cardiomyopathy • Stillbirth • Large for gestational age/macrosomia • Birth trauma	• Respiratory distress syndrome • Hypoglycemia • Hypocalcemia • Hyperviscosity • Polycythemia • Hyperbilirubinemia • Cardiomyopathy	• Obesity • Type 2 diabetes • Metabolic syndrome

pregnancy study group in India) has endorsed the WHO criteria and recommended universal screening at first contact and again at 24 to 28 weeks using a 2 hour 75 g OGTT with a threshold plasma glucose concentration of greater than 140 mg/dL at 2 hours (Table 2).[2]

RATIONALE FOR NONFASTING STATUS OGTT

Adequate and brisk insulin response in normal women maintains euglycemia state despite glucose challenge where as women with GDM have an increase in glycemic levels with glucose challenge due to impaired insulin secretion.

Advantages

- A single test procedure to screen and diagnose gestational diabetes mellitus in the community
- It leads to least disturbances to routine activity and economical
- The pregnant women need not be fasting
- It requires only a single sample (compared to three with IADPSG and four with the Carpenter and Coustan criteria)
- There is clarity of labelling the different magnitude of abnormal glucose intolerance in pregnancy and outside pregnancy.

Disadvantages

- Nonfasting OGTT has been shown to have low sensitivity in two studies done by Mohan et al.[4] and Vijayalakshmi et al.[5] They concluded that DIPSI non fasting OGTT criteria cannot be recommended for diagnosis of GDM due to low sensitivity
- Venous plasma glucose values also depend on the timing of the day when it was done. Lee et al.[6] and Goldberg et al.,[7] in their study observed that glucose tolerance decreases in the afternoon and evening as detected by glucose tolerance tests and give rise to false positive results which will lead to unnecessary diet control, insulin therapy, regular follow-up and anxiety
- Pulkit et al.[8] found that diagnosis of GDM by DIPSI leave 22.36% undiagnosed cases which can easily be detected using IADPSG criteria and concluded that IADPSG criteria is better for screening GDM than DIPSI as it missed substantial number of patients.

WHAT IS THE INTERNATIONAL ACCEPTANCE FOR SCREENING?

IADPSG is the outcome based screening test and adapted by my many professional bodies. For the IADPSG criteria, an OGTT is done in the fasting state using 75 g of glucose at 24–28 weeks, and GDM is diagnosed if any one of the following cut-points is met, i.e., fasting ≥92 mg/dL, or 1 hour ≥180 mg/dL or 2 hour ≥153 mg/dL.[9]

WHAT IS THE IMPROVEMENT IN MATERNAL AND NEONATAL OUTCOME WITH EARLY DIAGNOSIS AND TREATMENT OF MILD HYPERGLYCEMIA?

To clarify the adverse outcomes associated with degrees of maternal glucose intolerance less severe than overt diabetes mellitus HAPO study was done. It studied both primary and secondary outcomes.[10]

Primary Outcomes

- Birth weight above the 90th percentile for gestational age
- Primary cesarean delivery
- Clinical neonatal hypoglycemia
- Cord-blood serum C-peptide level above the 90th percentile (fetal hyperinsulinemia).

Secondary Outcomes

- Premature delivery (before 37 weeks of gestation)
- Shoulder dystocia or birth injury.
- Need for intensive neonatal care
- Hyperbilirubinemia
- Preeclampsia.

The data showed associations between increasing levels of fasting, 1-hour, and 2-hour plasma glucose obtained on oral glucose-tolerance testing and birth weight above the 90th percentile and cord blood serum C-peptide level above the 90th percentile, with weaker associations between glucose levels and primary cesarean delivery and clinical neonatal hypoglycemia.

It also found positive associations between increasing plasma glucose levels and each of the five secondary outcomes examined: premature delivery, shoulder dystocia or birth injury, intensive neonatal care, hyperbilirubinemia, and pre-eclampsia.

Here I would like to highlight that IADPSG is the only screening test which is based on outcome.

CONCLUSION

Indian population is diverse and variable. We must do screening at first contact and again at 24–28 weeks using a 2 hour 75 g OGTT with a threshold plasma glucose concentration of greater than 140 mg/dL at 2 hours. In order to obtain international standardization, we recommend, wherever possible, a single

TABLE 2: With 75 g OGTT (WHO criteria)[3]

Plasma glucose	*In pregnancy*	*Outside pregnancy*
2 h ≥200 mg/dL	Diabetes mellitus	Diabetes mellitus
2 h ≥140 mg/dL and ≤199 mg/dL	Gestational diabetes mellitus	Impaired glucose tolerance
2 h ≥120 mg/dL and ≤139 mg/dL	Gestational glucose intolerance	–
2 h <120 mg/dL	Normal	Normal

step fasting OGTT using 75 g glucose and the IADPSG criteria be used, with two step procedure remaining a viable option.

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CHAPTER

Systemic Lupus Erythematosus with Pregnancy

Subhash C Biswas

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease which predominantly affects women (female:male = 9:1) in reproductive age group (15–45 years). Pregnancy remains a high-risk situation with this disease. Both maternal and fetal mortality and morbidity are still significantly increased despite improvements in pharmacotherapy. A systematized approach, with close monitoring by a multidisciplinary team, is essential for optimal outcomes. A high proportion of lupus patients can now look forward to a successful pregnancy. This article reviews the current concepts regarding SLE.

DIAGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS

The American College of Rheumatology[1] has criteria for the classification of patients as having SLE. If a patient has, at any time in his or her medical history, 4 of the 11 criteria documented, the diagnosis of SLE can be made with about 95% specificity and 85% sensitivity.

The following laboratory studies[2] are recommended with the first visit when pregnancy is confirmed:

- Renal function tests, including determination of the glomerular filtration rate (GFR), urinalysis, and tests of the urinary protein-to-creatinine (P/C) ratio
- Complete blood count
- Test for anti-Ro/SSA and anti-La/SSB antibodies
- Lupus anticoagulant and anticardiolipin antibody studies
- Antidouble-stranded DNA (anti-dsDNA) test
- Complement studies (CH50 or C3 and C4).

In first 2 trimesters, a monthly platelet count or CBC is recommended. In addition, the following studies are recommended at the end of each trimester of pregnancy:

- Determination of the GFR and measurement of the urinary P/C ratio
- Anticardiolipin antibody measurement
- Complement studies (CH50 or C3 and C4)
- Anti-dsDNA study.

In pregnant patients with renal disease, renal biopsy may need to be performed to differentiate preeclampsia from active lupus nephritis when differentiation on clinical grounds is not possible.

- Ultrasonography: At first prenatal visit to accurately estimate the gestational age
- Serial fetal echocardiography: To detect fetal heart block at an early stage.

EFFECT OF PREGNANCY ON SYSTEMIC LUPUS ERYTHEMATOSUS

Risk of disease flare ranging between 23 and 65% is one of the major issues during pregnancy; but about 20% of flares develop within 3 months after delivery. Defining lupus activity during pregnancy can be difficult. Fatigue and mild arthralgia are common among normal pregnant women and can be confused with SLE flares. Edema may normally appear during the last trimester of pregnancy. Up to 300 mg/day of proteinuria can appear in normal pregnancy lupus activity scales (SLEPDAI, LAI-P) have been developed but not yet fully established. The clinical recognition of SLE flares still relies on the skill of the physician.

The postpartum period, represents an additional thrombotic risk in patients with SLE who have APS.

Most flares during pregnancy occur in the second and third trimesters. It is not possible to predict when an individual patient will flare, it is more likely if disease has been active within 6 months of conception, SLE remains stable in about 30% of the patients.

Possible causes of flares during the postpartum period include the following:

- Decreased levels of anti-inflammatory steroid
- Elevated levels of prolactin (i.e., proinflammatory hormone)
- Changes in the neuroendocrine axis
- Changes in estrogen and progesterone levels
    - A high level of anti-dsDNA antibodies correlates the high risk of disease exacerbation and fetal prematurity.

Complement levels tend to rise during pregnancy, thus reducing their ability to act as useful markers of disease activity. The variation of C3 and C4 levels, rather than their absolute values, should be taken into account.

EFFECT OF SYSTEMIC LUPUS ERYTHEMATOSUS ON PREGNANCY

Active disease at the time of conception is a strong risk factor for poor outcome. Maternal morbidity might be potentially life threatening during an SLE exacerbation, and treatment itself is limited because some of the drug therapies are teratogenic and fetotoxic. The rate of full term delivery is decreased to 26% if SLE is highly active at the time of conception.[3] Other predictors of poor outcome are renal involvement, hypertension, and APS. There are other significant adverse effects during pregnancy like premature rupture of membranes, infections, intra-uterine growth restriction, hypertension and gestational diabetes. The major issues in SLE pregnancy are increased incidence of fetal loss and preterm birth. Preeclampsia occurs in 22–30% compared to 5–7% in healthy women. Live birth rates of 66–91% have been reported in recent studies.[3]

The prognosis for both mother and child is best when:

- Systemic lupus erythematosus is quiescent for at least 6 months before the pregnancy
- When the mother's underlying renal function is stable and normal or near normal. Although the risk of adverse effects on the fetus are minimized
- If conception and pregnancy occur in the absence of glucocorticoids or other immunosuppressive drugs
- Continuing glucocorticoids at the lowest effective dose and/or cautious use of hydroxychloroquine, azathioprine may be preferred in some patients.

Preeclampsia occurring in approximately 13% of patients is often difficult to distinguish from lupus nephritis.[4]

Both conditions present with proteinuria, hypertension, thrombocytopenia, and deterioration of renal function. However, low or decreasing levels of complement, active urine sediment or evidence of disease activity in other organs would point to SLE flare. The measurement of new biomarkers for preeclampsia such as vascular endothelial growth factor receptor or placental growth factor appears promising. Preeclampsia is most likely in patients with antiphospholipid antibodies (APLA), diabetes mellitus, or a past history of preeclampsia.

Rates of fetal loss in any trimester are substantially higher (20%) in patients with SLE than in control groups.[5] First-trimester losses are associated with APLA, and with markers of lupus activity (e.g., low complement concentrations and increased anti-dsDNA antibodies) and renal disease. Late losses are associated with APLA. Hypercoagulable states other than APS are also associated with increased fetal loss.[6]

ANTENATAL COUNSELING

Educating patient and spouse about appropriate contraception is key to avoid unplanned pregnancies. The suitable contraceptives[7] to women with rheumatologic disease are barrier methods, progestin-only methods and IUD. The disease is not in itself a contraindication to pregnancy, with the exception of organ-system complications such as pulmonary hypertension and renal failure.

Continuing immunosuppression and close rheumatologic follow-up are important methods to improve the pregnancy outcome. It should be inactive for at least 6 months prior to conception.

Prepregnancy counselling includes pertinent information about the risks of adverse outcomes, both for the baby and herself, and the planning of antenatal care.

The medication that the patient is taking to control her disease would also need to be reviewed at this time to evaluate their safety. Most forbidden medications should be stopped and be substituted by alternative immunosuppressant and antihypertensive drugs. Patients may need to be reminded about the importance of using contraception while they are taking methotrexate, leflunomide, cyclophosphamide, and mycophenolate.

PLACENTAL PATHOLOGY IN SYSTEMIC LUPUS ERYTHEMATOSUS PREGNANCY

Several mechanisms have been proposed to justify placental compromise. Immunoglobulin and complement deposition in the walls of decidual blood vessels cause vasoconstriction and thrombosis and it suggests that maternal autoantibodies and immune complexes are important. APL antibodies can also cause direct damage to the placental phospholipid membrane, as a consequence of which the placental growth and the fetal-maternal circulation is compromised.

Placental villi are much thinner and scarce in number, with fewer ramifications.

Placental villus dysplasia is caused by placental vasculopathy that is autoimmune in nature. Granular IgG, IgA, IgM, and C3, as well as immunocomplex, especially DNA-anti-DNA-Ab complex deposits, can be found on the wall of villus vessels or in trophoblast membranes by immunohistology. Excessive intervillous fibrin deposition and infarction were noted in almost all cases. Low placental weight appears directly related to restricted fetal growth but was not significantly related to fetal death.

MANAGEMENT

In general, an integrated team consisting of a rheumatologist, an obstetrician experienced with high-risk care, a pediatric cardiologist in cases of fetal heart block in patients with positive SSA and SSB antibodies and a nephrologist (if renal disease is present or if it develops later) are needed to manage care of a pregnant patient with SLE.

Nonpharmacotherapy

Before initiating therapy, perform preconception counseling, including discussions of teratogenicity and adverse effects of SLE medications as well as contraception once therapy is begun.

Pharmacotherapy

None of the medications used in the treatment of SLE is absolutely safe during pregnancy. Although in studies, hydroxy-

chloroquine (HCQ)[8] and low-dose steroids have been safely used for flares of SLE during pregnancy, most of those drugs should be avoided during the first trimester. Therefore, the decision to use medications should be made after careful assessment of the risks and benefits in consultation with the patient.

Laboratory monitoring during pregnancy:

- Initial evaluation: Hb, WBC, DLC, platelets, urinalysis with microscopy, 24-hours urinary estimation of protein and creatinine, blood urea, glucose and serum creatinine, serum lipids
- If patient is nephrotic or on steroids, Coombs' test, aPL (IgG and IgM, aCL, LAC), VDRL, anti-dsDNA, C3. Anti-Ro and anti-La should be done if there is a past history of giving birth to a baby with neonatal lupus
- Monthly laboratory assessment includes: Hb, WBC, DLC, platelets, urinalysis (with 24-hr analysis if nephritis), chemistry panel as above, anti-dsDNA and C3. Elevated anti-dsDNA and low C3 indicate active SLE or impending flare in over 80% of patients
- In case of anemia, peripheral smear should be reviewed and Coombs' test repeated.

Blood pressure should be measured at every visit and more frequently in patients with nephritis. Fetal health should be monitored with repeated ultrasound examinations, fetal heart monitoring and nonstress test. The prime focus of the entire exercise of follow up should be early detection and prompt treatment of lupus flare during pregnancy and the postpartum period. Presence of nephritis with or without hypertension is an indication for low-dose daily aspirin from 10th week till 36th week for prevention of preeclampsia. Indications for cesarian section include maternal reasons or fetal reasons. Lupus flares should be treated with the appropriate steroid dose. Cytotoxic drugs such as cyclophosphamide and methotrexate should be avoided during first trimester except in rare circumstances such as pulmonary alveolar hemorrhage due to SLE. Azathioprine and cyclosporine can be used in pregnancy with active SLE. Warfarin and Coumadin must be avoided during the organogenesis.

More safety data are needed for mycophenolate mofetil. Hydroxychloroquine is the wonder drug to improve both fetal and maternal outcome. Hydroxychloroquine should not be stopped in early pregnancy, because this could precipitate a flare, and its long half-life means the fetus would continue to be exposed to the drug for several weeks, even after discontinuation. If antiphospholipid syndrome is present, there is greatly increased risk of thrombosis and fetal loss. Warfarin must be omitted as early as possible after conception and daily subcutaneous injections of low molecular weight heparin (either enoxaparin 40 mg/day or dalteparin 5,000 units per day) along with low dose aspirin must be continued until delivery. Low dose aspirin is usually withheld 3 days prior and heparin is omitted 12 hours before termination. Warfarin is restarted after one week. Corticosteroids are not recommended for APS alone because they increase maternal morbidity. In refractory cases, IVIG can be tried. A neonatologist should be available at the time of delivery. During the postpartum period, the mother should be watched for infection and disease exacerbation; both require aggressive treatment, when detected. Breastfeeding is an important issue to be addressed after successful pregnancy outcome. Majority of drugs are excreted in human milk in variable amounts. From neonatal perspective, maternal intake of prednisolone up to 30 mg/day, warfarin, cyclosporine in standard doses and weekly chloroquine for malaria prophylaxis are considered safe. If the dose of prednisolone is greater than 30 mg/day, feeding should be avoided for 4 hours after ingestion of the morning dose of steroid. However, breastfeeding is contraindicated if mother is on cyclophosphamide, azathioprine, hydroxychloroquine for SLE, salicylates, indomethacin and sulindac.

NEONATAL SYSTEMIC LUPUS ERYTHEMATOSUS

The newborn may be affected by the onset of neonatal lupus erythematosus[9] (neonatal LE), manifested as rash, congenital heart block (CHB) and leukocytopenia, anemia, and thrombocytopenia.

Neonatal lupus erythematosus is caused by the passage through the placenta of anti-Ro/SSA and anti-La/SSB antibodies that may exert direct toxic effects on the cardiac conduction tissue, impairing the normal function of the sinus and the atrioventricular node by interfering with the calcium channels.

Neonatal lupus with or without congenital heart block is exceedingly rare, being seen in the 1% of SLE women who have anti-SSA (Ro) and/or SSB (La) antibodies.

Neonatal lupus rash manifests as annular inflammatory lesions similar to those of adult subacute cutaneous SLE, usually on the face and scalp, which appear after sun or ultraviolet light exposure in the first 2 weeks of life. The rash disappears spontaneously within 6 months as do blood count abnormalities.

In severe cases, topical steroids may be used. Residual hypopigmentation or telangiectasia may persist for up to 2 years, but scarring is unusual.

Neonatal SLE, although rare, carries a significant mortality rate (24% of cases) and morbidity when the fetal heart is the targeted organ and almost half of the surviving children require pacing in the first year of life; a recurrence rate of 16% in subsequent pregnancies CHB occurs between 18 and 30 weeks, and fetal echocardiography should be performed over this period to enable early detection.

Incomplete blocks may resolve upon treatment of the mother with high-dose betamethasone (12 mg/week). Although CHB is not amenable to curative treatment, its adverse effects on heart function can be corrected by betamethasone therapy.

Due to a recurrence rate of 16% in subsequent pregnancies, prophylaxis therapies, including treatment with intravenous immunoglobulin between 12 and 24 weeks of gestation has been suggested in women with previously affected in CHB.

When hydrops fetal is develops, dexamethasone, salbutamol or digoxin may all have a place; however, as always, fetal benefit must be weighed against maternal risk.

Other rarer features of neonatal SLE are abnormal liver function tests and thrombocytopenia; these manifestations are transient, resolving by the age of 1 year, and infants are usually asymptomatic.

At 12–15 weeks' gestation, elevated levels of FMS-like tyrosine kinase 1 (sFlt1) were the strongest predictor of severe

adverse pregnancy outcomes. At 16–19 weeks, the combination of sFlt1 and placental growth factor (PlGF) was most predictive of severe adverse pregnancy outcome, with risk greatest for subjects with both PlGF in lowest quartile (<70.3 pg/mL) and sFlt1 in highest quartile (>1,872 pg/mL). When the sFlt1/PlGF ratio at 16–19 weeks was used as a screening test with a cutoff of more than 3.45, the positive predictive value was 41% and the negative predictive value was 97%.

Women who have antibodies to Ro/SSA and/or La/SSB are at increased risk of pregnancies complicated by fetal heart block. The goal is to detect fetal heart block at an early stage, when therapeutic interventions with steroid may prevent its progression.

ANTIPHOSPHOLIPID SYNDROME

Approximately 30–40% of women with SLE have aPL antibodies. For a diagnosis of APS, the clinical features of previous vascular thrombosis or obstetric complications must be present in addition to aPL.

Pregnancy losses occur in more than 50% of women with medium or high immunoglobulin (Ig) G anticardiolipin (aCL) tests and are more likely in women with a history of at least one fetal death. Anticoagulation is the preferred treatment: the current choices lie between aspirin, heparin or both.

Optimal treatment for women with one or more late pregnancy losses (second/third trimester) but no history of thromboembolism is controversial, most obstetricians support the use of heparin in addition to low-dose aspirin.

Intravenous immunoglobulin (IVIG) has also been used during pregnancy, in conjunction with heparin and low-dose aspirin.

Women with APS on warfarin because of previous thrombosis, who want to become pregnant, should be switched to subcutaneous heparin early enough to ensure that there is no fetal exposure during weeks 6 and 12 of gestation.

It should be remembered that both, warfarin and heparin, are perfectly safe during lactation.

Rash and arthritis can be managed with nonsteroidal anti-inflammatory drugs (NSAIDs), low-dose prednisolone (up to 10 mg/day) or hydroxychloroquine.

Ibuprofen and diclofenac are generally safe during pregnancy but should be avoided after 34 weeks of gestation.

Paracetamol and codeine-based analgesia may be used and are preferable for pain relief.

A few antihypertensive drugs are contraindicated during pregnancy (ACE inhibitors, angiotensin receptor antagonists, diuretics), given their toxicity on the fetal kidneys, causing renal failure and oligohydramnios. We should rely on old drugs such as methyldopa, nifedipine, and labetalol.

The biological drugs [e.g., anti-tumor necrosis factor (TNF) agents and rituximab] are currently not recommended during pregnancy, due to the potential trans-placental transfer. The puerperium is also a high-risk period for thromboembolic complications. A close surveillance in the first 6 weeks after delivery is warranted.

CONCLUSION

Though pregnancy constitutes a major challenge in majority of women with SLE, now they can have a successful pregnancy. A coordinated multidisciplinary team approach with judicious pharmacotherapy play the key role of success. Gone are the days when physicians would advise against pregnancy in women with LUPUS.

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CHAPTER

Asymptomatic Bacteriuria in Pregnancy

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INTRODUCTION

Asymptomatic bacteriuria (ASB) also labeled as covert bacteriuria refers to persistent, actively multiplying bacteria within the urinary tract without any symptoms or signs of acute urinary tract infection (UTI). It is diagnosed if a single bacterial species is isolated in a concentration greater than 100,000 colony forming units per milliliter of urine in clean-catch midstream urine specimens.

PREVALENCE

The prevalence of ASB is almost similar in pregnant and non-pregnant women and depends upon the population studied and varies between 2 and 10%.[1,2] The highest incidence is in African-American multiparas with sickle-cell trait, and the lowest incidence is in affluent white women of low parity. The causes of asymptomatic bacteriuria are unclear, but it is more frequent in diabetics and women of low socioeconomic status and can vary by ethnic group**.** Increased prevalence in low socioeconomic group of women may be due to early treatment of minor symptoms in high socioeconomic group women.[3] An increased risk for bacteriuria is also seen in women with a history of recurrent urinary-tract infections and anatomical abnormalities of the urinary tract.[4]

PATHOPHYSIOLOGY

Various bacteria causing ASB, originate from the large bowel, colonize the urinary tract transperineally and the most common infecting organism is *Escherichia coli*, which is responsible for 75–90% of bacteriuria during pregnancy. Other organisms frequently responsible for urinary tract infection include *Klebsiella*, *Proteus*, coagulase negative staphylococci and *Pseudomonas*.[5] The stasis associated with ureteropelvic dilatation due to progestogenic effect of pregnancy leads to more chances of upper urinary tract infection in pregnancy in women with ASB, which may be as high up to 30%.[3] In spite of progestogenic effect on ureter and urinary bladder, increased nutrient content of the urine and the presence of potential pathogens in most gravidas, only a minority of pregnant women develop bacteriuria.[6] Susceptible women may differ immunologically from those who resist infection, they are less likely to express antibody to the O antigen of *E. coli* and may display less effective leucocyte activity against the organism. Specific virulence determinants in uropathogenic strains of *E. coli*, allow adherence to uroepithelial cells and prevent bacteria from urinary lavage, allowing multiplication and tissue invasion and thus are associated with invasive infection and pyelonephritis in pregnancy. Adherence is the single marker most frequently associated with progression to pyelonephritis, and the frequency of virulence is lower in *E. coli* associated with asymptomatic bacteriuria compared to pyelonephritis. Only 22% of strains of *E. coli* isolated from women with asymptomatic bacteriuria had the capacity to adhere to uroepithelial cells compared with 75% in the group of women who developed acute pyelonephritis.[7]

DIAGNOSIS

As the name implies, asymptomatic bacteriuria is generally the absence of symptoms, although many women may report experiencing occasional episodes of dysuria, urgency and frequency retrospectively.[3] There should be a simple, safe, precise and validated screening test for ASB. The gold standard test for asymptomatic bacteriuria is urine culture and it is diagnosed if a single bacterial species is isolated in a concentration greater than 100,000 colony forming units per milliliter of urine in clean-catch midstream urine specimens.[8] For urine collected via bladder catheterization, the threshold is 100 colony forming units of single species per milliliter.[9] The use of antiseptic solutions for vulval cleansing should be avoided as it may result in a false-negative culture, soap solution or distilled water is satisfactory.

While several rapid screening tests, urine dipstick for leukocyte esterase or nitrites to detect bacteriuria have been evaluated, the general conclusion is that none performs adequately to replace the semiquantitative culture for

the detection of asymptomatic bacteriuria in pregnancy. A systematic review of diagnostic tests for asymptomatic bacteriuria in pregnancy that included eight prospective studies where any one or a combination of rapid urine tests were compared with urine culture, and the review did not support the use of any test other than urine culture for the diagnosis of asymptomatic bacteriuria.[10]

RECOMMENDATIONS FOR ASYMPTOMATIC BACTERIURIA SCREENING TESTS IN PREGNANCY

Given the evidence that effective antimicrobial therapy of ASB in pregnancy significantly reduces the risk of pyelonephritis, routine screening for the presence of clinically significant bacteriuria in all pregnant women has become necessary

- The UK's National Institute for Health and Care Excellence (2016) recommends that women should be offered routine screening for ASB by midstream urine culture early in pregnancy to reduce the risk of developing pyelonephritis[11]
- The American Academy of Family Physicians (2015) endorses the recommendations of the US Preventive Services Task Force[12]
- The American Academy of Pediatrician (2012) jointly with the American College of Obstetricians and Gynecologists (2012) advise to treat ASB and then to test for cure[13]
- The US Preventive Services Task Force (2008)[14] recommends screening of all pregnant women at 12–16 weeks' gestation (or first prenatal visit) for ASB using a urine culture, and that treatment with antibiotics significantly reduces the incidence of symptomatic maternal urinary tract infections. The evidence informing the reaffirmation of the original recommendation from 2004 is mainly drawn from a Cochrane review of treatment effectiveness[15]
- The Infectious Diseases Society of America (2005) recommends screening for asymptomatic bacteriuria by urine culture for pregnant women in early pregnancy, and treatment if results are positive, and then periodic re-testing for recurrent bacteriuria after therapy.[16]

CLINICAL CONSEQUENCES OF ASYMPTOMATIC BACTERIURIA

There is some association between ASB with pyelonephritis, preterm birth and low birth weight. Studies found that ASB in pregnancy is significant clinically because 20–30% of untreated cases progress to acute pyelonephritis.[3] If initial positive urine culture results are promptly treated, fewer than 1% of women develop a urinary tract infection. A meta-analysis of 13 randomized or quasi-randomized controlled trials (RCTs) of antibiotic treatment versus no treatment for pregnant women with asymptomatic bacteriuria found that treatment substantially decreased the risk of the development of pyelonephritis [odds ratio (OR) 0.24, 95% confidence interval (CI) 0.19, 0.32].[15]

The results of the studies on perinatal outcomes of untreated ASB are controversial, although a number of them demonstrated a relationship of ASB in pregnant mothers and the risk of premature delivery and/or lower birth weight, some other studies failed to prove the association.[17] In the Cochrane Review that included ten randomized or quasi-randomized controlled clinical trials where the outcome of preterm delivery or low birth-weight was reported, antibiotic treatment was shown to be associated with a reduction in this outcome (OR 0.60, 95% CI 0.45, 0.80).[18] There is, however, disquiet over these results because of the poor methodological quality of the studies included in this review, for this reason, conclusions about the strength of the association between preterm delivery and asymptomatic bacteriuria need to be drawn cautiously.

The mechanism for an association between preterm labor and asymptomatic bacteriuria has not been established, but a theoretical argument is made for a causative role for the production of phospholipase A2 by microorganisms, which then can initiate labor through the activation of prostaglandin.[19] While this mechanism has been well defined for intra-amniotic infection and symptomatic pyelonephritis, there has been no recent research to explore the mechanisms through which asymptomatic bacteriuria exerts adverse pregnancy outcomes.

TREATMENT

The presence of ASB in a pregnant woman is an absolute indication for initiation of the treatment. The benefits of such a strategy with bacteriological follow-up were summarized by Smaill and Vazquez for the Cochrane Library, on the basis of the results of 14 RCTs, embracing 2302 pregnant women with ASB, in which the effects of different antibiotics given for different duration were compared to placebo or untreated groups.[15] The analysis of 5 of these trials, involving 820 pregnancies, showed that antibiotics effectively cleared ASB. Management of ASB in pregnancy consists of short-term, usually 5–7 days, oral antibiotic therapy (Table 1). Recently, a growing number of authors suggest that a reasonable first choice drug in the second and third trimester is the nitrofurantoin.[20,21] As shown by most recent studies, nitrofurantoin is active against nearly 90% of *E. coli* strains isolated from urine, including 89% of extended spectrum β-lactamase (ESBL)-producing strains.

TABLE 1: Treatment of asymptomatic bacteriuria (doses for normal renal function)

Screening (obligatory)	*1st prenatal visit or 12–16 weeks of pregnancy*
First-line treatment	• Amoxicillin 500 mg every 8–12 h—for 3–7 days • Cephalexin 500 mg every 12/6 h—for 3–7 days
FDA category B	• Amoxicillin/clavulanic acid 500 mg every 12 h—for 3–7 days • Nitrofurantoin 100 mg every 12 h—for 5–7 days • Cefuroxime 250 mg, every 12 h—for 3–7 days • Cefpodoxime 100 mg every 12 h—for 3–7 days
FDA category C	• Trimethoprim with sulfamethoxazole 960 mg every 12 h for 5 days

FOLLOW-UP URINE CULTURES

All pregnant women with ASB should have periodic screening after therapy, since as many as one-third of them experience a recurrent infection.[22] Follow-up cultures should be obtained one to two weeks after treatment and then repeated once a month. In case of persistent or recurrent bacteriuria, longer antibiotic therapy using the same agent (e.g., 7 instead of 3 days of treatment) or another first line drug is recommended. Subsequent treatment courses are administered until the bacterial counts drop to nonsignificant levels. If bacteriuria persists despite repeated courses of therapy, as well as in women with additional risk factors (e.g. immunosuppression, diabetes, sickle cell anemia, neurogenic bladder) or recurrent/persistent UTIs before pregnancy, one should consider antimicrobial prophylaxis.

CONCLUSION

Screening for asymptomatic bacteriuria is included as one of the cost-effective strategies for maternal and neonatal health in developing countries. Treatment of asymptomatic bacteriuria decreases the incidence of antenatal pyelonephritis. The reduction in low birth-weight and preterm birth with antibiotic treatment is consistent with theories about the role of infection in adverse pregnancy outcomes, but this association should be interpreted with caution given the very poor quality of the included studies. A semi-quantitative urine culture remains the best test for detecting bacteriuria.

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CHAPTER

Pregnancy and Jaundice

Narendra K Gajjar

INTRODUCTION

The incidence of jaundice in pregnancy in India varies from 0.4 to 0.9/1000 deliveries. Maternal mortality is around 18%. Main causes of maternal mortality are coagulation failure, hemorrhage, hepatic coma, renal failure and septicemia. Incidence of preterm labor is increased and the perinatal mortality is around 23%.[1]

Jaundice is yellow discoloration of skin, conjunctiva, sclera and mucosa associated with rise in serum bilirubin above 2 mg/dL (normal 0.2–01 mg/dL) Latent jaundice: 1–2 mg/dL. It occurs due to increased production of bilirubin or impaired hepatocyte transport or conjugation or impaired excretion of bilirubin into intestine.[2]

The occurrence of hepatobiliary disease with or without jaundice during pregnancy provides interesting and urgent diagnostic challenge to obstetrician and hepatologist. Advances in understanding and management of liver disorders unique to pregnancy and hepatobiliary disease in general have resulted in a significant improvement in maternal and fetal outcome.[3]

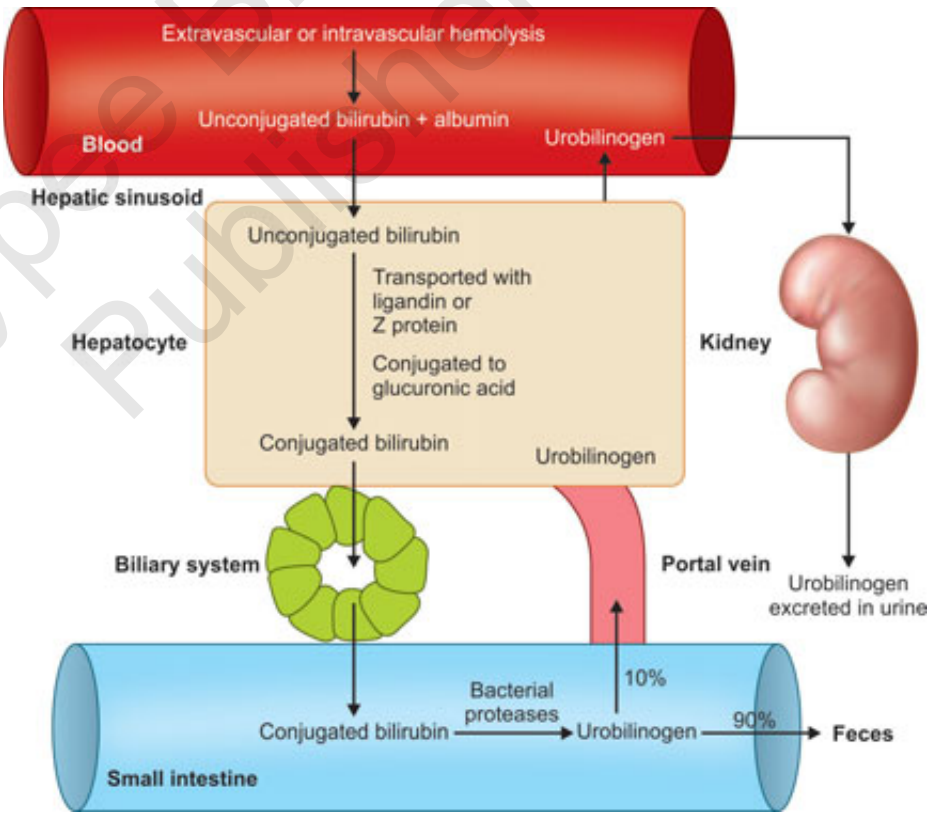


Figure 1: Mechanism of conjugation of bilirubin in liver.

LIVER IN NORMAL PREGNANCY

In pregnancy plasma volume increases by 50%, but with disproportionate increase in red cell mass by 20%, there is resultant hemodilution. This phenomenon should be kept in mind during interpretation of all serum concentrations used in evaluation of hepatic function during pregnancy. Serum albumin decreases, serum cholesterol, triglyceride and fibrinogen increases. Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), prothrombin (PT), bile acid levels are not affected. Serum alkaline phosphatase level almost doubles due to its placental isozyme bilirubin, gamma-glutamyltranspeptidase(GGTP) slightly decreases.[4,5]

Jaundice is a clinical manifestation of liver disorders or hematological disorders or some conditions unique to pregnancy.

Liver disorders that occur in pregnancy can be divided into three groups:[4,5]

1 Liver diseases unique to pregnancy
   - Hyperemesis gravidarum
   - Intrahepatic cholestasis of pregnancy
   - In pre eclampsia and eclampsia, HELLP syndrome
   - Acute fatty liver of pregnancy.
2 Liver diseases coincidental to pregnancy
   - Viral hepatitis A, B, C, D, E herpes simplex
   - Malaria, sickle cell crisis, leptospirosis
   - Gallstones, Budd-Chiari syndrome
   - Drugs.
3 Pregnancy in preexisting liver disease
   - Chronic viral hepatitis, hepatitis B virus (HBV), hepatitis C virus (HCV), nonalcoholic fatty liver disease
   - Portal hypertension, autoimmune hepatitis, Wilson's disease
   - Primary biliary cirrhosis, primary sclerosing cholangitis.
   - Liver tumors.[4,5]

A careful clinical history, physical examination, appropriate laboratory tests and radiological investigations should allow a diagnosis within short time. Liver biopsy is rarely required.

Important points in history:

- Duration of jaundice, interval between symptoms and jaundice
- Exposure to contaminated food or water
- Exposure to medication over-the-counter (OTC), prescribed by physician, complementary or alternative, herbal or vitamin preparations, anabolic steroids, parenteral exposure, transfusions, intravenous abuse, tattoos, sexual activity, use of alcohol
- Past history of jaundice may suggest chronic hepatitis, cirrhosis, intrahepatic cholestasis or genetic nonhemolytic hyperbilirubinemia
- Family history of hemolytic anemia, sickle cell disease, congenital hyperbilirubinemia.[4]

Symptoms

Yellow coloring of skin and eyes, pruritus, nausea, vomiting, weakness, fever, headache dyspepsia, anorexia, loss of appetite, fat intolerance, changes in color of urine (dark yellow) and stool (light colored), right upper quadrant abdominal pain, biliary colic, arthralgia, myalgia, rash, etc.

Appearance of jaundice within 2 weeks of constitutional symptoms like nausea, vomiting, anorexia may suggest hepatitis or calculus biliary obstruction. If such symptoms appear more than 2 weeks prior to jaundice, it may suggest chronic hepatitis or alcoholism or exposure to toxins.

Signs and symptoms of liver disease in pregnancy are not specific, but the underlying disorder can have significant effects on maternal and fetal outcome. Early recognition can be lifesaving.

In addition to routine clinical examination, systemic examination and obstetric evaluation, palpation of liver for enlargement, surface consistency, tenderness along with splenic enlargement and examination for ascites is helpful.

Skin may show scratch marks due to pruritus and bruising due to disturbed coagulation. Spider telangiectas on trunk, arms, and hands may be normal in pregnancy but its presence may suggest chronic hepatocellular jaundice.[4,6]

Investigations

- Complete blood count [hemoglobin (Hb), total count (TC), differential unit (DC), platelet count, indices]
- Blood group, blood sugar, peripheral smear
- Liver function tests: ALT, AST, serum bilirubin, alkaline phosphatase, serum albumin, and globulin, lactate dehydrogenase (marker of hemolysis) elevated >600 U/L in HELLP syndrome, gamma-glutamyl transferase (GGT)
- *Renal function tests:* Urine—routine and microscopy, serum urea, uric acid, creatinine
- *Coagulation profile:* Prothrombin time (PT), activated partial thromboplastin time (APTT), serum fibrinogen, fibrin degradation product (FDP), D-diamer
- Serum electrolytes
- IgM HAV (hepatitis A virus)
- HBsAg (hepatitis B virus)
- Antibodies and PCR tests for HCV (hepatitis C virus)
- IgM HEV (hepatitis E virus)
- Tests for HSV (herpes simplex virus)
- USG, CT scan for hemorrhage in liver, MRI, liver biopsy rarely
- Tests for fetal surveillance—electronic fetal monitoring, ultrasonography, color Doppler.[6]

LIVER DISEASES UNIQUE TO PREGNANCY

Hyperemesis Gravidarum

Persistent vomiting associated with weight loss greater than 5% of prepregnancy body weight and large ketonuria in 1st trimester. It is related to rapidly rising serum levels of chorionic gonadotropin or estrogen or both. About 10% cases need hospitalization for hyperemesis. Acidosis results from starvation and alkalosis from loss of hydrochloric acid in vomitus and hypokalemia. Severe cases may have psychological component also.

Existence of jaundice induced by hyperemesis is controversial. It is caused by conjugated hyperbilirubinemia. Bilirubin level may be normal or mildly elevated. Serum alanine aminotransferase activity is increased <500 IU/L.

Treatment

Correction of dehydration by IV crystalloid solutions, antiemetic—ondansetron, vitamin B6 + Doxylamine, correction of electrolyte deficiency and acid-base imbalance.

Intrahepatic Cholestasis of Pregnancy

Recurrent jaundice of pregnancy/cholestasis hepatosis/icterus gravidarum.

It is the second common cause of jaundice in pregnancy next to viral hepatitis.

Incidence 0.6%—variations due to genetic influence. Cause is unknown. High estrogen concentrations in susceptible or defects in secretion of sulfated progesterone metabolites may play a role. Some cases are related to many gene mutations that control hepatocellular transport systems (mutation of MDR 3 gene in progressive familial intrahepatic cholestasis). Drug like azathioprine impaired canalicular transport of bile acids and aggravate the disorder.

Main symptom is pruritus in late 2nd trimester, increases as pregnancy advances. Constitutional symptoms like anorexia, malaise are rare. Jaundice in 10% of cases. USG is helpful to exclude cholelithiasis and biliary obstruction. Pruritus usually precedes 3 weeks of abnormal biochemical tests and resolves 48 hours postpartum. Biochemical abnormalities resolve within 2–8 weeks.[4] Etiopathology of pruritus is explained in the flowchart 1.

Treatment

Antihistaminics and topical emollients, cholestyramine 4 g TID, ursodeoxycholic acid 600 mg/day for 20 days followed by drug-free period of 14 days and repeat course.

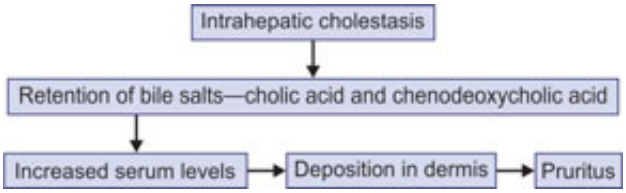
Fetal Complications

MSL due to increased colonic motility by bile acids, fetal distress and meconium passage, preterm labor, CTG abnormalities, RDS, IUFD.

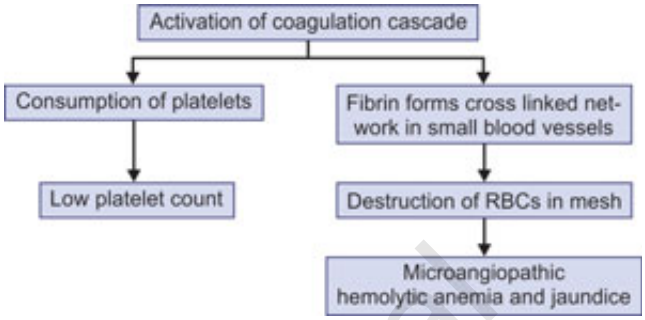
Fetal monitoring by CTG on alternate day and weekly assessment of amniotic fluid followed by elective delivery at 38 weeks of pregnancy.

HELLP Syndrome

- Louis Weinstein named HELLP syndrome in 1980
- H—Hemolysis, E—Elevated Liver enzymes; L—Low platelet count.
- Incidence 0.5–0.9% of all pregnancies in preeclampsia cases 10–20%.
- 70% cases in antepartum period, out of which 50% during 27–37 weeks of gestation, 14% after 37 weeks and 6% cases before 27 weeks



Flowchart 1: Etiopathology of pruritus.



Flowchart 2: Etiopathogenesis of consumptive coagulopathy.

- 30% cases in postpartum period

Exact cause is not known. HELLP need not be accompanied by severe hypertension. Mild preeclampsia can trigger events leading to HELLP. In many cases preeclampsia is diagnosed before development of HELLP. In some cases symptoms of HELLP syndrome are 1st warning signs of preeclampsia. Preeclampsia and HELLP may have a common cause.Defective trophoblastic invasion leads to inadequate placental perfusion, hypoxia, endothelial cell dysfunction, hypertension, proteinuria, platelet activation, aggregation and eventually activation of coagulation cascade.[4]

Liver is the main affected organ. Liver enzymes are elevated due to periportal hemorrhage and necrosis caused by ischemia.[4] Etiopathogenesis of consumptive coagulopathy is shown in flowchart 2.

Risk Factors

History of HELLP in previous pregnancy (19–27%). Preeclampsia (PIH), age >25 years, multiparity, obesity, diabetes, lack of exercise, poor nutrition, Caucasians.[6]

Symptoms

Fatigue, feeling of not well-being (Malaise) since few days (90%), viral type illness which may exacerbate during night.

Pain—Right upper quadrant or epigastric (86–90%). It may be fluctuating or colicky, radiating pain in neck, shoulder, upper arm of liver origin.[6]

Nausea and/or vomiting (45–84%)—worsening, headache (50%).[6]

Fluid retention and excessive weight gain, dyspnea, blurring of vision, epistaxis or other bleeding that will not stop easily, seizures rarely.[6]

Signs

Right quadrant tenderness on palpation (86%), enlarged liver. Hypertension—diastolic BP >110 mmHg (66%), tachycardia, tachypnea, demonstrable edema (55–67%), proteinuria—(86–100%), Jaundice—(5%), occasionally hypoglycemia, non-cardiogenic pulmonary edema, coma, cortical blindness, transient diabetes insipidus due to increased vasopressinase, because of impaired hepatic metabolism of this enzyme.[6]

Diagnosis

In some cases of developing HELLP syndrome, hypertension and proteinuria may not be present and its symptoms may be easily mistaken for other conditions like cholecystitis,

TABLE 1: Mississippi-triple class classification

	Severe (class 1)	*Moderate (class 2)*	*Mild (class 3)*
Platelets	≤50,000/μL/cmm	100,000–150,000/cmm	100,000–150,000/cmm
Serum glumatic oxaloacitic transaminase (SGOT)	≥70 IU/L	≥70 IU/L	≥40 IU/L
Lactate dehydrogenase (LDH)	≥600 IU/L	≥600 IU/L	≥600 IU/L
Incidence of bleeding	13%	8%	No increase

esophagitis, gastritis, hepatitis, or idiopathic thrombocytopenia.[6]

Any pregnant woman who presents with malaise or a viral-type illness or right upper quadrant/epigastric pain in the third trimester should be evaluated with complete blood cell count and liver function tests. Early diagnosis is critical because the morbidity and mortality rates associated with HELLP syndrome have been reported to be as high as 25%.[6]

Tenessee classification system (Sibai 2004—strict criteria for diagnosis)

1. Abnormal peripheral smear for the diagnosis of intravascular hemolysis
2. Elevated serum bilirubin >1.2 mg/dL
3. Elevated LDH levels > 600 u/L
4. Platelet count <100,000/cmm
5. SGOT level >70 IU/L.

Severe and moderate class indicate—severe hemolysis. Mild indicates clinically significant transition stage which may progress (Table 1).

Differential Diagnosis

Inflammatory and infective conditions: Urinary tract infection (UTI), acute pancreatitis, gastritis and gastric ulcers cholecystitis and cholangitis (gall- bladder disease), hepatitis, placental abruption, renal colic, eclampsia, hyperemesis, hemolytic anemia.

Acute fatty liver of pregnancy, jaundice—viral hepatitis, thrombocytopenia, ITP, folate deficiency, SLE, benign thrombocytopenia of pregnancy, antiphospholipid antibody syndrome, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome.

Maternal Complications in HELLP

Maternal complications in HELLP are given in table 2.

TABLE 2: Maternal complications in HELLP

Placental abruption	15.4%
DIC, hemorrhage, hematoma	5–56%
Cerebral—edema, hemorrhage, infarction, stroke, thrombosis	10.6%
Eclampsia	6%
Ascites, pleural effusion	9.6%
Acute renal failure, nephrogenic diabetes insipidus	7.7%
Pulmonary edema	4.8%
Retinal detachment	2.5%
Liver—subcapsular hematoma, hemorrhage in liver, rupture liver	1.9%

Maternal mortality up to 25%.

Death due to rupture of liver, cerebral hemorrhage (stroke), DIC, ARDS, renal failure, sepsis.

Neonatal complications: Preterm labor 70%, IUGR, neonatal thrombocytopenia, intraventricular hemorrhage, RDS.

Perinatal mortality—7.4–34%, stillbirth 51/1,000 (higher than eclampsia)

DIC: 20% of women with HELLP syndrome develop DIC but when HELLP is complicated by acute renal failure incidence of DIC increases up to 84%. Many patients of HELLP syndrome demonstrate no abnormalities on coagulation studies, although an underlying coagulopathy is usually present.

Management

Definitive therapy is delivery though appropriate for mother but may not be so for fetus. Assessment of liver functions, renal functions, and coagulation profile should be made. Before delivery, aggressive obstetric management should be directed toward stabilization of the affected organ systems.

Control of Convulsions and Hypertension

Prophylactic magnesium sulfate to prevent seizures. HELLP syndrome should be treated with a bolus of 4 g of magnesium sulfate in 20% solution IV initially. This dose is followed by a maintenance infusion of 1 g per hour. The infusion should be titrated to urine output, respiratory rate, and reflexes.

- Patient should be observed for signs and symptoms of magnesium toxicity. If toxicity occur
- 10 mL calcium gluconate 10% over 10 minutes should be given intravenously
- Antihypertensive treatment reduces risk of maternal cerebral hemorrhage, placental abruption and sezures
- Hydralazine, initial dose 5 mg intravenously followed by small incremental doses of 2.5–5 mg every 15–20 minutes until the desired blood pressure is achieved
- *Labetalol:* 20 mg IV repeated every 10 min—max 300 mg, oral: 100 mg BD
- *Nifedipine:* 10 mg tab orally, action starts in < 20 min (peak action 60 min), 10 mg every 15 min, max 180 mg/day. sublingual route is not preferred.

Fluid and Electrolyte Balance

Cautious balance to be maintained between hypoperfusion and pulmonary edema. Ideally guided by central venous pressure (CVP) measurement or more accurately pulmonary artery wedge pressure. Fluid intake limited up to 150 mL/h.

Stabilization of Patient

Monitoring of vital functions and transfusions. Between 38 and 93% of patients with HELLP syndrome need some form of blood product.

Correction of Coagulopathy and Anemia

Patients with a platelet count greater than 50,000 per mm^3 and S. fibrinogen levels >100 mg/dL are less likely to bleed. These patients do not require components unless the platelet count drops to less than 50,000 per mm.[3] Patients who undergo cesarean section should be transfused if their platelet count is less than 50,000 per mm^3. Patients with DIC should be given fresh frozen plasma, cryoprecipitate, platelets and packed red blood cells.

Delivery

Prior to 27 weeks—termination of pregnancy after stabilization of patient and correction of underlying coagulopathy.

After 27 weeks delivery within 24 hours after stabilization of patient and corticosteroids coverage. Expectant management does not improve perinatal outcome. Insufficient evidence to conclude benefits of corticosteroids for maternal condition.

Mode of delivery depends up on obstetric factors and rapidity of worsening of disease. Either cesarean section or induction of labor may be appropriate as per clinical findings and favorability of cervix. The cesarean section rate has climbed up from 10% to 50% with low perinatal mortality rate and maternal mortality rate in cesarean group. Ergometrine not to be used after delivery. $MgSO_4$ should be continued 24 hours after delivery.

Hepatic Hemorrhage

Surgery/embolization/recombinant factor VIIa.

Alert

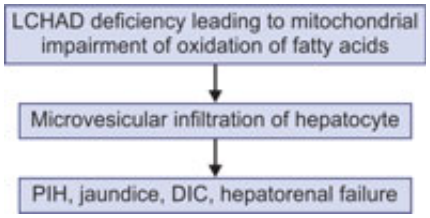
Multiorgan failure.

Recovery

Most of the patients begin to recover within 2 days after delivery. Patients with complications like placental abruption, DIC or renal disease need extensive treatment.
Risk of recurrence in subsequent pregnancy is low.

Acute Fatty Liver of Pregnancy

Autosomal recessive inherited disorder (Flowchart 3).



Flowchart 3: Incidence: 1 in 1,000 pregnancies

It is more common in nulliparous woman with male fetus. presents late in 3rd trimester of pregnancy. Recurrence, more likely if woman has a homozygous enzyme deficient fetus.

Symptoms like malaise, anorexia, nausea, vomiting, epigastric pain and progressive jaundice develop over several days to weeks. Persistent vomiting is the major symptom in many cases. About 50% of women have signs of preeclampsia—hypertension, proteinuria, and edema. Severe liver dysfunction leads to hypofibrinogenemia, hypoalbuminemia, hypercholesterolemia, thrombocytopenia, prolonged clotting time. Impaired cholesterol synthesis leads to damage to erythrocyte membrane and hemolysis.
Laboratory findings: Jaundice—hyperbilirubinemia <10 mg%, SGOT in hundreds, Neutrophilia,↑PT, ↑Creatinine and ↑Uric acid.

Maternal Complications

Hypoglycemia, hepatic encephalopathy (in 60%), severe coagulopathy (in 55%) renal failure (in 50%), hemorrhage, acidosis, acute pancreatitis, sepsis, GI bleeding, ascites.

Maternal mortality has improved now. Fetal mortality—15–20%.

Treatment

Expeditious delivery and maximal supportive care, which may include intensive care unit monitoring, blood component therapy, glucose infusion, sodium restriction, diuretic agents, mechanical ventilation, and dialysis. The role of hepatic transplantation in accute fatty liver of pregnancy appears limited. The risk of mortality during AFLP must be compared with the short- and long-term morbidity and mortality associated with liver transplantation. Liver function usually returns to normal within a week in postpartum period (Table 3).[7]

TABLE 3: Comparison of different causes of jaundice in pregnancy

Disorders	*Gestational period at presentation*	*Prevalence*	*Symptoms*	*Specific laboratory tests*	*Outcome*	*Treatment*
Hyperemesis gravidarum	First trimester; resolves after 20 wk	<2% (primigravid)	Nausea and vomiting	AST, ALT <500 IU/L; ALT >AST; low TSH , bilirubin normal /mild rise	Electrolyte imbalance, complications of retching. Thiamine and vitamin K deficiency	IV fluids; thiamine pyridoxine; promethazine ondansetron

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Disorders	Gestational period at presentation	Prevalence	Symptoms	Specific laboratory tests	Outcome	Treatment
Intrahepatic cholestasis of pregnancy	Second trimester	<10% multifetal gestations	Pruritus is main symptom resolves in postpartum period	AST, ALT <1000 IU/L; GGT normal; bile acid levels high (10–14 umol /L; PT normal; bilirubin <6 mg/dL, clay stool, steatorrhea	Increased gallstones and risk for fetal distress, MSL increases. Reoccurs in subsequent pregnancy	UDCA, delivery if fetal distress is imminent or at 38 weeks
Eclampsia, preeclampsia	Beyond 20 weeks; recurs	5% nulliparous, multifetal gestations	High blood pressure, proteinuria, edema, seizures, renal failure, pulmonary edema	Uric acid level elevated	Maternal mortality, 1%; prematurity and fetal death, 5–30%	Labetalol, nifedipine, methyldopa, magnesium sulfate; early delivery
HELLP syndrome	Beyond 22 weeks and after delivery; 20% progress from severe eclampsia	0.5%	Abdominal pain, seizures, renal failure, pulmonary edema, liver hematoma and rupture	Platelets <100,000/ mm^3; hemolysis; high LDH level; AST, ALT 70–600 IU/L; Uric acid normal / elevated. Bilirubin up to 5–6 mg% in terminal stage	Hepatic rupture, with 60% maternal mortality; DIC 20–40%; fetal death, 1–30%	Prompt delivery, correction of coagulopathy, magnesium sulfate, antihypertensive drugs
Acute fatty liver of pregnancy	Third trimester; 50% have eclampsia	1/13,000; primiparous, multifetal gestations	Progress quickly to FHF, diabetes insipidus, hypoglycemia	TC elevated. Platelets <100,000/ mm^3; AST, ALT >300 IU/L; PT elevated; fibrinogen level low; bilirubin level increased <10 mg%;. Hypoglycemia common. Uric acid elevated. CT scan may show fatty liver	DIC 75%, maternal mortality <20%; fetal mortality up to 45%; test for LCHAD	Prompt delivery; correction of coagulopathy, renal dysfunction, electrolyte imbalance. Liver transplantation controversial
Acute viral hepatitis	Any stage of gestation	No specific predilection but more common in women with risk factors like contaminated food and water or parenteral transmission or high risk sexual behavior	Nausea, vomiting, anorexia, headache. malaise, fever, epigastric pain may precede jaundice 1 to 2 weeks	ALT >1000 IU/ Bilirubin 5–20 mg% TC normal , uric acid and CT scan normal. DIC rare	Usually complete clinical cure except cases of chronic hepatitis B, HEV and HSV	Early delivery is not recommended

LIVER DISEASES COINCIDENTAL TO PREGNANCY

Acute Viral Hepatitis

Most common cause of jaundice in pregnancy. No increased risk of fetal malformation but perinatal mortality is increased due to higher rate of prematurity and stillbirth.

Early Delivery is not Required

Viral markers help in diagnosis. Immunoprophylaxis of fetus is important. 5 distinct types. Hepatitis A, hepatitis B, hepatitis C, hepatitis D (B associated delta virus), hepatitis E. Immune response to virus causes hepatocellular necrosis (Table 4).

Many infections are subclinical

- Symptoms like nausea, vomiting, headache, malaise may precede jaundice by 2 weeks
- Serum transaminase levels ranging from 400-4000 u/L and its peak may not correspond to disease severity
- S bilirubin levels are higher (5–20 mg/dL) may continuously rise.
- No association with preeclampsia
- Coagulopathy can occur in fulminating hepatic necrosis

TABLE 4: Important features of different types of viral hepatitis

	Hepatitis A	*Hepatitis B*	*Hepatitis C*
Virus	• 27 nm RNA picornavirus	• DNA Hepadnavirus	• Single-stranded RNA flaviviridae virus
Mode of transmission	• Fecal-oral route • Ingestion of contaminated food, water or blood	• Parenteral route, IV drug abuse, homosexuals, blood and blood products, vertical transmission	• Same like hepatitis B, more prevalent in IV drug users, hemophilics and high risk sexual behavior, vertical transmission
Incubation period	• 4 weeks	• 6 weeks to 6 months	• 6–10 weeks
Antigens	• Hepatitis A antigen	• HBcAg core antigen • HBsAg surface antigen appear first, HBeAg-antigen suggest presence of viral particles and chronic infection • Sero+ve cases are at higher risk of hepatocellular carcinoma	• HCV core antigen
Antibodies	• IgM may appear as early as 5 days before symptoms and persists for several months	• Anti-HBc (IgM) appear within 4 weeks and persists up to 22 weeks • Anti-Hbc (IgG) appear after 6 weeks and persists longer. • Anti-HBs appear after at 22 weeks and persists for years. • Anti-HBe appear after 16 weeks and persists longer	• Anti-HCV antibodies may be detected after 15 weeks or may not be detectable. It usually does not prohibit transmission. So seropositivity and screening program is not useful in pregnancy
Chronic infection (hepatitis lasts longer than 6 months)	• Not seen	• 5–10% adults • 70–90% infants	• 86% of sero +ve cases have chronic infection
Fulminating hepatic necrosis and long-term complications	• Very rare	• Higher rate of fulminating hepatic necrosis, cirrhosis and hepatocellular carcinoma	• Very slow progression to cirrhosis (20–30 years)
Maternal mortality	• Can occur in under-privileged population. Incidence very low	• Higher incidence relatively	• Does not affect course of pregnancy, no increase in maternal mortality
Perinatal outcome	• Increased rate of preterm birth	• Increased rate of preterm birth, stillbirth with high viral load	• Does not affect course of pregnancy, no effect on perinatal outcome even in cases of high viral load
Vertical transmission	• No transplacental transmission but it can occur in NICU in postpartum period	• Transplacental can occur. In postpartum period also through breast milk. Higher rate 85%	• 5–6%
Prenatal screening	• Not useful	• Helpful to diagnose chronic hepatitis and in prevention of neonatal transmission	• Not recommended
Co-infection with HIV	• No effect	• Relatively more common with increased liverrelated morbidity	• Does not worsen prognosis but risk of vertical transmission is increased
Immunization	• *Active:* Formalin inactivated vaccine to susceptible persons • *Passive:* 0.02 mL/kg immunoglobulin for recent exposure during pregnancy	• High risk susceptible seronegative mother—Hepatitis B vaccine can be given during pregnancy • For baby at birth • Hepatitis B vaccine and immunoglobulin to neonate of hepatitis B seropositive mother. Complete vaccination lowers down the risk of transmission due to breastfeeding	• No vaccine because antibodies do not prevent transmission

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	Hepatitis A	*Hepatitis B*	*Hepatitis C*
Treatment	• Balanced diet, diminished activity, watch for fuminant liver disease	• Balanced diet, diminished activity, watch for coagulopathy	• Balanced diet, diminished activities
Prevention	• Vaccination, avoid contaminated food and water and handling feces, secretions without wearing gloves, hygienic practices, hand washing etc.	• Vaccination, avoid needle stick injury, proper transfusion protocols, screening during pregnancy, safety measures for sex and universal precautions during labor and surgery.	• Avoid needle stick injury, only judicial transfusions, safety measures for sex and universal precautions during labor and surgery. Testing of blood donors

- Usually there is complete clinical and biochemical recovery within 1–2 months in all cases of hepatitis A and most of the cases of hepatitis B.

Hepatitis D (Delta hepatitis)—Defective RNA virus (Hybrid particle with HBsAg coat and a delta core. Virus must co-infect with hepatitis B virus. Transmission is similar to hepatitis B. Chronic infection with B and D hepatitis is more severe and up to 75% of co-infected patients develop cirrhosis. Neonatal transmission is unusual in cases having vaccination of hepatitis B.

Hepatitis E—Waterborne RNA virus, enteric transmission with epidemic outbreaks resembling hepatitis A. It is more severe during pregnancy with higher incidence of transplacental vertical transmission.

Herpes simplex virus: Many subclinical cases.Severe hepatitis in pregnancy and immunocompromised patients. Jaundice usually not present. Orogenital eruptions help in diagnosis. Confirmation by serology and inclusion bodies in liver biopsy. Mortality high up to 43%. Acyclovir is effective in treatment.

Other Causes of Jaundice in Pregnancy

- Leptospirosis, malaria, sickle cell crisis and hemolytic jaundice are treated as in nonpregnant woman
- *Gall-stones*: Pregnancy increases cholelithiasis. It may present as biliary colic, acute cholecystitis or acute pancreatitis. USG is helpful in diagnosis
- ERCP with minimal fluoroscopy can be done
- Cholecystectomy may be required, open or laparoscopic depending up on stage of gestation.

Drugs

Drug induced cholestasis can present with asymptomatic disease where the only clinical manifestation is an elevation in alkaline phosphatase. Moreover, the target of injury can vary from a mixed hepatocellular cholestatic injury, to impairment of canalicular bile flow resulting in pure intrahepatic cholestasis, or to an "obstructive" drug induced cholangiopathy where the initial site of injury is located at various levels of the bile duct epithelium.

Nitrofurantoin, anabolic steroids, chlorpromazine, prochlorperazine, cimetidine, erythromycin, estrogen, and statins can cause cholestasis and jaundice.

Methyldopa and labetalol have been associated with hepatotoxicity including liver failure.[8]

Liver tumors (adenoma) can enlarge and rupture during pregnancy so pregnancy is contraindicated in presence of unresected adenoma.

PREGNANCY IN PRE-EXISTING LIVER DISEASE

Chronic Hepatitis

Continuing hepatic necrosis, inflammation and fibrosis leading to cirrhosis due to chronic infection with HBV, HCV viruses or autoimmune chronic hepatitis

Pregnancy outcome depends up on intensity of disease and presence of portal hypertension. Long term prognosis is poor so woman should be counseled regarding possibility of liver transplantation. Termination of pregnancy and sterilization.

Autoimmune Hepatitis

Autoimmune hepatitis is a progressive liver disease that predominantly affects women of all ages and can manifest at any time during gestation and the postpartum period.[4]

The disease activity is usually attenuated during pregnancy, and dosages of medication can be decreased because of the state of immune tolerance induced by the pregnancy.

Flares occur in 11% of patients during gestation and up to 25% in the postpartum period.[7]

There is an increased risk of prematurity, low-birth-weight infants, and fetal loss.

Pregnancy does not contraindicate immunosuppressive therapy. Both prednisone and azathioprine (FDA category D at dosages <100 mg/day) are considered safe during pregnancy and lactation.

Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis

Primary biliary cirrhosis and primary sclerosing cholangitis are autoimmune diseases that can overlap with autoimmune hepatitis.

Pregnancy is rare in these conditions and carries a high risk of prematurity, stillbirths, and liver failure.

In patients with primary biliary cirrhosis, pregnancy can induce a new-onset pruritus or worsen a preexisting pruritus.

Diagnosis is not different from that in the nonpregnant woman. Ursodeoxycholic acid is considered FDA category B and can be continued safely in pregnancy

Primary sclerosing cholangitis is rarely described in pregnancy; pruritus and abdominal pain seem to be the major symptoms.

Alkaline phosphatase and γ-glutamyl transferase levels are elevated. Diagnosis relies on clinical and ultrasound findings. No specific treatment exists for primary sclerosing cholangitis, but ursodeoxycholic acid and stabilization of cirrhosis, when present, have been associated with good outcome.

Wilson's Disease

Wilson's disease is an inherited autosomal recessive defect of copper transport.

Fertility in Wilson's disease is decreased but can improve with therapy.[7]

Treatment should be initiated before conception and should not be interrupted during pregnancy, because of the risk of fulminant liver failure.

The treatment of choice in pregnancy is zinc sulfate 50 mg three times daily (FDA category C), because of its efficacy and safety for the fetus.

Patients who are treated with d-penicillamine (FDA category D) or trientine (FDA category C) before pregnancy require a dose reduction by 25—50% of that in the pre-pregnancy state especially during the last trimester, to promote better wound healing if a cesarean section is to be performed.

Nonalcoholic Fatty Liver Disease

Obesity, type 2 diabetes mellitus and hyperlipidemia coexist. It may be asymptomatic with elevated aminotransferase levels. It may progress to cirrhosis. Weight loss, control of diabetes and dyslipidemia are recommended.

Cirrhosis and Pregnancy

Usually infertile but women with symptomatic cirrhosis and pregnancy have poor outcomes. Hepatic failure, variceal hemorrhage, preterm delivery, IUGR as well as maternal death can occur.

Portal Hypertension and Esophageal Varices

Portal vein pressure may rise due to intrahepatic or extrahepatic resistance to flow. Bleeding from esophageal varices can be severe and life-threatening, especially if it is due to cirrhosis. Endoscopic, band ligation or sclerotherapy or balloon temponade or transjugular intrahepatic portosystemic stent shunting can control bleeding.

Pregnancy after Liver Transplantation

Close surveillance for hypertension, graft rejection, pre-eclampsia, renal dysfunction is necessary. Perinatal mortality is also higher.

Jaundice in pregnancy should be jointly managed by a coordinated team of senior obstetrician, hepatologist, hematologist, intensivist, neonatologist and physician.

Early diagnosis, timely obstetric intervention, better fetal surveillance with anticipation, recognition and proper management of complications like hemorrhage, liver failure, renal dysfunction, coagulopathy, encephalopathy, acidosis, CV stroke, along with advanced neonatal services have improved maternal and neonatal outcome.

Good antenatal care, early recognition and control of preeclampsia, screening and prophylaxis against viral hepatitis will decrease incidence of jaundice in pregnancy.

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CHAPTER

Pregnancy with Hyperthyroidism

Monika Singh, Uma Pandey

INTRODUCTION

Pregnant women with hyperthyroidism need careful evaluation and management as some may be at increased risk of fetal loss, preeclampsia, heart failure, premature labor, and having a low birth weight baby. Graves' disease (80–85%) is the most common cause of maternal hyperthyroidism during pregnancy and it occurs in 1 in 1,500 pregnant patients.[1] In addition to other usual causes of hyperthyroidism, very high levels of hCG, seen in severe forms of morning sickness (hyperemesis gravidarum), may cause transient hyperthyroidism. As 123 Iodine thyroid scanning is contraindicated during pregnancy due to the small amount of radioactivity, which can be concentrated by the baby's thyroid. The diagnosis of hyperthyroidism can be somewhat difficult during pregnancy. Consequently, diagnosis is based on a careful history, physical exam and laboratory testing.

CLINICAL FEATURES

Many of the typical features are common in normal pregnancy, including heat intolerance, tachycardia, palpitations, palmar erythema, emotional liability, vomiting and goiter.

The most discriminatory features in pregnancy are weight loss, tremor, a persistent tachycardia, lid lag and exophthalmos. The latter feature indicates thyroid disease at sometime rather than active thyrotoxicosis. Thyroid-associated ophthalmopathy may occur before hyperthyroidism and is present in up to 50% of patients with Graves' disease. If thyrotoxicosis occurs for the first time in pregnancy, it usually presents late in the first or early in the second trimester.

PATHOGENESIS

Causes of Hyperthyroidism in pregnancy are given box 1. Almost 85% of cases of hyperthyroidism in pregnancy are due to Graves' disease (GD). Graves' disease is an autoimmune disorder caused by TSH receptor–stimulating antibodies. More frequent than GD as the cause of thyroid function tests demonstrating hyperthyroxinemia is "gestational transient thyrotoxicosis," which is limited to the first half of pregnancy. This condition, characterized by elevated FT4 and suppressed serum TSH, is diagnosed in about 1–3% of pregnancies.[2] This frequency depends on the geographic area and is secondary to elevated hCG levels. Often it is associated with hyperemesis gravidarum, defined as severe nausea and vomiting in early pregnancy with more than 5% weight loss, dehydration, and ketonuria. Hyperemesis gravidarum occurs in 3–10 per 1,000 pregnancies.[3] Other conditions associated with hCG-induced thyrotoxicosis include multiple gestation, hydatidiform mole, and choriocarcinoma. Most cases present with marked elevations of serum hCG. A TSH receptor mutation leading to functional hypersensitivity to hCG also has been recognized as a rare cause of pregnancy-associated hyperthyroidism. More rarely in women of childbearing age, hyperthyroidism may be due to toxic multinodular goiter or toxic adenoma, or occasionally subacute thyroiditis, acute thyroiditis, iodine, amiodarone or lithium therapy.

Effect of Pregnancy on Thyrotoxicosis

Thyrotoxicosis often improves during pregnancy, especially in the second and third trimesters. As with other autoimmune

BOX 1 Causes of hyperthyroidism in pregnancy

- Graves' disease
- Transient gestational hyperthyroidism
- Toxic multinodular goiter
- Single toxic adenoma
- Subacute thyroiditis
- Trophoblastic tumor
- Iodide induced hyperthyroidism
- Struma ovarii
- Thyrotropin receptor mutations
- TSH-secreting pituitary adenoma
- Functional thyroid cancer metastases,
- Overtreatment with or factitious intake of thyroid hormone

conditions, there is a state of relative immunosuppression in pregnancy and levels of TSH receptor-stimulating antibodies may fall with consequent improvement in Graves' disease and a lower requirement for anti-thyroid treatment. Exacerbations may occur in the first trimester, possibly related to hCG production, and in the puerperium (especially if there has been improvement during pregnancy) related to a reversal of the fall in antibody levels seen during pregnancy. Pregnancy has no effect on Graves' ophthalmopathy.

Effect of Thyrotoxicosis in Pregnancy

If thyrotoxicosis is severe and untreated, it is associated with inhibition of ovulation and infertility. Those who do become pregnant and remain untreated have an increased rate of miscarriage, fetal growth restriction (FGR), preterm labor and perinatal mortality. Thyrotoxicosis may lead to sinus tachycardia, supraventricular tachycardia or atrial fibrillation. If poorly controlled, a thyroid crisis (storm) in the mother and heart failure may develop, particularly at the time of delivery.[4] For those with good control on anti-thyroid drugs or with previously treated Graves' disease in remission, the maternal and fetal outcome is usually good and unaffected by the thyrotoxicosis. Rarely, retrosternal extension of goiter may cause tracheal obstruction or dysphagia. This is a particular problem if the patient needs to be intubated.

Fetal and Neonatal Thyroid Dysfunction

Improvement of Graves' hyperthyroidism during a woman's pregnancy is often associated with a reduction in the titer of maternal serum TRAb concentrations and a change from stimulatory to blocking antibodies. If antibodies do not decline they will cross the placenta and stimulate the fetal thyroid, evidenced by signs of fetal hyperthyroidism such as tachycardia, intrauterine growth retardation, cardiac failure, and the development of fetal goiter.

One to five percent of neonates of mothers with Graves' disease have hyperthyroidism as a result of the transplacental passage of maternal TRAb concentrations.[5] Presentation of neonatal hyperthyroidism may be delayed as antithyroid drugs administered to the mother are cleared more rapidly from the fetal circulation than maternal stimulating antibodies. Maternal euthyroidism is particularly important in the later stages of pregnancy, as poorly controlled hyperthyroidism can lead to suppression of the fetal pituitary thyroid axis resulting from placental transfer of thyroxin. The condition may last up to six months. Subclinical hyperthyroidism has no known associated adverse pregnancy outcomes.

DIAGNOSIS

Serum TSH may decrease in the first trimester of normal pregnancy as a physiological response to the stimulating effect of hCG upon the TSH receptor. A peak hCG level typically occurs between 7 and 11 weeks gestation. In particular, a serum TSH below 0.1 mU/L (in some cases even undetectable may be present in approximately 5% of women by week 11 of pregnancy. Normal TSH level in different trimester is given in table 1.

TABLE 1: Normal TSH level in pregnancy

Trimesters	*ATA 2011[6]*	*Endocrine Society 2013[7]*
I	0.1–2.5 *mIU/L	≤2.5 mIU/L
II	0.2–3 mIU/L	≤3 mIU/L
III	0.3–3 mIU/L	≤3 mIU/L

Note: American Thyroid Association (ATA) 2017 guidelines recommends, if internal or transferable pregnancy-specific TSH reference ranges are not available, an upper reference limit of *4.0 mU/L may be used.

Any subnormal serum TSH value should be evaluated in conjunction with serum TT4 (or FT4) and T3 values.[8] The biochemical diagnosis of overt hyperthyroidism is confirmed in the presence of a suppressed or undetectable serum TSH and inappropriately elevated serum TT4/FT4, or T3.

Gestational Transient Thyrotoxicosis versus Graves' Hyperthyroidism in Pregnancy

Diagnosing the cause of the disease is essential in any patient with thyrotoxicosis. In early pregnancy, the differential diagnosis in the majority of cases is between Graves' hyperthyroidism and gestational transient thyrotoxicosis in both situations, common clinical manifestations include palpitations, anxiety, tremor, and heat intolerance. A careful history and physical examination is of utmost importance in establishing the etiology. The findings of no prior history of thyroid disease, no stigmata of GD (goiter, orbitopathy), a self-limited mild disorder, and symptoms of emesis favor the diagnosis of gestational transient thyrotoxicosis.

If other causes for thyrotoxicosis are suspected, measurement of TRAb is indicated. If this is negative or thyroid nodules are suspected based on clinical examination, a thyroid ultrasound should be performed to evaluate nodularity. Serum hCG is higher on average in gestational transient thyrotoxicosis than in patients with GD, but overlap is considerable and the clinical usefulness of such measurement is limited. In the presence of a nodular goiter, a serum TT3 determination is helpful in assessing the possibility of the "T3 toxicosis" syndrome. TT3 determination may also be of benefit in diagnosing T3 thyrotoxicosis caused by GD. In general, serum T3 tends to be disproportionately elevated more than T4 in cases of thyrotoxicosis caused by direct thyroid hyperactivity. In comparison, T4 tends to be disproportionately elevated beyond T3 when thyrotoxicosis is caused by destructive processes such as thyroiditis.

MANAGEMENT OPTIONS

Antithyroid Drugs

Thionamide ATDs [MMI, carbimazole (CM), and PTU] are the mainstays of treatment for hyperthyroidism. They reduce iodine organification and coupling of monoiodotyrosine and diiodotyrosine, therefore inhibiting thyroid hormone synthesis. Because the block is not absolute and the thyroid contains a depot of thyroid hormone bound to Tg, the normalization of thyroid function tests takes place gradually over weeks.

Carbimazole and propylthiouracil (PTU) are the most commonly used anti-thyroid drugs. Most patients are initially

treated with 15–40 mg carbimazole or 150–400 mg PTU for 4–6 weeks.[9] PTU is usually avoided because of the rare complication of liver failure. The onset of action of anti-thyroid drugs is delayed until the pre-formed hormones are depleted, a process which can take 3–4 weeks. The dose is then gradually reduced to a maintenance dose of 5–15 mg carbimazole or 50–100 mg of PTU.[20] Therapy is continued for 12–18 months after the initial presentation of Graves' disease, but relapse rates are high.[10] Treatment options following relapse include radioiodine, surgery or long-term anti-thyroid drugs.

Beta-blockers

These are often used in the early management of thyrotoxicosis or during relapse to improve sympathetic symptoms of tachycardia, sweating and tremor. β-blockers also reduce peripheral conversion of T4 into T3.

They are discontinued once the anti-thyroid drugs take effect and there is clinical improvement, usually evident within 3 weeks.

Doses of propranolol of 10–40 mg three times daily for such short periods of time are not harmful to the fetus.[11] Drugs commonly used in Hyperthyroidism are discussed in table 2.

Surgery

Thyroidectomy is rarely indicated in pregnancy, but if required, is best performed in the second trimester.[12] It is usually reserved for those with dysphagia or stridor related to a large goiter, those with confirmed or suspected carcinoma and those who have allergies to both anti-thyroid drugs. Approximately, 25–50% of patients will become hypothyroid following thyroid surgery, and therefore close follow-up is required to ensure rapid diagnosis and treatment with replacement therapy. Hypocalcemia due to removal of the parathyroid glands is also a risk, reported in 1–2% of cases.

Radioactive Iodine

Radioiodine therapy is contraindicated in pregnancy and breastfeeding since it is taken up by the fetal thyroid (after 10–12 weeks) with resulting thyroid ablation and hypothyroidism.

Diagnostic radioiodine scans (as opposed to treatment) are also contraindicated in pregnancy but may be performed if a mother is breastfeeding, although mothers should stop breastfeeding for 24 hours after the procedure.

Pregnancy should be avoided for at least 4 months after treatment with radioiodine in view of the theoretical risk of chromosomal damage and genetic abnormalities.

Management of Gestational Transient Thyrotoxicosis

The management of women with gestational transient thyrotoxicosis depends on the severity of symptoms. In women with hyperemesis gravidarum, control of vomiting and treatment of dehydration with intravenous fluids is the customary treatment.[13] Women with severe hyperemesis gravidarum need frequent medical visits for management of dehydration and electrolyte abnormalities. In some cases, hospitalization is required. Antithyroid drugs (ATDs) are not indicated because the serum T4 returns to normal by 14–18 weeks gestation and ATD use in early pregnancy increases risk of birth defects. Importantly, obstetrical outcome was not improved in isolated cases in which gestational transient thyrotoxicosis was treated with ATDs. In situations in which symptomatic therapy is indicated, small amounts of β blockers given over a limited time period may be useful, and close follow-up with repeat investigation for the cause of disease should be performed.

ATA 2017 recommends supportive therapy, management of dehydration, and hospitalization if needed. ATDs are not recommended, though β-blockers may be considered.

Women with GD Seeking Future Pregnancy

The planning of therapy in relation to possible future pregnancy should be discussed with all women of childbearing age who develop thyrotoxicosis. In general, pregnancy should be postponed until a stable euthyroid state is reached. As a guide, two sets of thyroid function test within the reference range, at least 1 month apart, and with no change in therapy between tests, can be used to define a stable euthyroid state. The use of contraception until the disease is controlled is strongly recommended.

A hyperthyroid patient who desires future pregnancy may be offered ablative therapy using ^{131}I, thyroid surgery, or medical therapy. Advantages and disadvantages of each therapeutic option is, detailed in table 3.

Ablative Therapy

If the patient opts for radioactive iodine ablative therapy prior to pregnancy, the following recommendations should be provided:[14]

- TRAb levels tend to increase following ^{131}I therapy and may remain elevated for many months following ^{131}I therapy. Therefore, patients with high TRAb levels or severe hyperthyroidism may favor consideration of other therapeutic options such as surgery

TABLE 2: Drugs used in hyperthyroidism[4]

Drugs	*Mode of action*	*Dose*	*Adverse effects*
Propylthiouracil	Inhibits thyroxine synthesis; inhibits peripheral conversion of thyroxine to triiodothyronine	Starting: 300–450 mg/day; maintenance: 50–150 mg/day	Rash, fever, agranulocytosis, Lever failure
Carbimazole	Inhibits thyroxine synthesis	Starting: 15–40 mg/day; maintenance: 5–15 mg/day	Rash, fever, aplasia cutis and methimazole embryopathy
Propranolol	Reduces adrenergic symptoms	10–40 mg, 3–4 times/day (short-term use only)	Bronchospasm, intrauterine growth restriction, neonatal hypoglycemia

TABLE 3: Advantages and disadvantages of therapeutic options for women with Graves' disease seeking future pregnancy[14]

Therapy	*Advantages*	*Disadvantages*
Antithyroid drugs	• Effective treatment to euthyroid state within 1–2 months, Often induces gradual remission of autoimmunity (decreasing antibody titers)	• Medication adverse effects (mild 5–8%; severe 0.2%) • Birth defects associated with use during pregnancy (MMI 3–4%; PTU 2–3% though less severe) • Relapse after drug withdrawal likely in 50–70%
Radioactive iodine	• Easy oral administration • Reduction in goiter size • Future relapse of hyperthyroidism very rare	• Repeat therapy at times necessary • Rising antibody titers following treatment may contribute to worsening orbitopathy or fetal risk • Lifelong need of levothyroxine therapy following ablation
Thyroidectomy	• Definitive therapy of hyperthyroidism. Stable euthyroid state easily achieved on replacement levothyroxine therapy • Post-surgery, gradual remission of autoimmunity occurs • Goiter disappears	• Life-long need for levothyroxine • Supplementation • Surgical complications occur in 2–5% • Healing and recovery from surgery • Permanent neck scar

- Young patients with severe GD may not become stably euthyroid within the first year after ^{131}I therapy
- If ^{131}I therapy is planned, a pregnancy test should be performed 48 hours before ^{131}I ablation to confirm absence of unexpected pregnancy
- Conception should be delayed 6 months and until a stable euthyroid state is reached after ablation and initiation of LT4 replacement therapy.[15]

Antithyroid Drugs

If the patient chooses antithyroid drug (ATD) therapy, the following recommendations should be given.

- The increased risk of birth defects associated with both propylthiouracil (PTU) and methimazole (MMI) use during early pregnancy should be reviewed[16,17]
- If possible, ATDS should be avoided in the first trimester of pregnancy, but when necessary PTU is generally favored
- Consideration can be given to discontinuing PTU after the first trimester and switching to MMI to decrease the risk of liver failure in the mother.

Management of Patients with Graves' Hyperthyroidism during Pregnancy

Thionamide ATDs (MMI, carbimazole [CM], and PTU) are the mainstays of treatment for hyperthyroidism during pregnancy. The initial dose of ATD depends on the severity of the symptoms and the degree of hyperthyroxinemia.In general, initial doses of ATDs during pregnancy are as follows:[9]

- Methimazole (MMI): 5–30 mg/day (typical dose in average patient 10–20 mg)
- Carbimazole: 10–40 mg/day
- Propylthiouracil (PTU): 100–600 mg/day (typical PTU dose in average patient 200–400 mg/day).

The equivalent potency of MMI to PTU is approximately 1:20 (e.g., 5 mg MMI = 100 mg of PTU).[20] Ten milligrams of CM is rapidly metabolized to approximately 6 mg of MMI. Because the half-life of PTU is shorter than that of MMI, PTU dosing should generally be split into two or three daily doses. In comparison, MMI can generally be given in one daily dose. In rare cases of severe hyperthyroidism, twice or three times daily dosing may be of benefit.

Importantly, side effects occur in 3–5% of patients taking thionamide drugs, the majority of which are allergic reactions such as skin rash, whereas the severe side effects of agranulocytosis (0.15%) and liver failure (<0.1%) are rare. Most side effects develop within the first months following initiation or reinitiation of therapy.[17] In 2010, the US Food and Drug Administration (FDA) called attention to the risk of hepatotoxicity in patients exposed to PTU because PTU had been found to be third on the list of drugs leading to liver transplantation in the United States.[21] An advisory committee recommended limiting the use of PTU to the first trimester of pregnancy.

The greatest risk surrounding the use of ATDs in pregnancy is related to their potential teratogenic effects. Aplasia cutis, syndrome of methimazole/carbimazole embryopathy which also includes dysmorphic facies are associated with MMI/CM use. Apart from this defects with a statistically significant association with the use of MMI include choanal or esophageal atresia; various types of abdominal wall defects including umbilicocele; and eye, urinary system, and ventricular septal defects. Recent studies have shown that these complications are more common than previously thought, and they affect 2–4% of children who have been exposed to MMI in early pregnancy, especially during gestational weeks 6–10.[19]

PTU was previously considered a safe medication for use during gestation. Recently, however, a Danish study revealed that 2–3% of children exposed to PTU developed birth defects associated with this therapy. The defects were primarily face and neck cysts (often considered to be minor birth defects) and urinary tract abnormalities (in males). Prior to the recent investigation, such abnormalities were not commonly associated with PTU exposure, likely because they were diagnosed later in life when complications ensued. Importantly, however, most affected patients received surgery for the abnormality. Thus, PTU-associated birth defects appear less severe than MMI-associated birth defects but occur with similar incidence.[18]

Beta-adrenergic blocking agents, such as propranolol 10–40 mg every 6–8 hours may be used for controlling hyper-

metabolic symptoms until patients have become euthyroid on ATD therapy.[11] The dose should be reduced as clinically indicated. In the vast majority of cases the drug can be discontinued in 2–6 weeks. Long-term treatment with β-blockers has been associated with intrauterine growth restriction, fetal bradycardia, and neonatal hypoglycemia.

ATA RECOMMENDATIONS 2017[14]

- Women taking MMI or PTU should be instructed to confirm potential pregnancy as soon as possible. If the pregnancy test is positive, pregnant women should contact their caregiver immediately
- In a newly pregnant woman with GD, who is euthyroid on a low dose of MMI (≤5–10 mg/d) or PTU (≤100–200 mg/d), the physician should consider discontinuing all antithyroid medication given potential teratogenic effects. The decision to stop medication should take into account the disease history, goiter size, duration of therapy, results of recent thyroid function tests, TRAb measurement, and other clinical factors
- Following cessation of antithyroid medication, maternal thyroid function testing (TSH, and FT4 or TT4) and clinical examination should be performed every 1–2 weeks to assess maternal and fetal thyroid status. If the pregnant woman remains clinically and biochemically euthyroid, test intervals may be extended to 2–4 weeks during the second and third trimester
- In pregnant women with a high-risk of developing thyrotoxicosis if antithyroid drugs were to be discontinued, continued antithyroid medication may be necessary. Factors predicting high clinical risk include being currently hyperthyroid, or requirement of >5–10 mg/d MMI or >100–200 mg/d PTU to maintain a euthyroid state. In such cases PTU is recommended for the treatment of maternal hyperthyroidism through 16 weeks of pregnancy
- Pregnant women receiving MMI who are in need of continuing therapy during pregnancy should be switched to PTU as early as possible
- If ATD therapy is required after 16 weeks gestation, it remains unclear whether PTU should be continued or therapy changed to MMI
- In women being treated with ATDs in pregnancy, FT4/TT4 and TSH should be monitored approximately every 4 weeks
- Antithyroid medication during pregnancy should be administered at the lowest effective dose of MMI or PTU, targeting maternal serum FT4/TT4 at the upper limit or moderately above the reference range.

FETAL/NEONATAL SURVEILLANCE

Because of the risk of fetal thyroid dysfunction in women with raised TRAb concentration or those taking antithyroid drugs, serial ultrasound scans of the fetus should be performed. Ultrasound evidence of fetal thyroid disease includes intrauterine growth restriction, tachycardia, cardiac failure, hydrops, advanced bone age, and goiter.[22] If fetal hyperthyroidism is diagnosed, treatment involves modulation of maternal antithyroid drugs. If fetal hypothyroidism has resulted from administration of antithyroid drugs to the mother, this treatment should be decreased or stopped and administration of intra-amniotic thyroxine considered. Early delivery may need to be considered in the case of fetal thyroid dysfunction, depending on the gestation at diagnosis and the severity of fetal symptoms.

If a high TRAb concentration has been noted at 30 weeks, the neonate should be tested for hyperthyroidism after six hours and, if the test is positive, carbimazole should be started. If the mother has been taking an antithyroid drug up until delivery, the baby should be screened again several days later as he or she may well be euthyroid at birth but develop hyperthyroidism as the antithyroid drug is metabolized.[23] The mother can be reassured that the disease in her baby will be self-limiting to about three months because of the disappearance of the thyrotropin receptor stimulating antibodies in the baby during this time.

CONCLUSION

Although untreated hyperthyroidism has potentially serious adverse effects on the mother and fetus, when treated promptly and monitored appropriately, the outcome for mother and fetus can be excellent. Prepregnancy planning and counseling are important. Treatment should be discussed with patient (effect on patient, effect on fetus, breast feeding). Start propylthiouracil. Patient's euthyroid should be rendered—continue with low dose of an antithyroid drug up to and during labor. Thyroid function should be monitored regularly during gestation (every 4–6 weeks) and adjust the dose of antithyroid drug if necessary. Serial ultrasonography of the fetus should be done. Checking TRAb at 30–36 weeks' gestation if hyperthyroidism is caused by Graves' disease is necessary. Inform the pediatrician that the woman has hyperthyroidism and that the neonate may therefore be at risk of hyperthyroidism. Review management postpartum and check for exacerbation. Check infant for thyroid dysfunction if indicated. The mother has a significant risk of exacerbation of hyperthyroidism postpartum, and thyroid function should be checked at 6 weeks and 3 months post-delivery. The decision to treat hyperthyroidism in lactating women should be guided by the same principles applied to nonlactating women.

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CHAPTER

Pregnancy with Gastrointestinal Infections

Ritu Dargan

INTRODUCTION

Gastrointestinal infections are among the most commonly encountered infections in primary care. Acute gastroenteritis is the rapid onset of diarrhea of less than 14 days duration (with or without nausea, vomiting, fever, or abdominal pain). It may be caused by infections and also by non-infectious toxins in food. While most gastrointestinal infections are self-limiting and resolve within a few days, in specific populations like pregnant women, newborns or infants, immunocompromised individuals or the elderly they can become potentially serious.

Gastrointestinal infections in pregnancy are relevant because:

- Pregnant women may be more vulnerable to complications, so there should be a lower threshold for investigation, admission and treatment.
- Febrile illness in pregnancy may cause miscarriage or premature labor.
- In the uncommon event of progression to critical illness, fetal well-being is at risk.
- Acute abdominal conditions are more difficult to diagnose during pregnancy.
- Certain gastrointestinal infections like Listeriosis and *Salmonellosis* can directly harm the fetus therefore it is important to arrive at a diagnosis, initiate appropriate treatment and infection control measures.

Predisposing factors for gastrointestinal infections include:

- Poor sanitation
- Low socioeconomic status
- Contact with animals, contaminated food or water
- Immunocompromised status (HIV positive women)
- Hospitalization
- Use of antibiotics
- Travel to an area with an outbreak.

ETIOLOGY

The cause for gastrointestinal infections may be viral, bacterial or parasitic infections or at times be due to food toxins from contaminated food.

Viral

The most common viruses causing gastroenteritis are Adenovirus or Rotavirus, these usually cause self-limiting disease.

Bacterial

Various organisms are responsible common one being *Escherichia coli* which is the most commonly isolated organism in individuals suffering from gastroenteritis. Organisms like *Listeria monocytogenes, Salmonella enteritidis* and *Campylobacter jejuni* though rare can result in an adverse maternofetal outcome. Outbreaks of cholera caused by *Vibrio Cholera* may cause the pregnant women in the affected population to get infected. Women with history of hospitalization or antibiotic use usually have *Clostridium difficile* isolated from their stool samples.

Cryptosporidium spp. may cause diarrhea in immunocompromised individuals, for example, women who test positive for the human immunodeficiency virus.

COURSE OF THE DISEASE

Most of the infections are self-limiting and relatively harmless; but some may lead to adverse outcomes for mother or fetus. This may occur because of the severity of the infection and delay in initiating treatment and on some occasions certain infections like listeriosis or Salmonollosis may prove to have a poor prognosis for the fetus and more so if the infection occurs in the third trimester, thus warranting a detailed study of these infections.

Listeriosis

Infection with *Listeria monocytogenes* can lead to a rare but serious food-borne illness termed listeriosis. *Listeria monocytogenes* is also an uncommon but probably underdiagnosed cause of neonatal sepsis.

Listeria spp. is tolerant of low temperatures (4–10°C), high pH, and high salt concentrations, which explains its ability to grow in a wide variety of environments, including soil, sewage,

manure, raw vegetables, smoked fish, milk, processed and refrigerated foods.[1,2] The incidence of such infections appear to be increasing in several countries worldwide.[3,4] In India, this pathogen has been isolated from humans, animals and foods.[5]

Listeria monocytogenes a food-borne pathogen is known to cause serious invasive illness, mainly in certain well-defined high-risk groups such as pregnant women, elderly and immunocompromised patients, newborns and infants.[2] Pregnant women account for one-sixth of all cases of listeriosis and are about 10 times more likely than the general population to be affected by listeriosis.[2] Of the pregnant women listeriosis affects around 1 in 10,000 pregnancies. [6] A recent review found pregnant women had a significantly higher rate for listeriosis compared with nonpregnant reproductive aged women.[7] It is unclear why pregnant women still account for a significant number of these reported cases. One hypothesis is that pregnant women are susceptible because of decreased cell mediated immunity.[8] Another is that placental trophoblasts are susceptible to invasion by *Listeria monocytogenes.*[9] It can cross the placenta, perhaps due to its intracellular life cycle. Listeriosis in pregnancy threatens the fetus and newborn through direct infection of the placenta and chorioamnionitis, and is frequently fatal.

Maternal listeriosis causes fetal infection that characteristically produces disseminated granulomatous lesions with microabscesses. Chorioamnionitis is common with maternal infection and placental lesions include multiple well demarcated macroabscesses.[10]

Salmenollosis

Infections from Salmonella species continue to be a major and increasing cause of food-borne illness. Nontyphoid *Salmonella* gastroenteritis is contracted through contaminated food.

Shigellosis

Bacillary dysentery caused by *Shigella* is a relatively common, highly contagious cause of inflammatory exudative diarrhea.

Protozoal Infections

Parasitic infections like *Giardia lamblia* may not show up on stool microscopy and may require specific identification and treatment. *Entamoeba* spp. are commonly responsible in tropical regions.

CLINICAL PRESENTATION

The commonly presenting symptoms include diarrhea, vomiting, and abdominal pain, some may present with a low grade fever. Patient may give history of passing blood/mucus in stool. Bloody diarrhea is usually seen in Shigellosis. Oliguria may be present in case of dehydration.

In listeriosis the major manifestation in pregnancy is bacteremia which results in the spreading of the organism to the placenta, where local cellular immune responses are suppressed to prevent rejection of the fetus. This allows the bacteria to replicate efficiently. During the bacteremic phase, most mothers experience a mild flu-like illness. Febrile gastroenteritis is now a well-recognized clinical presentation of Listeria infection.[11] Other symptoms include nausea, vomiting, headache and myalgias. Most of these symptoms typically resolve within 2 days of onset without treatment. Usually these symptoms may precede obstetrical complications like preterm labor or septic abortion by 2–14 days (normally 3–7 days). While the infection may cause only mild to moderate symptoms in the mother, it may have devastating results for the fetus and can include preterm labor, stillbirth, and septic abortion. Women suffering from listeriosis may have subtle symptoms, presenting as fever without an identified source, gastroenteritis, or chorioamnionitis, and rarely meningitis or maternal mortality.[12-14] Only 26% of pregnant listeria afflicted women present with fever.[1,12]

Listeriosis in pregnancy may be asymptomatic or may cause a febrile illness that is confused with influenza, pylonephritis or meningitis.[1] Occult or clinical infection may also stimulate labor. Discolored brownish or meconium-stained amniotic fluid is common with fetal infection even in preterm gestations.

Perinatal listerial infection is the most common clinical syndrome caused by *Listeria monocytogenes.* In a review by Mylonakis,[13] infection resulted in abortion and still birth in 20% and neonatal sepsis developed in 68% of the surviving newborns.

Despite the paucity of maternal clinical signs, pregnancy related listeriosis results in fetal death in 20–30% of cases.[12,14,15]

If recognized early, treatment of maternal septicemia can prevent infection in the fetus and result in improved neonatal outcome.

Therefore, it is important to have a high index of suspicion for listeriosis in pregnant women with acute gastroenteritis with fever, and consideration should be given to obtaining a blood culture in every pregnant woman with fever. Even without treatment, maternal symptoms usually resolve after delivery.

In Salmenollosis symptoms usually begin within 6–48 hours of exposure. Patients usually complain of nonbloody diarrhea, abdominal pain, fever, chills, nausea and vomiting. Rare case reports have linked *Salmonella bacteremia* with abortion.[16] Some cases of fetal mortality due to transplacental passage of organisms and maternal mortality has also been reported in women infected with *Salmonella enteritidis* and *Campylobacter jejuni.*[17,18]

Women with bacillary dysentery due to *Shigella* present with clinical manifestations ranging from mild diarrhea to severe dysentery, bloody stools, abdominal cramping, tenesmus, fever and systemic toxicity.

Most individuals infected with *Entameba histolytica* are asymptomatic. Amoebic dysentery, however may take a fulminant course during pregnancy, with fever, abdominal pain and bloody stools. Prognosis is worse if complicated by a hepatic abscess.

DIFFERENTIAL DIAGNOSIS

It is important to consider the following conditions in which diarrhea may be a misleading symptom, thus confusing the clinical picture.

- Ectopic pregnancy may have symptoms of diarrhea due to pelvic irritation; signs may be subtle and sometimes are easily missed
- Appendicitis too can also present with diarrhea/vomiting and abdominal pain and is more difficult to more difficult to diagnose in pregnancy
- Urinary tract infection or pyelonephritis may at times mimic acute gastroenteritis
- Food poisoning due to toxins in food may present with diarrhea without infection and is usually self-limiting
- Inflammatory bowel disease and Ulcerative colitis are other conditions that may present in a similar fashion.

EVALUATION AND MANAGEMENT

Assessment

- Check temperature, blood pressure, pulse rate and respiratory rate
- Perform a thorough abdominal examination, particularly to rule out uterine contractions, chorioamnionitis and other possible diagnoses, e.g., appendicitis, preterm labor
- Fetal assessment. Fetal heart rate can be checked with Doppler scanning, or later in pregnancy, cardiotocography to monitor the fetal heart, and contractions may be required
- Assess for features of dehydration:
  - *Mild dehydration:* Lassitude, anorexia, nausea, light-headedness, postural hypotension
  - *Moderate dehydration:* Apathy, tiredness, dizziness, muscle cramps, dry tongue, sunken eyes, reduced skin elasticity, postural hypotension (systolic blood pressure >90 mmHg), tachycardia, oliguria
  - *Severe dehydration:* Profound apathy, weakness, confusion (leading to coma), shock, tachycardia, marked peripheral vasoconstriction, systolic blood pressure <90 mmHg, oliguria or anuria.

Investigations

- Stool investigations—microscopy (include ova, cysts and parasites), culture and sensitivity.
  - A stool sample should be sent for microbiological investigation if:
    - There is blood and/or mucus in the stool.
    - The patient is immunocompromised.

Blood Tests

- Renal function and electrolytes if patient appears dehydrated.
- CBC and platelet count if there is suspected hemolytic uremic syndrome (rare but associated with infection with *E. coli* O157)
- Blood cultures if systemically unwell or where there is suspicion of *Listeria* spp. as stool examination in these women may at times be inconclusive.
- Further tests if relevant to exclude other causes e.g., urine microscopy, abdominal ultrasound or pelvic ultrasound.

A positive culture of meconium or amniotic fluid associated with an ill infant is highly suggestive of neonatal *Listeria* infection. Culture of stool to routinely diagnose infection beyond the immediate postnatal period is not recommended because *Listeria* can be isolated in only about 5% of stool from healthy adults.[19]

Management

General Points

- Notification and infection control measures may be required
- Most gastrointestinal infections in pregnancy only require rehydration and fetal monitoring
- Hospital admission is required for fetal distress, premature labor or significant dehydration
- Specific antibiotics are rarely required but may be indicated depending on the results of stool culture and advice from microbiology.

Who Needs Admission?

Hospital admission may be needed if there is:

- A suspected serious cause requiring investigation/treatment, e.g., *Listeria* spp.; *E. coli* O157
- Moderate-severe dehydration or inability to retain oral fluids
- Severe dehydration or shock
- Significant co-existing illness e.g., renal impairment, inflammatory bowel disease, diabetes, immunocompromise, obstetric complications.

Other factors when considering admission include recent foreign travel, poor home circumstances and low level of support, fever, bloody diarrhea, abdominal pain and tenderness, fecal incontinence, diarrhea lasting more than ten days, coexisting medical conditions.

Conservative management is the mainstay of treatment for diarrhea in pregnancy. It is important to identify the extent of dehydration and to treat accordingly.

Fluid Replacement

Rehydration is the mainstay of management in women with gastroenteritis. This is usually in the form of oral fluids and sometimes in case of severe dehydration the need for intravenous replacement may arise using normal saline or Ringer lactate with potassium supplementation in amounts to restore maternal blood volume and to ensure uteroplacental perfusion. It is important to monitor vital signs and urine output.

Use of Antimotility Agents

For moderately severe afebrile illness without bloody diarrhea antimotility agents such as Loperamide may be useful. Bismuth Subsalicylate may also alleviate symptoms.

Probiotics

These may be co-prescribed and have a role to play in antibiotic induced diarrhea. Evidence suggests probiotics are safe in pregnancy.[20]

Antibiotics

Antibiotics are not usually recommended as they have no effect on viral infections, may cause side effects and overuse increases

the risk of resistant bacteria developing. Therefore, judicious use of antimicrobial agents is warranted. Antibiotics may be recommended in particularly severe cases of gastroenteritis, or if a specific bacteria has been identified as the cause. For moderate to severely ill women some recommend empirical treatment with Ciprofloxacin, 500 mg twice a day for 3–5 days. Specific pathogens are treated as needed when identified.

In cases of listeriosis early initiation of adequate antibiotic treatment and delivery improves fetal outcome and is recommended by most experts.[6,21] Treatment with Ampicillin plus Gentamycin is usually recommended because of synergism against *Listeria* species. Trimethoprim- Sulphamethoxazole can be given to penicillin allergic women however but there is a teratogenic risk in the first trimester and a risk of neonatal hemolysis and methemoglobinemia in the third trimester. Cephalosporins in listeriosis are NOT effective. Maternal treatment in most cases is also effective for fetal infection.[22]

In salmonellosis, antimicrobials are not recommended in uncomplicated infections because they do not commonly shorten illness and may prolong the convalescent carrier state. If gastroenteritis is complicated by bacteremia, Fluoroquinolones and third generation cephalosporins are the preferred treatment.

In Shigellosis, again antimicrobial therapy is imperative and effective treatment during pregnancy includes Fluoroquinolones, Ceftriaxone or Azithromycin. Antimicrobial resistance is rapidly emerging and antibiotic susceptibility testing can help guide appropriate therapy.[1]

Campylobacter may be treated with Azithromycin, *Clostridium difficile* with oral Metronidazole or Vancomycin.

For amebiasis or Giardiasis the therapy is similar to that for nonpregnant women and Metronidazole or Tinidazole is the preferred drug for amebic colitis and invasive disease. Noninvasive infections may be treated with Paromomycin.[23]

Anticholinergics/antispasmodics are not recommended.

There is little evidence on the use of oral rehydration salt (ORS) solution. For adults able to maintain their fluid intake, ORS solution does not provide any benefits in terms of reducing the duration of diarrhea or the number of stools.

Consumption of solid food should be guided by appetite. The person should eat small, light meals and avoid fatty, spicy, or heavy food. There is little evidence on any benefit of fasting or dieting for the treatment of acute diarrhea.

It is important to educate the woman and her escort regarding measures to prevent spread of infection, e.g., hands should be washed thoroughly, towels should not be shared, soiled clothing and bed linen should be washed separately from other clothes, at the highest temperature they will tolerate, and toilet seats, flush handles, wash hand basin taps, surfaces and toilet door handles should be cleaned at least daily with hot water and detergent.

Women may be advised rest until at least 48 hours after the woman is free from diarrhea and vomiting.

PROGNOSIS AND COMPLICATIONS

Maternal Complications

- Dehydration and electrolyte disturbance
- Hemolytic uremic syndrome (HUS), which is a rare occurrence. HUS is characterized by acute kidney injury, hemolytic anemia and thrombocytopenia
- Reactive complications, e.g., arthritis, carditis, urticaria, erythema nodosum, conjunctivitis and Reiter's syndrome. They are associated with *Salmonella* spp., *Campylobacter* spp., *Shigella* spp. infections. There are usually no reactive complications associated with viral or parasitic gastroenteritis
- Systemic invasion by *Salmonella* spp. may cause endovascular infections and localized infections in bones, joints, meninges, or in the gallbladder
- Toxic mega colon caused by fulminant colitis is rare
- Guillain-Barré syndrome is associated with a number of viruses, especially cytomegalovirus (CMV), but *Campylobacter jejune* has been the most commonly isolated pathogen in several studies
- Malnutrition
- Irritable bowel syndrome
- Secondary lactose intolerance.

Fetal and Neonatal Complications

In most cases, gastroenteritis during pregnancy has no adverse effects on neonatal outcome. However, possible complications are:

- Febrile illness which may possibly cause miscarriage or premature labor
- Severe dehydration can lead to a reduction in placental flow.

Listeriosis[6,24]

- May cause intrauterine death or severe neonatal infection.
- Neonatal infection can cause pneumonia, sepsis, or meningitis
- Neonatal presentation varies but most present around 36 hours after birth with respiratory distress, pneumonia, meningitis or sepsis. There may be a rash, known as granulomatosis infantisepticum. There can be a late-onset illness usually seen 2–3 weeks postnatally
- The case fatality rate for fetal or neonatal listeriosis is 10–50%.

Salmonella spp.

The maternal prognosis is excellent; however, rarely, the fetus may be affected. There are case reports of intrauterine death, premature delivery and neonatal infection.

Campylobacter spp.

Rarely, this has been linked to fetal death, premature labor or neonatal sepsis (from case reports).[25]

Hemolytic uremic syndrome may complicate *E. coli* O157 or *Shigella* spp. infections.

Ascending infection with *E. coli* O157 is a cause of stillbirth.[26]

PREVENTION[27]

Prevention is key. Pregnant women should be advised to practice a high standard of food hygiene. Some points to be kept in mind are:

- Do not allow frozen food from a shop to defrost before putting it into the freezer; observe the use-by dates
- Cook all raw food fully; cook eggs until the yolk is set; chilled food must be thoroughly rewarmed. Avoid uncooked or undercooked ready meals
- Vegetables eaten raw should be washed thoroughly
- Regular hand-washing, especially after using the toilet, handling animals or soil and before preparing or eating food; wash hands after handling raw foods
- Keep raw and cooked food separate (including utensils)
- Do not reheat food more than once.

Advice for Preventing Listeriosis

Listeria spp. can be transmitted to pregnant women via food. It has been found in a variety of foods at all stages of preparation, from raw to well-cooked left-overs, and will still grow on food that is stored in a fridge.

Certain foods should be avoided:

- Refrigerated pâté or meat spreads (canned ones may be eaten)
- Processed and cold meats, e.g., hot dogs—unless reheated to steaming hot
- Unpasteurized dairy products
- Soft cheeses
- Cold, smoked or raw seafood.

Prevention of traveler's diarrhea and antibiotic-associated diarrhea may be aided by taking probiotics, e.g., lactobacilli.

CONCLUSION

Gastrointestinal and liver disease may make a pregnancy a high-risk one. Extreme vigilance is needed to detect early signs and symptoms of liver and gastrointestinal dysfunction and to distinguish these from the anticipated physiological changes that may occur in pregnancy. Prompt management can lead to better outcomes for both mother and baby. Management of these disorders requires a concerted effort between the primary care physician, gastrointestinal specialists and obstetricians.

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CHAPTER

Bronchial Asthma in Pregnancy

Alka A Mukherjee

INTRODUCTION

Asthma is a one of the most common chronic medical condition in pregnancy that complicates approximately 4–8% of pregnancies and second most common reason for administration of prescription drugs in pregnancy.[4] It is common in young women. In general, the prevalence of and morbidity from asthma are increasing, although asthma mortality rates have decreased in recent years. The symptoms get reversed often require intervention. Many recent reports have suggested a 2–4-fold rise in the prevalence of asthma.[2] Managing asthma and its complications in pregnancy is quite different as both the illness and effect on the developing fetus must be considered. Most important goal of treating asthma in pregnancy is to optimized fetal as well as maternal health. Studies have shown that pregnant women with asthma have an increased risk of adverse perinatal outcomes,[3] while controlled asthma is associated with reduced risk.[4,5] Well-controlled asthma has been associated with favorable outcomes in pregnancy where as poorly controlled asthma has been associated with increased rate of preterm delivery, preeclampsia, low birth weight, growth restriction, cesarean delivery, and maternal morbidity and mortality as demonstrated by Sorensen et al. and Bracken et al.[1] Severe asthma tend to worsen during pregnancy than mild asthma. Exacerbations more common between 24 and 36 weeks of pregnancy.[6]

PATHOPHYSIOLOGY

- Asthma is a chronic inflammatory disorder of the airways characterized by increased responsiveness of tracheobronchial tree to multiplicity of stimuli with a major hereditary component
- This increased airway responsiveness and persistent sub-acute inflammation have been associated with genes on chromosomes 5, 11, and 12 that include cytokine gene clusters, β-adrenergic and glucocorticoid receptor gene, and the T-cell antigen receptor gene (McFadden, 2005)
- Around 30–40% of patients with asthma report perimenstrual worsening of symptoms. Likelihood of female hormones influencing asthma seems obvious though exact mechanism remains undetermined. Considerable evidence suggests that female sex hormones have effects on several cells and cytokines involved in inflammation specifically attributed to estrogens. Increase in B cell differentiation, decrease in T cell suppression activity and number, and increase in antibody production. Evidence suggests that progestrone can act as a glucocorticoid agonist and suppress histamine release from basophils. Both estrogen and progesterone are involved in eosinophillic infiltration in many organs, both can reduce the oxidative burst after the phagocytic stimulus. Estradiol enhances eosinophillic adhesion to human mucus. Microvascular endothelial cells, the combined effect with the progesterone induces eosinophillic degrannulation. There appears to be a cyclic variation in lymphocyte β2 adrenoreceptor density in healthy women with higher levels during luteal phase. This upregulation is as a result of progesterone rather than estrogen[8]
- In asthmatic women, in fact there is downregulation of β2 adrenoreceptors. As pregnancy progresses and progesterone levels increases, similar effects may be seen causing worsening in control of asthma in some pregnant asthmatic women. Maternal plasma cortisol levels increase with pregnancy. Cortisol's effect on asthma during pregnancy are more variable. Several prostaglandins play a major role in asthma as bronchodilators and bronchoconstrictors, amniotic fluid contain large amounts of these PGs. There is a 10–30-fold increase in PGF2-alfa during pregnancy. And its levels have been found to correlate with estrogen levels[8]
- In susceptible individuals, there is inevitably an environmental allergic stimulant such as influenza or cigarette smoke
- There is also a possible influence of fetal sex and maternal asthma during pregnancy. Reports have suggested that asthma attacks or worsening asthma during pregnancy who are associated with female fetus. The mechanisms leading to changes require further investigation, one possible cause there may be abnormal levels of placental enzymes that may lead to reduced fetal growth in female infants of pregnant asthmatic women[8]

- Inflammation is caused by response of mast cell, lymphocytes, eosinophils, and bronchial epithelium. A number of inflammatory mediators by these and other cells include histamine, leukotrienes, prostaglandins, cytokines including IgE

(Strunk and Bloomberg,2006)[1]

- As F series prostaglandins and ergonovine exacerbate asthma, hence should be avoided if possible.

Anatomical Changes in Soft Tissues of Respiratory Tract during Pregnancy

- Reversible airway obstruction from bronchial smooth muscle contraction, vascular congestion, tenacious mucus, and mucosal edema. Hyperemia, friability, mucosal edema, and hyper secretion of the airway mucosa are most pronounced in the upper airways, especially during the third trimester
- Nasal obstruction, epistaxis, sneezing episodes, and vocal changes may occur, and these may worsen when the individual lies down
- Nasal and sinusoidal polyposis is often seen and tends to recur in women with each pregnancy. Caution—nasal decongestant spray should be used with because of their long term effect on the mucosa.

Physiologic Changes during Pregnancy

- Both hormonal and mechanical changes can influence the respiratory functions and can lead to an exacerbation of asthma
- A progesterone mediated first trimester causes an increase in in tidal volume leading to secondary increase in minute ventilation volume

TABLE 1: Pulmonary function in pregnancy

Parameter	*Change*
Oxygen consumption	Increases by 20–50%
Minute ventilation	Increases by 50%
Tidal volume	Increases by 40%
Respiratory rate	Unchanged/slightly increases
PaO_2	Increases by 10%
$PaCO_2$	Decreases by 15%
HCO_3	Decreases by 15%
FRC	Decreases by 20%

PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; HCO_3, bicarbonate FRC, functional residual capacity.

TABLE 2: Changes in lung function values during pregnancy

Respiratory rate	*Unchanged*
FEV1	Unchanged
Peak expiratory flow rate	Unchanged
Minute volume/ventilation	Increased by 30–50%
Tidal volume	Increased by 30–50%
FVC	Unchanged
FEVl/FVC	Unchanged
Maximum mid expiratory flow rate (forced expiratory flow 25–75)	Unchanged
Functional residual volume	Decreased by 18%

FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity;

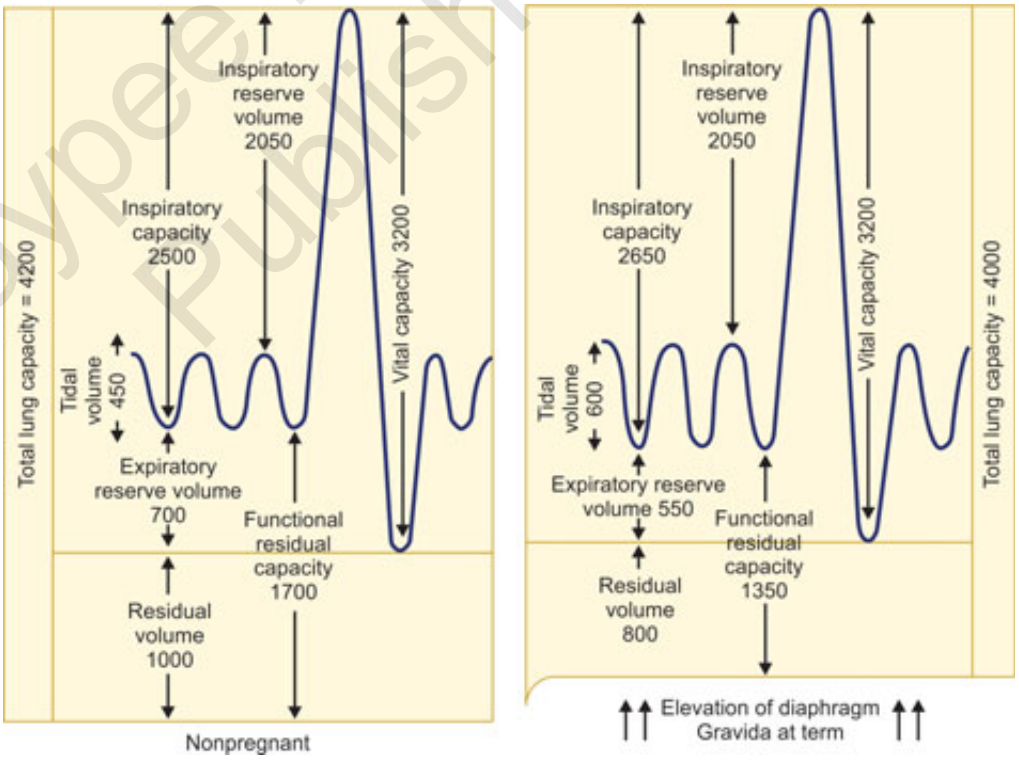

Figure 1: Changes in lung volumes during pregnancy.

TABLE 3: ACOG practice bulletin: Classification of asthma severity and control in pregnant patients

Asthma severity (Controlt†)*	*Symptom frequency*	*Nighttime awakening*	*Interference with normal activity*	*FEV1 or peak flow (predicted percentage of personal best)*
Intermittent (well controlled)	2 days per week or less	Twice per month or less	None	More than 80%
Mlid persistent (not well controlled)	More than 2 days per week, but not daily	More than twice per month	Minor limitation	More than 80%
Moderate persistent (not well controlled)	Dally symptoms	More than once per week	Some Imitation	60–80%
Severe persistent (very poorly controlled)	Throughout the day	Four times per week or more	Extremely limited	Less than 60%

*Assess severity for patients who are not taking long-term-control medications.
†Assess control in patients taking long-term control medications to determine whether step-up therapy, step-down therapy, or no change in therapy is Indicated.
Abbreviation: FEV1, forced expiratory volume in the first second of expiration.

- Pregnancy induced hyperventilation leads to compensatory respiratory alkalosis, increase in PH may lead to more severe respiratory compromise than similar ABG in nongravida
- Mechanical changes include elevation of uterus, secondary elevation of diaphragm, decreased diameter of chest, and increased intra-abdominal pressure.[8]

Criteria for Diagnosis

- A history of variable respiratory symptoms
- Typical symptoms are wheeze, shortness of breath, chest tightness, cough
- Usually have more than one of these symptoms
- The symptoms occur variably over time and vary in intensity
- The symptoms often occur or are worse at night or on waking
- The symptoms often occur with or worsen with viral infections
- Measurement of FEV1 and FVC by spirometry: FEV1/FVC ratios <0.7 and > 20% diurnal variation in PFFR for 3 or more days per week during a two week diary is diagnostic.[6]

Effects of pregnancy on asthma: Conventional wisdom is that asthma in pregnancy follows the "one-third rule" (Fig. 2):

- One-third will improve
- One-third will deteriorate
- One-third will remain unchanged.

Asthma during pregnancy has been associated with considerable maternal morbidity. Effects are variable (Table 4).

Figure 2: Changes in asthma severity

TABLE 4: Rate of exacerbation and hospitalization as per the severity of asthma

Severity of asthma	*Exacerbation during pregnancy %*	*Hospitalization rate %*
Severe	51.1	26.9
Moderate	25.7	6.8
Mild	12.6	2.3

Note: 55% of asthmatics have at least one exacerbation during pregnancy.

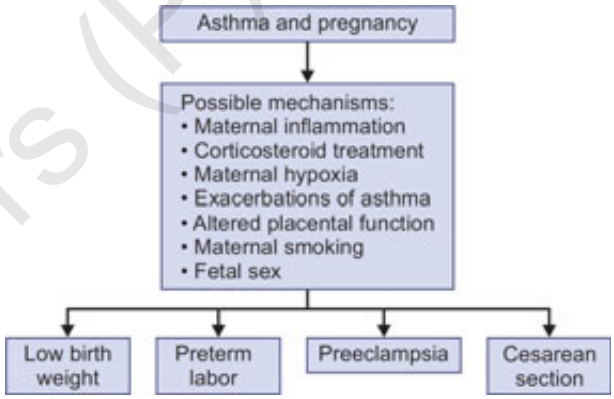

Figure 3: Effect of Asthma on Pregnancy.

EFFECT OF ASTHMA ON PREGNANCY

Compared with women without a history of asthma, women with asthma have been reported to have higher risks for complications of pregnancy even after adjustments for potential confounders.

Risks are:

- Preeclampsia
- Gestational diabetes
- Placental abruption
- Placenta praevia
- Preterm birth
- Preterm premature rupture of the membranes
- Breech presentation
- Hyperemesis
- Pulmonary embolism
- Maternal intensive care admission

- Increased risk of congenital malformations associated with exacerbations in first trimester
- Increased incidence of cesarean section
- Status asthmatics—muscle fatigue with respiratory arrest, pnemothorax, pnuemomediastinum, acute cor pulmonale, and cardiac arrhythmias.

Fetal effects:

- With reasonable control of asthma, perinatal outcomes are generally good
- The fetal response to maternal hypoxemia is decreased umbilical blood flow, increased systemic and pulmonary vascular resistance, and decreased cardiac output. More severe maternal asthma, more is the fetal growth restriction
- Increased low birth weight
- Increased premature delivery
- Increased risk of fetal death

Neonatal effects:

- Increased neonatal hypoxemia
- Low newborn assessment scores
- Increased perinatal mortality.

MANAGEMENT OF CHRONIC ASTHMA

The most recent management guidelines of the working group on asthma and pregnancy include the following:

Patient Education

General asthma management and its effect on pregnancy:

- The patient should be made aware that controlling asthma in pregnancy is especially important for the well-being of the fetus
- Teach them how to recognize signs and symptoms of asthma early
- Improve compliance with medication
- Seek prompt treatment when necessary
- Prompt management of allergic rhinitis, sinusitis, gastrointestinal reflux
- Should have a basic understanding of the medical management of asthma during pregnancy, including self-monitoring of peak expiratory flow rates (PEFRs) and the correct use of inhalers. She should be instructed on proper PEFR technique: make the measurement while standing, take a maximal inspiration, and note the reading on peak flow meter
- Women who smoke should be encouraged to quit. Active smoking, but not passive smoking, has been associated with increased asthma symptoms and fetal growth abnormalities
- Women should also be instructed to avoid and control other asthma triggers
- The importance of adherence to treatment should be stressed
- Patients should be provided with a schedule for maintenance medications and doses of rescue therapy for increased symptoms
- A written asthma action plan is optimal.

Avoidance or Control of Asthma Triggers

- Limiting adverse environmental exposures during pregnancy is important for controlling asthma. Irritants and allergens that provoke acute symptoms also increase airway inflammation and hyper-responsiveness. Association of asthma with allergies is common

Written Asthma Action Plan for Patient Education

General information:

Name:

Emergency contact no:

Ambulance/emergency phone no:

Name of physician:

Triggers/allergy:

Severity of asthma—intermittent/mild persistent/moderate persistent/severe persistent:

Parameter	*Green zone*	*Yellow zone*	*Red zone*
Complaints			
• Breathing • Cough/wheez • Activity/work • Sleep	• Good • No • Active • Sleep well	• Problematic • Present • Partially active • Sleep poorly	• Too much problematic • ++++ • Inactive • Do not sleep
Peak flow meter capacity	>80%	50–80%	<50%
Control medication a. Name of medication b. How much to take c. When to take	– – –	A. If symptoms return to green zone after 1 hour of quick relief treatment 1. Take quick relief medication every 4 hours for 1–2 days 2. Contact physician for follow up B. Symptoms do not return– 1. Quick treatment again 2. Consult physician for modifying medicine routine	A. Go to hospital/call ambulance, if 1. Still in red zone 2. Trouble walking or talking because of shortness of breath 3. Blue fingernails or lips

Figure 4: Zone wise division on the basis of signs and symptoms.[2]

- A total of 75–85% patients with asthma have positive skin tests to common allergens—animal dander, house dust mites, cockroach antigens, pollens and molds
- Other nonimmunologic triggers include tobacco smoke, strong odors, air pollutants, food additives like sulfites, drugs like aspirin and β-blockers
- Strenuous physical activity
- Exercise induced asthma can be avoided with inhalation of albuterol 10–20 minutes before exercise
- Stuffed animals in the bed
- Measures for avoiding asthma triggers—using allergen-impermeable mattress and pillow covers, removing carpeting, weekly washing of bedding in hot water, avoid tobacco smoke, inhibiting mite and mold growth by reducing humidity, and leaving house when it is vacuumed
- The use of allergen immunotherapy or allergy shots—effective in improving asthma in allergic patients. However, anaphylaxis is a risk for allergy injections—especially early in the course of immunotherapy, when the dose is being escalated—and anaphylaxis during pregnancy has been associated with fetal and maternal death
- In a patient who is receiving a maintenance or near-maintenance dose, not experiencing adverse reactions to the injections, and apparently deriving clinical benefit, continuation of immunotherapy is recommended. In such patients, a dose reduction may be considered to further decrease the chance of anaphylaxis. Risk-benefit considerations do not usually favor beginning allergy shots during pregnancy.

Objective Assessment of Pulmonary Function and Fetal Wellbeing

Monitor with FEV1 or PEFR twice daily. FEV1 ideally is > 80% of predicted. For PEFR, predicted value ranges from 380 to 550 L/min. each woman has her own baseline value and therapeutic adjustment (ACOG 2008).

Mainstay of maternal monitoring is spirometry and peak flow assessment. Exhaled nitric oxide fraction (FeNO), a marker of eosinophilic lung inflammation, is the new monitoring modality.[3,4]

Pharmacologic Therapy

In general, asthma medications used in pregnancy are chosen based on the following criteria:

- Inhaled medications are generally preferred because they have a more localized effect with only small amounts entering the bloodstream
- When appropriate, time-tested older medications are preferred since there is more experience with their use during pregnancy
- Medication use is limited in the first trimester as much as possible when the fetus is forming. Birth defects from medications are rare (no more than 1% of all birth defects are attributable to all medications
- In general, the same medications used during pregnancy are appropriate during labor and delivery and when nursing.

Medications for Asthma

Medications for asthma are divided into:

- Long-term controllers that prevent asthma manifestations—inhaled corticosteroids, long-acting β-agonists, leukotriene modifiers, and theophylline
- Rescue therapy, such as with albuterol, to provide quick relief of symptoms
- Asthma medication has been reported to significantly decline in the first trimester according to the number of prescriptions filled; a 23% decrease in inhaled corticosteroids, a 13% decrease in β-agonist, and a 54% decrease in rescue corticosteroids was noted
- It is safer for pregnant women with asthma to be treated with asthma medications than to have asthma symptoms and exacerbations.

Inhaled Corticosteroids

- Inhaled corticosteroids are the preferred treatment for the management of all levels of persistent asthma during pregnancy
- Beclomethasone is more effective than theophylline in improving pulmonary function
- No consistent evidence links inhaled corticosteroids use to increases in congenital malformations or adverse

TABLE 5: Step therapy medical management of asthma during pregnancy[2]

Type of Asthma	*Steps to be followed*
Mild intermittent	SOS medication—albuterol
Mild persistent	Corticosteroids—low dose and inhaled/LABA/LTRA/Theophylline
Moderate persistent	Corticosteroids—low/medium dose and inhaled/LABA/LTRA/theophylline
Moderate persistent	Corticosteroids—medium dose, inhaled and LABA/medium dose inhaled steroids + LTRA/theophylline
Severe persistent	High-dose inhaled corticosteroid and LABA
Severe persistent	High-dose inhaled corticosteroid and LABA and oral prednisone

*Theophylline (serum level, 5–12 µg/mL).
LABA, Jong-acting ß-agonist: LTRA, leukorriene-recopter agonist.

TABLE 6: Typical dosages of asthma medications[2]

Medication	*Doses*
Albuterol MDI	2-4 puffs: 4–6 hourly
Salmeterol DPI	1 blister BID
Formoterol	1 capsule BID
Montelukast	1 tablet of 10 mg Hs
Prednisone	7.5–60 mg 1 day for active symptoms or maintenance of severe persistent asthma
Theophylline	200 mg BID/Day orally. Maintain serum levels between 5 and 12 µg/mL

DPL, dry-powder inhaler; MDI, metered-dose inhaler.

perinatal outcomes. However, more data are available on budesonide use during pregnancy, it is the preferred inhaled corticosteroid, and it is the only inhaled corticosteroid with an FDA pregnancy category B rating.[2]

Inhaled β2-agonists

- Use of inhaled β2-agonists is currently recommended for all levels of asthma during pregnancy. Albuterol has a rapid onset of effect in the relief of acute bronchospasm through smooth muscle relaxation and is an excellent bronchoprotective agent for pretreatment before exercise
- However, they are associated with tremor, tachycardia, and palpitations. They do not block the development of airway hyperresponsiveness
- An increased frequency of bronchodilator use could be an indicator of the need for additional antiflammatory therapy. Appropriate (β2-agonist use appears to be safe during pregnancy[2]
- Salmeterol and formoterol are long-acting β-agonist (LABA) preparations, safe to use by inhalation route, and should only be used in combination with inhaled corticosteroids during pregnancy. They have been shown to be more effective than leukotriene-receptor antagonists (LTRAs) and theophylline as add-on therapy to inhaled corticosteroids. The efficacy of these drugs during pregnancy is largely extrapolated from studies performed in nonpregnant patients.

Omalizumab

- Omalizumab is a humanized monoclonal antibody to immunoglobulin (Ig) E and is an FDA category B drug
- Due to paucity of safety data and the potential risk of anaphylaxis, omalizumab should not be initiated during pregnancy; a possible exception may be the patient who has allergies and remains uncontrolled despite medical management, however, can continued among women with severe asthma who become pregnant.

Theophylline

- Theophylline is an alternative treatment for mild and moderate persistent asthma during pregnancy
- Adverse effects—insomnia, heartburn, palpitations, and nausea; with high doses jitteriness, tachycardia, and vomiting in neonates
- Dosing guidelines have recommended that serum theophylline concentrations be maintained at 5–12 μg/mL during pregnancy[2]
- Treatment with cimetidine, erythromycin, or azithromycin can decrease clearance with resultant toxicity; in such cases, it may be appropriate to decrease the dosage of theophylline by half
- Theophylline is only indicated for chronic therapy and is not effective for the treatment of acute exacerbations during pregnancy
- Theophylline has not "been shown to be associated with congenital anomalies[2]
- In one randomized controlled trial, no differences were found in asthma exacerbations or perinatal outcomes in a cohort that received theophylline compared with the cohort that received inhaled beclomethasone[79]
- However, the theophylline cohort had significantly more reported side effects and discontinuation of study medication, and they had an increased proportion of those with an FEV1 lower than 80% predicted.

Leukotriene Moderators

- Leukotrienes are arachidonic acid metabolites that have been implicated in causing bronchospasm, mucous secretion, and increased vascular permeability. Bronchoconstriction associated with aspirin ingestion can be blocked by LTRAs
- Montelukast and zafirlukast are both designated pregnancy category B
- Although human data are limited for LTRA use in pregnancy, their use has not been associated with an increase in congenital anomalies
- Leukotriene modifiers are less effective as single agents than inhaled corticosteroids and are less effective than LABAs as add-on therapy.[2]

Oral Corticosteroids

- Prednisone is indicated for the maintenance therapy of severe persistent asthma. For outpatient treatment of acute exacerbations, prednisone may be given 40–60 mg per day in one or two divided doses for 3–10 days
- Oral corticosteroid use during the first trimester of pregnancy was associated with a threefold increased risk for isolated cleft lip (background incidence is about 0.1%) with or without cleft palate

TABLE 7: Comparative daily doses for inhaled corticosteroids (doses in μg/puff/inhalation)[2]

Medication	*Daily dose*	*Low dose*	*Medium dose*	*High dose*
Beclomethasone MDI	40–80	80–240	240–480	>480
Budesonide DPI	90–180	180–540	540–1080	>1080
Flunisolide MDI	80	320	320–640	>640
Fluticasone MDI	44.110–220	88–264	264–440	>440
Fluticasone DPI	50.110–250	100–300	300–500	>500
Mometasone DPI	110–220	110–220	220–440	>440
Ciclesonide MDI	80–160	160–320	320–640	>640

*Note that total daily puffs are usually divided as a twice-a-day regimen.
DPI, dry-powdcr inhaler; MDI, metered-do inhaler.

- Oral corticosteroid use has also been associated with an increase incidence of preeclampsia, preterm delivery, and low birth weight
- The National Asthma Education and Prevention Program recommends the use of oral corticosteroids when indicated for the long term management of severe persistent asthma or for exacerbations during pregnancy.

MANAGEMENT OF ALLERGIC RHINITIS AND GASTROESOPHAGEAL REFLUX

- Rhinitis, sinusitis, and gastroesophageal reflux may exacerbate asthma symptoms, and their management should be considered an integral aspect of asthma care
- Inntranasal corticosteroids are the most effective medications for control of allergic rhinitis
- Loratadine and cetirizine are recommended second-generation antihistamines
- Oral decongestant ingestion during the first trimester has been associated with gastroschisis; therefore, short-term (≤3 days) intranasal decongestants or intranasal corticosteroids should be considered before use of oral decongestants
- Controlling gastroesophageal reflux with acid reducers may improve asthma control.

ANTENATAL ASTHMA MANAGEMENT

Antenatal Management

- Women should be encouraged to stop smoking. Reference to smoking cessation programs may prove helpful
- Avoid known trigger factors
- Reassurance regarding the asthma medications to improve compliance
- Home peak flow monitoring and personalized self-management plans should be encouraged
- Counseled about indications for an increase in inhaled steroid dosage and if appropriate given an emergency supply of oral steroids
- Serial growth scans in women with severe asthma.

MANAGEMENT OF ACUTE ASTHMA IN PREGNANCY/LABOR

Acute severe asthma, any one of:

- Peak expiratory flow (PEF) 33–50% best or predicted
- Respiratory rate ≥25/min
- Heart rate ≥110/min
- Inability to complete sentences in one breath.

Life threatening asthma, in a patient with severe asthma any one of:

- Peak expiratory flow <33% best or predicted
- SpO_2 <92%
- PaO_2 <8 kPa
- Normal or raised $PaCO_2$ (4.6–6.0 kPa)
- Silent chest, cyanosis, poor respiratory effort
- Arrhythmia, exhaustion, hypotension, altered consciousness.

Near Fatal Asthma

Raised $PaCO_2$ and/or requiring mechanical ventilation with raised inflation pressures.

Treatment of Acute and Severe Asthma

- Severe asthma in pregnancy is a medical emergency and should be vigorously treated in hospital in conjunction with the respiratory physicians
- Treatment of severe asthma is not different from the nonpregnant patients.

Treatment should include the following:

- High flow oxygen to maintain saturation of 94–98%
- Beta 2-agonists administered via nebulizer which may need to be given repeatedly
- Nebulized ipratropium bromide should be added for severe or poorly responding asthma
- Corticosteroids (intravenous hydrocortisone 100 mg) and / or oral (40–50 mg prednisolone for at least 5 days)
- Chest radiograph should be performed if there is any clinical suspicion of pneumonia or pneumothorax or if the woman fails to improve
- Management of life-threatening or acute severe asthma that fails to respond should involve consultation with the critical care team and consideration should be given intravenously β2 agonists, intravenous magnesium sulfate and intravenous aminophylline.

Intrapartum Management

- Asthma attacks are exceedingly rare in labor due to endogenous steroids
- Women should not discontinue their inhalers during labor as there is no evidence to suggest that β2-agonists inhalers will impair uterine contractions
- Women receiving oral steroids (7.5 mg/day for >2 weeks) should receive parenteral hydrocortisone 50–100 mg three times a day to cover the stress of labor
- Prostaglandin E2 (PGE2) are safe to use
- Use of prostaglandin F2α to treat life-threatening PPH may be unavoidable, but it can cause bronchospasm and should be used with caution
- Ergometrine may cause bronchospasm especially when general anesthesia is used
- Regional rather than general anesthesia is preferable because of the decreased risk of chest infection and atelectasis
- Cesarean section is reserved only for obstetric indications only.

Postnatal Management

- All the drugs including oral steroids are safe in breast feeding mothers
- The risk of strong genetic predisposition to of atopic disease developing in the child of a woman with asthma is about 1 in 10, or 1 in 3 if both parents are atopic. Hence, advice about primary prevention measures to be given like:
  - There is some evidence that breast feeding may reduce the risk of asthma in baby
  - A smoke-free environment should be recommended for all children.[7]

TABLE 8: Home management of acute asthma exacerbations. Response after treatment. Use albuterol MDI 2–4 puffs and then measure PEFR [2]

Parameter	*Poor response*	*Incomplete response*	*Good response*
PEFR (Predicted)	<50%	50–80%	>80%
Symptoms	Shortness of breath, severe wheez	Persistent wheez and shortness of breath	No wheez, no shortness of breath
Fetal movements	Decreased	Decreased or normal	Normal
How to manage	Repeat albuterol 2–4 puffs by MDI Seek emergency care	• Repeat albuterol 2–4 puffs by MDI at 20 min interval for 2 times • Still no improvement, seek emergency care	Continue albuterol 2–4 puffs by MDI, every 3–4 h

MDI, metered-dose inhaler; PEFR, peak expiratory flow rate.

Advice should be given regarding:

- In general medicines used to treat asthma are safe in pregnancy
- The risk of harm to the fetus from severe or chronically undertreated asthma outweighs any small risk from the medications used to control to control asthma
- Use all the drugs mentioned in the table as normal in pregnancy including oral steroid tablets
- Blood levels of theophylline in pregnant women with acute severe asthma and in those critically dependent on therapeutic theophylline levels
- No adverse perinatal outcome and exposure to sodium cromoglicate and nedocromil sodium has been documented.

Breastfeeding

- In general, only small amounts of asthma medications enter breast milk
- Prednisone, theophylline, antihistamines, inhaled corticosteroids, LTRAs, and 32-agonists are not considered to be contraindications for breastfeeding
- In sensitive neonates, theophylline may cause vomiting, feeding difficulties, jitteriness, and cardiac arrhythmias.

Constraints in Managing Asthma during Pregnancy

- Poorly controlled asthma is associated with significant morbidity and is also potentially fatal for both the mother and the fetus. However, reluctance to the regular inhaled treatment due to ignorance and low illiteracy among the asthma patients in India is a major challenge to the treating physician
- The cost of diagnosis and inhaled medicines is beyond the reach of the majority and therefore international guidelines may not be appropriate for such patients
- A large prevalence of tuberculosis, which is an important cause of cough, adds to the difficulties of diagnosis and management in India
- The asthma patients with pregnancy should be managed with affordable medicines early and aggressively for any exacerbations to prevent resultant damage to the fetus in the long run
- Since exposures to tobacco smoke and air pollution leads to increase in severity of asthma symptoms, decreased response to treatment, and accelerated decline in lung functions; thus all pregnant asthmatics should be advised to avoid both active and passive smoking as well as air pollution (outdoor/indoor) in the form of smoke and fumes especially due to the use of biomass fuels for cooking in the rural areas
- Dyspnea or breathlessness during pregnancy is quite common among Indian women due to many causes like anemia, congestive heart failure, hypertension besides asthma and this remains a challenge among the treating physician to differentiate and classify the patient correctly.

Solutions to Constraints

- Treat exacerbations aggressively and prevent future exacerbations with regular controller options (inhaled and oral)
- Avoid the use of antibiotics, except to control bacterial infections and infectious exacerbations
- The addition of oral theophylline and other oral medication should normally be considered only if inhaled treatments have failed to provide adequate relief
- Drugs like aspirin and penicillin, sedatives or anesthetic drugs which have potential to induce asthmatic attack should be used cautiously and judiciously.

Management of Acute Asthma in Pregnancy/Labor

The main goal is to maintain sufficient oxygenation of the fetus by preventing hypoxic episodes in mother.

CONCLUSION

Asthma is the most common chronic disease to affect pregnant women. Exacerbations occur in up to 45% of pregnant women with asthma. Asthma should be managed during pregnancy as for other adults. During pregnancy, the doctor must classify severity of asthma and should ensure that stepwise treatment be started as quickly as possible (upregulation or downregulation). Minimize use of short-acting inhaled β2-agonist. For persistent asthma during pregnancy, first-line controller therapy consists of inhaled corticosteroids. During pregnancy, budesonide is the preferred inhaled corticosteroid.

BOX 1 Emergency department and hospital-based management of asthma exacerbation[2]

A. Initial assessment and treatment

1. History and examination – auscultation, use of accessory muscles, heart rate, respiratory rate, PEFR or FEV, oxygen saturation and other tests as indicated:
2. If severe exacerbation (FEV1, or PEFR is <50% with severe symptoms at rest), high-dose albuterol by nebulization every 20 minutes or continuously for 1 hour, inhaled itratropium bromide, and systemic corticosteroids
3. Intiate fetal assessment (consider fetal monitoring and/or BPP if fetus is potentially viable)
4. Abbuterol by MDI or nebulizer, up to three doses in the first hour.
5. Oral corticosteroid if no immediate response is seen or if the patient was recently treated with a systemic corticosteroid
6. Oxygen to maintain pulse oximetry saturation >95%
7. Repeat assessment: symptoms, physical examination, PEFR, oxygen satutation
8. Continue albuterol every 60 minutes for 1–3 hours provided improvement is evident

B. Repeat assessment

1. Symptoms, physical examination, PEFR, oxygen satutation, other tests as needed
2. Continue fetal assessment

C. Response after repeat assessment[2]

- Good
  - FEV1 or PEFR ≥70%
  - Response sustained 60 minutes after last treatment
  - No distress
  - Physical examination: Normal
  - Reassuring fetal status
  - Discharge home
- Incomplete
  - FEV or PEFR ≥50% but <70%
  - Mild or moderate symptoms
  - Continue fetal assessment until patient has stabilized
  - Monitor FEV, or PEFR, oxygen saturation, pulse
  - Continue inhaled albuterol and oxygen
  - Inhaled ipratropium bromide
  - Systemic (oral or IV) corticosteroid
  - Individualize decision for hospitalization
- Poor
  - FEV1 or PEFR >50%
  - PCO_2 <42 mmHg
  - Symptoms severe, drowsiness, confusion
  - Continue fetal assessment
  - Admission to ICU

D. Impending or actual respiratory arrest

- Admission to ICU
- Intubate and mechanical ventilation with 100% O_2
- Nebulization with albuterol and inhaled ipratropium bromide
- IV corticosteroids

E. ICU

- Oxygen
- Intubation, mechanical ventilation
- Hourly/continuous inhalation of albuterol + inhaled ipratropium bromide
- IV corticosteroid
- Continuous fetal monitoring

F. Discharge

- Continue treatment with albuterol
- Oral/systemic steroids
- Continue/initiate inhaled steroid
- Patient education about medicine use, action plan and follow up

BPP, biophysical profile; FEV1, forced expiratory volume In 1 second; ICU, intensive care unit; MDI, metered-dose inhaler; PCO_2, partial pressure of carbon dioxide; PEFR, peak expiratory flow rate.

For pregnant women with asthma. Recommended rescue therapy is inhaled salbutamol. Maternal and fetal well-being can be improved by identifying and controlling or avoiding exposure to tobacco smoke and other allergens and irritants. Risk-benefit considerations do not usually favor beginning allergen immunotherapy during pregnancy. In general, only small amounts of asthma medications enter breast milk during breastfeeding. Use of prednisone, theophylline, antihistamines, inhaled corticosteroids, β2-agonists, and cromolyn is not contraindicated.[8] Severe and poorly controlled asthma may be associated with increased prematurity, preeclampsia, growth restriction, and a need for cesarean delivery. Severe asthma exacerbations can result in maternal morbidity and mortality and can have commensurate adverse pregnancy outcomes.

The management of asthma during pregnancy should be based on objective assessment, trigger avoidance, patient education, and step therapy. Asthma medications should be continued during pregnancy.

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CHAPTER

Viral Infections in Pregnancy

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INTRODUCTION

Immunologic changes of pregnancy induce a state of increased susceptibility to intracellular pathogens, like viruses. Viral infections in pregnancy are a major cause of morbidity and mortality for both mother and fetus. Infections can occur in the neonate transplacentally, perinatally (from vaginal secretions or blood) or postnatally (from breast milk or other sources). Perinatal outcomes from viral infections during pregnancy can range from no effect to pregnancy loss to fetal infection with resulting congenital viral syndromes. The importance of understanding the role of viral infection during pregnancy is becoming more relevant as we confront growing risks of pandemics, which may significantly affect the pregnant mother and the fetus.[1] There is strong epidemiologic evidence that pregnant women are at higher risk of severe illness and mortality from viral infections.[2,3] The risk of infection is usually inversely related to gestational age at acquisition.[4]

In this chapter, the main viral infections associated with pregnancy are reported and their effects on fetus and mother are discussed.

HERPES SIMPLEX VIRUS

Herpes simplex virus (HSV)-1 and HSV-2 are DNA viruses known to be infectious in humans. HSV-1 and 2 are transmitted across epithelial mucosal cells as well as through skin interruptions and migrate to nerve tissues where they persist latent. HSV-1 predominates in orofacial lesions and typically is found in the trigeminal ganglia, while HSV-2 is most commonly found in the lumbosacral ganglia. Both HSV-1 and HSV-2 can cause genital lesions and shedding.

Clinical Features

Primary HSV infection leads to vesicular lesions, result in more severe disease than that in the non-pregnant ones, in particular, gingivostomatitis and vulvovaginitis herpetica and there is a tendency towards dissemination. Recurrent episodes of HSV infection are characterized by the presence of antibody against the same HSV type as in the first episode. The herpes outbreaks are usually mild (7–10 days) with less severe symptoms than the first episode.

Fetal Effects

Risk of neonatal infection is as low as 1% if mother acquires HSV in first trimester due to formation of protective antibodies. Whereas the risk significantly, rises to 30–50% if mother gets infected in last trimester.[5] Transmission of HSV during pregnancy is uncommon; about 85% of perinatal transmission occurs during the intrapartum period. Of known infected infants, only 30% are mothers who had symptomatic HSV or a sexual partner with clinical infection.[6] The acquisition of genital herpes has been associated with spontaneous abortion, intrauterine growth retardation, preterm labor, congenital and neonatal herpes infections.[7] Congenital HSV infection (approximately 4% of all neonatal HSV infections) results in an infant born with microcephaly, hydrocephalus, chorioretinitis and vesicular skin lesions.[8] Three subtypes of infection have been identified: (1) disease localized to the skin, eye or mouth; (2) encephalitis, with or without skin, eye or mouth involvement; (3) disseminated infection that involves multiple sites, including the central nervous system, lung, liver, adrenals, skin, eye or mouth. There is virtually no mortality among infants with disease limited to the skin, eyes and mouth, but mortality increases to 15% among infants with encephalitis and 57% among infants with disseminated disease, even with antiviral therapy. Long-term morbidity is common in infants who survive with encephalitis or disseminated disease, and may include seizures, psychomotor retardation, spasticity, blindness or learning disabilities.[9]

Diagnosis

Diagnosis is by direct immunofluorescent staining using fluorescein-conjugated monoclonal antibodies to HSV.[10] The sensitivity of this test is 80–90%, very high compared with viral culture. The polymerase chain reaction (PCR) is a more sensitive assay.

Treatment

Antiviral therapy with acyclovir is the treatment modality in primary episode or active recurrent genital HSV at or beyond 36 weeks of gestation.[11] Acyclovir therapy will decrease viral shedding, prevent neonatal herpes; reduce the need for cesarean delivery and decreases clinical recurrences of herpes simplex virus infection. Valacyclovir is a promising substitute of acyclovir with similar efficacy and less frequent dosing.

Rupture of membranes for more than four to six hours, use of fetal scalp electrode monitoring, use of vacuum and forceps before delivery increases the risk of transmission of HSV to the infant.[12] Any patient who has active genital lesions, as well as a pregnant woman with recurrent HSV, or prodromal symptoms (such as vulvar pain or burning at delivery) of HSV infection should undergo cesarean section. [11] Cesarean delivery is not recommended for women with a history of HSV infection but no active genital disease during labor.

The HSV-exposed neonate should undergo cultures at 24–48 h, and then weekly of conjunctiva, nose, mouth, urine and rectum for HSV-1 or HSV-2. Empiric acyclovir may be instituted in infants born to mothers with suspected primary HSV infection.[12]

RUBELLA (GERMAN MEASLES)

The rubella virus, an enveloped RNA virus, is classified as a togavirus. It is transmitted through respiratory droplets is a self-limiting infection but the virus can have grave effects on the fetus. It causes mild symptoms like coryza, fever, malaise and rash. The rash characteristically begins on the face and spreads to the trunk and extremities.

Fetal Effects

Risk of congenital defects (congenital rubella syndrome CRS) is 90% if infection occurs before 11 weeks and minimal if occurs after 16 weeks.[13] Congenital rubella syndrome comprises of sensorineural deafness, pulmonary stenosis, patent ductus venosus, cataract, mental retardation, microcephaly, thrombocytopenia, purpura.[14] Late manifestations include diabetes mellitus, growth hormone deficit and thyroiditis.

Diagnosis, Management, and Prevention

Diagnosis is by four-fold rise in rubella immunoglobulin G, positive immunoglobulin M, and positive culture from blood/cerebrospinal fluid. Fetal infection is diagnosed by PCR on chorionic villous sampling.

Management depends on period of gestation and immune status.[15]

- If patient has immunity (IgG +ve) and >12 weeks then no testing is required.
- If patient has immunity and <12 weeks then rise in IgG without rise in IgM means reinfection. Risk of CRS is 8% and needs counselling
- If patient has no immunity/unknown status then
  - <16 weeks: High risk of CRS, hence termination can be offered
  - 16–20 weeks: CRS is rare (1%)
  - >20 weeks: reassurance as no case of CRS is documented after 20 weeks.

Treatment is mainly symptomatic. Prevention is by rubella vaccine or measles-mumps-rubella (MMR) to all adolescent girls and to women attending infertility or pre-conception clinics, if not vaccinated before.

CYTOMEGALOVIRUS

Cytomegalovirus is the most common intrauterine infection.[16] Congenital CMV infection occurs in 0.2–2.2% of live births worldwide. It may result from transplacental acquisition of either a primary or recurrent (i.e., cytomegalovirus infection that occurs in the context of preconceptual immunity) maternal infection.[17]

Fetal Effects

Rate of transmission to the fetus in primary maternal infection is 40%; and approximately 65% of these infants have CMV disease at birth. With recurrent infection risk of transmission to the fetus is lower, from 0.5 to 1.5%; most of these infants appear normal at birth.[18] Cytomegalic inclusion disease (CID) is the most severe form of congenital CMV infection. Approximately 10% of infants with congenital infection have clinical evidence of disease at birth. CID is characterized by intrauterine growth retardation, hepatosplenomegaly, hematological abnormalities (particularly thrombocytopenia) and cutaneous manifestations, including petechiae and purpura (blueberry muffin baby). The most significant manifestations of CID are microcephaly, ventriculomegaly, cerebral atrophy, chorioretinitis and sensorineural hearing loss. Most infants who survive symptomatic CID have significant long-term neurological and neurodevelopmental sequelae, even 10% of asymptomatic neonates eventually develop neurologic sequelae. It has been estimated that congenital cytomegalovirus may be second only to Down syndrome as an identifiable cause of mental retardation in children.[18] Symptomatic neonates have a mortality rate of up to 30%, and 70–90% of survivors have some morbidity in the form of neurologic impairment, including hearing loss, mental retardation and visual disturbances.[17]

Diagnosis and Treatment

Diagnosis in mother is made by serologic testing and in neonates; the primary diagnostic tool is viral culture and PCR of amniotic fluid obtained from amniocentesis.[19] Nucleic acid amplification test of amniotic fluid is gold standard for diagnosis of fetal infection.[20] USG findings like presence of IUGR, cerebral ventriculomegaly, microcephaly, intracranial calcifications, hyperechogenic bowel and liver calcifications.[20] Treatment is supportive. Due to absence of effective therapy, termination of pregnancy is advised if fetal infection is detected. In infants, antiviral therapy with ganciclovir may be of benefit in reducing the prevalence of neurodevelopmental sequelae, like sensorineural hearing loss.[18] Prevention is an important tool to save the neonate from this deadly virus. Routine screening is not recommended but it can be done in women who develop influenza like symptoms or have sonographic features of CMV infection.

VARICELLA ZOSTER

Varicella zoster is a DNA herpes virus. 95% adults acquire immunity by vaccination, occurrence of disease or by herd immunity. The virus causes primary infection chicken pox and secondary infection herpes zoster. It rarely infects in pregnancy, if infects causes fatal complications for both mother and fetus.

Symptoms

Varicella transmission occurs by direct contact or respiratory droplets. It is characterized by fever, malaise and vesicular rash on trunk, face, scalp, extremities and oropharynx. The lesions on skin are at various stages and pruritic. Five to twenty percent of women develop pneumonia which presents as medical emergency.[21] Before the advent of antiviral therapy mortality was high which fell to 1–2% after its advent.

Fetal Effects

Transplacental transmission occurs depending on time of affection resulting in spontaneous abortion, congenital varicella syndrome (CVS), premature delivery, fetal growth restriction and postnatal infection. CVS is characterized by skin defects, nuerological defects (encephalitis, cortical atrophy, spinal cord atrophy, seizures, microcephaly, mental retardation, etc.), eye disease (microphthalmia, chorioretinitis, cataract, and optic atrophy), limb hypoplasia and affections of internal organs. Risk of acquiring CVS ranges from 0.4 to 2% with maternal varicella infection during the first 20 weeks of gestation.[22] Neonatal varicella occurs when mother is infected 4–5 days before to 2 days after delivery. The clinical picture may vary from skin lesions to systemic illness, which has a mortality rate of about 30%.[22]

Diagnosis

Maternal infection is diagnosed clinically. Congenital varicella is diagnosed by nucleic acid amplification test of amniotic fluid.[20] Features suggestive of CVS can be seen on ultrasound done 5 weeks after maternal infection. So serial ultrasound in mother is necessary if infection occurs in between 5 and 20 weeks of pregnancy. Varicella DNA can be detected by PCR in fetal blood, amniotic fluid or placental villi.[20]

Treatment

Treatment for pregnant woman primarily targets decreasing maternal morbidity, as no treatment regimen has shown a decrease in the incidence of vertical transmission. Infected pregnant women should be isolated and needs supportive care. Acyclovir 800 mg five times a day for 7 days within 24 hours of appearance of rash should be given. Severely sick women require hospitalization and intravenous (IV) Acyclovir treatment.[23] Delivery during viremic period is hazardous with maternal risks like bleeding, thrombocytopenia, disseminated intravascular coagulopathy and hepatitis. Delivery should be delayed until 5 days of onset of maternal illness. If anesthesia is required then epidural is safe than spinal anesthesia. Termination of pregnancy is indicated only if there are signs of fetal malformations. Neonates born to mothers with varicella between 5 days before and 2 days after the delivery should be given varicella zoster immunoglobulin. Prevention is by universal immunization in childhood and vaccination of non-immune adults with 2 doses of vaccine 4–8 weeks apart to prevent varicella in pregnancy. Vaccination is contraindicated in pregnancy.[23]

VIRAL HEPATITIS

Viral hepatitis is an infection that has serious implications during pregnancy. There are five different types of viral hepatitis: A, B, D, C, and E. It is an important cause of maternal mortality in India, accounting for 0.8–29.4% maternal deaths in various parts of India.[24] The mortality is 3.5-fold higher during pregnancy (an immunocompromised state) than in nonpregnant women. All hepatitis viruses except B are RNA viruses. Hepatitis A is not transmitted vertically to the fetus. Hepatitis B and C may be transmitted vertically to the fetus. Hepatitis D is a defective RNA virus that requires concomitant infection with hepatitis B. Hepatitis E has similar characteristics to hepatitis A but is a more serious with significant mortality in pregnant women.

Hepatitis A

Hepatitis A virus (HAV) is transmitted by the feco-oral route. Incidence of acute HAV infection in pregnancy is approximately 1:1000 women.[22] Vertical transmission during pregnancy or puerperium is rare.[25] The infection may cause an increased frequency of preterm birth. The diagnosis is made by determination of specific anti-hepatitis A virus IgM. Treatment consists of bed rest and adequate nutrition.

Hepatitis B

Hepatitis B virus is highly infectious and can be transmitted by infected blood, blood products, saliva, sexual intercourse or perinatally. Chronic infection follows acute HBV in about 10% of the cases. Pregnant women may be affected by acute HBV infection or have chronic infections. The acute infection is manifested by flu-like symptoms in approximately 25% of the patients and is asymptomatic in the rest. Approximately 90% of individuals have spontaneous complete resolution of the acute infection, less than 1% would die of fulminant hepatitis, and 5–10% would become chronic carriers manifested by the continuous presence of HbsAg in their serum.[26]

Diagnosis

The diagnosis of acute HBV infection is made by the presence of HBsAg early in the course of the disease, followed by the appearance of antibodies against the core (anti-Hbc), the envelope antigen (anti-Hbe), and the surface (anti-Hbs) antigens.

Fetal Effects

About 10–20% of women seropositive for HbsAg, having high viral load transmit the virus to their neonates in the absence of immunoprophylaxis. In women, who are seropositive for both HbsAg and HbeAg, vertical transmission is approximately 90%. In patients with acute hepatitis B, vertical transmission

occurs in up to 10% of neonates when infection occurs in the first trimester and in 80–90% of neonates when acute infection occurs in the third trimester.[27] Risk for HBV transmission at delivery is mainly due to exposure to cervical secretions and maternal blood. Transplacental transmission and transmission due to obstetrical procedures are less frequent causes, and breastfeeding does not appear to pose a substantial risk. Delivery decisions should be made in the context of the usual obstetric indications.

Management

Universal screening of all pregnant women should be done for identification of Hepatitis B surface antigen. Women found to be positive should also be screened for HIV and other forms of hepatitis such as hepatitis A and C. Monitoring of liver biochemical tests and viral load help guide management and extent of disease. All infants of mothers with HBV should receive passive-active immunization with hepatitis B IgG and the hepatitis B vaccine within 12 hours of delivery.[21]

Hepatitis C

Hepatitis C (HCV) is a condition that affects approximately 1.0–5% of all pregnancies and is more frequent in women with HIV infection. The risk factors for the acquisition of hepatitis C are similar as for hepatitis B but chronic infection following hepatitis B affects 10% of the cases while chronic liver disease follows hepatitis C in more than 50% of the cases. The majority of infections are asymptomatic. The rate of transmission is approximately 3–6% but this risk is much higher if the mother is also infected with HIV. The risk of vertical transmission correlates with the HCV RNA viral load of the mother.[28] HCV is rarely transmitted by breast-feeding. The role of cesarean delivery for the prevention of vertical transmission has not been clearly demonstrated. There is no effective treatment available to treat HCV infections in mothers and newborns. For this reason, routine HCV screening is not recommended at the present time.

Hepatitis E

The infection is mild and self-limited without chronicity or clinical sequelae. During pregnancy, the risk of fulminant disease and maternal mortality is 20% if presents during the third trimester. Premature deliveries with high infant mortality of up to 33% are also observed. Although the mechanism underlying the increased mortality is unknown, the reported complications include gestational hypertension, preeclampsia, proteinuria, edema, and kidney disease. One possible mechanism could be a direct or indirect effect on the kidneys, which may increase maternal mortality.[29]

HUMAN IMMUNODEFICIENCY VIRUS

According to World Health Organization (WHO), there are approximately 36.7 million people worldwide living HIV/acquired immunodeficiency syndrome in 2016. India has a HIV prevalence of 0.26% and prevalence in pregnant woman being 0.29%.[30] The prevention of parent to child transmission of HIV/AIDS (PPTCT) program was launched in India in 2002. The PPTCT program aims to prevent the perinatal transmission of HIV from HIV infected pregnant mother to her newborn baby. The National AIDS Control Organization (NACO) Technical Estimate Report 2015 estimated that out of 29 million annual pregnancies in India, 35,255 occur in HIV positive women. In the absence of any intervention, an estimated 10,361 infected babies will be born annually. Based on guidelines from WHO, Department of Aids Control, India has decided to provide lifelong antiretroviral therapy (ART), in which all pregnant women living with HIV receive a triple drug ART regimen regardless of CD4 count or WHO clinical stage, both for their own health and to prevent vertical transmission from mother to child and this would reduce transmission rate to less than 5% in breastfeeding population.[31]

Etiopathogenesis

HIV that causes acquired immunodeficiency syndrome (AIDS), belongs to lentivirus family of retrovirus. AIDS is commonly caused by HIV-1, which is found all over the world and responsible for most cases of HIV infections. HIV-2 is restricted to western Africa; less pathogenic; occurs and less easily transmitted.

Perinatal Transmission of HIV

HIV infection from an HIV-positive mother to her child can occur during pregnancy, labor, delivery or breastfeeding.[33] Direct transmission may occur in utero and via transplacental passage. Table 1 shows the estimated risk and timing of transmission in absence of intervention. Risk factors associated with transmission include high maternal plasma viremia, advanced clinical HIV-1 disease, reduced maternal CD4 count, presence of other STIs, smoking, absence of ART, obstetric procedures like amniocentesis, fetal scalp electrodes, vaginal delivery and a lengthy interval between rupture of the amniotic membrane and delivery. In addition, direct exposure to maternal blood, presence of ulcerative genital infection in the maternal vaginal tract at the time of delivery, illicit drug use during pregnancy, prematurity, and low birth weight, mixed feeding have all been associated with increased mother-to-child transmission.[34] HIV transmission to the fetus can occur as early as the 15th week of pregnancy. Prenatal infection may cause a HIV-specific embryopathy in the majority of infected children. It is characterized by a small forehead, short flat nose, pronounced philtrum, microcephaly, thick lips and hypertelorism.[34] Studies

TABLE 1: Estimated risk and timing of transmission in absence of intervention

Risk of HIV transmission	*Transmission rate (%)*
During pregnancy	5–10
During labor and delivery	10–15
During breastfeeding	5–20
Overall without breastfeeding	15–25
Overall breastfeeding to 6 months	20–35
Overall breastfeeding to 18–24 months	30–45

Source: NACO.

from developing countries show that an increased risk of preterm birth, still birth, intra uterine growth restriction and infant deaths born to HIV infected mothers. Various studies has shown that there is no accelerated progression of HIV-infection due to an intervening pregnancy.[35]

Laboratory Diagnosis of HIV

National AIDS Control Organization (NACO) recommends screening by enzyme linked immunosorbent assay (ELISA)/ rapid principle as initial screening at PPTCT center. When first test is reactive then it is confirmed by two tests using different system (ELISA/rapid test with different antigens or different principle of test). If the test is reactive in three different systems, then women is confirmed to have HIV infection. Western blot, polymerase chain reaction, p24 antigen detection are other tests which can be done to resolve discordant/indeterminate results.

Screening for HIV[31,36]

Screening for HIV is all offered as early as possible after pretest counseling during each new pregnancy, this enables prevention, detection, treatment and reduction of transmission. Post-test counselling for all pregnant women is very important so as to educate those with negative tests to remain un-infected; while for those with confirmed HIV positive tests-further counseling, support and referrals to care and treatment services. Partner/ Spouse and family (other children) testing is done for HIV as per ICTC guidelines. Retesting is recommended in third trimester, or during labor or shortly after delivery in high prevalence settings. Testing is also offered to all women of unknown HIV status presenting directly in labor or after delivery. As per PPTCT guidelines, ART may be initiated based on single positive test result during labor, confirmatory test may be done later.

National Guidelines for PPTCT of HIV in India[31]

With effect from 1st January 2014, NACO have decided to opt for lifelong triple drug ART to all pregnant and breastfeeding women regardless of CD4 count and clinical staging. Treatment in various scenarios is as follows (Table 2 shows antiretroviral drugs):

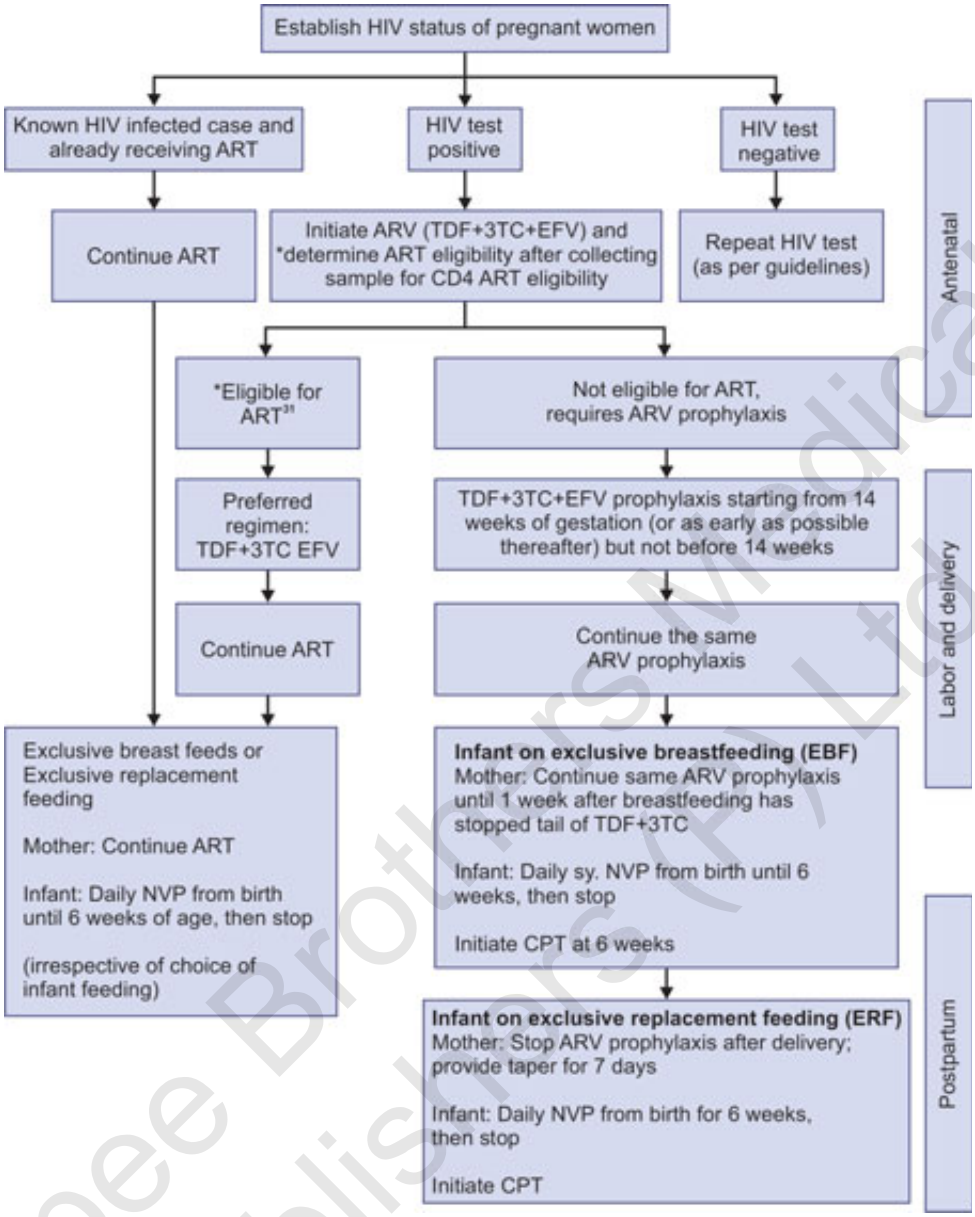
- The recommended first-line regimen for HIV infected pregnant women is tenofovir (TDF) (300 mg) + lamivudine (3TC) (300 mg) + efavirenz (EFV) (600 mg). Alternate first-line regimen includes AZT + 3TC + EFV or
  AZT + 3TC + NVP or TDF + 3TC+NVP. Table 2 shows the classification of antiretroviral drugs
- Women who have had previous exposure to NVP (or EFV) , require a protease-inhibitor based ART regimen TDF + 3TC + LPV/r (lopinavir/ritonavir). The dose will be TDF + 3TC (1 tablet daily) + LPV (200 mg)/r (50 mg) (2 tablets BD)
- Pregnant women already receiving ART: continue same regimen even in first trimester
- Pregnant women with HIV-2: HIV 2 less transmissible from mother-to-child. NVP and EFV are not effective against HIV-2 infection. Therefore, they are given 2NRTIs + LPV/r. AZT (instead of Syp NVP) to be given to babies in mothers with HIV-2
- Co-trimoxazole should be started if CD4 count is ≤250 cells/mm^3 and continued through pregnancy, delivery and breastfeeding as per national guidelines (dose: double strength tablet – 1 tab daily). Ensure women take folate supplements
- If a pregnant woman is detected to have both HIV-1 and HIV-2 infections, she should receive standard first ART regimen (TDF + 3TC + EFV) recommended for women with HIV-1 infection
- Intrapartum care: women on lifelong ART should receive ART as per usual schedule during labor and delivery
- Cesarean sections in HIV positive pregnant women should be performed for obstetric indications only following all safer surgical techniques. Elective caesarean section at 39 weeks' gestation can be done to minimize perinatal transmission of HIV if HIV RNA levels >1,000 copies/mL or unknown HIV levels near the time of delivery, irrespective of administration of ARV therapy. Elective caesarean section is not recommended for prevention of MCTC in women receiving combination ARV drugs with plasma HIV RNA levels <1,000 copies/mL near the time of delivery
- Management of HIV exposed infants (HIE): Newborn is started with 6 weeks of syrup NVP immediately after birth. NVP is extended to 12 weeks if duration of ART of mother is less than 24 weeks in antenatal period. Exclusive breastfeeding is recommended till 6 months followed by rapid weaning and avoiding mixed feeds. Cotrimoxazole started at 6weeks and continued until baby is 18 months old

TABLE 2: Classes of ARV drugs[31,32]

Entry inhibitors	*Nucleoside reverse transcriptase inhibitors*	*Non-nucleoside reverse transcriptase inhibitors*	*Protease inhibitors*
Maraviroc MVC Enfuvirtide T-20	• Zidovudine AZT* • Stavudine d4T* • Lamivudine 3TC* • Didanosine ddI* • Abacavir ABC* • Emtricitabine FTC • Tinofuvir TDF	• Nevirapine NVP* • Efavirenz EFV*	• Atazanavir ATV* • Ritonavir RTV* • Lopinavir LPV* • Saquinavir SQV • Indinavir IDV • Nelfinavir NFV • Amprenavir APV • Fosamprenavir FPV • Tipranavir TPV • Darunavir DRV

*Drugs are available in the NACO ART program.

Source: NACO.



Flowchart 1: Algorithm for management of HIV positive mother and infant (Source NACO).

or longer if baby is confirmed positive. Early infant diagnosis (EID) is done by HIV DNA polymerase chain reaction PCR at 6 weeks, repeat at 6 months, 12 months and 6 weeks after cessation of breast feeding. The test recommended for EID is by DBS (dry blood spot) (Flowchart 1).

H1N1 VIRUS

Influenza viruses that infect humans are classified into 3 principal types (A, B, and C), of which A viruses are further classified on the basis of 2 surface proteins, hemagglutinin (H) and neuraminidase (N). H1N1 designates a specific subtype of influenza A. In April 2009, human infection with H1N1 influenza virus of swine origin was detected in California and Texas. In India, first case was detected in on 13th May 2009 in Hyderabad.[37] Pregnant women are at high risk for severe complications of influenza during seasonal influenza and some studies suggest an increased risk for adverse outcomes among infants born to mothers infected with influenza during pregnancy.[38] Among patients with H1N1 infections, pregnant women accounts for 6–9% of ICU admissions and 6–10% of patients who died. There appears to be a risk of death among infected women in third trimester.[37]

Fetal Effects

The effects of maternal influenza infection on the fetus are not well understood. Viremia is believed to occur infrequently in influenza, and placental transmission of the virus is also rare. Studies suggested a possible increase in defects of the central nervous system, spontaneous pregnancy loss, fetal death, and preterm delivery especially among women with pneumonia.[22] Associations between maternal influenza infection and childhood leukemia, schizophrenia, and Parkinson disease

have been suggested by some studies.[22] Even if the influenza virus does not have a direct effect on the fetus, high fever that accompanies influenza could have adverse effects especially neural tube defects. Factors that might attenuate this risk include shorter fever duration, use of fever-reducing medications, and use of folic acid-containing supplements.[22]

Clinical Features[39]

Symptoms start with fever, body ache, rhinorrhea, throat pain which gets partial relief with symptomatic medications however cough, dyspnea and fever persists giving rise to suspicion of H1N1. This mild illness recovers in 50% of patients within 7 days of symptoms and a further 25% within 10 days. The signs and symptoms of severe disease includes dyspnea, chest pain, purulent or blood stained sputum (due to pneumonia), respiratory rate >30/min, marked tachycardia (due to myocarditis), hypoxia SpO_2 <94%, shock and altered consciousness. Sepsis may develop due to super added infections resulting in acute kidney injury. Disseminated intravascular coagulation, septic shock is seen in second week of infection. Patient succumbs to respiratory, cardiac or multi organ failure.

Diagnosis

RT-PCR on throat swab is the gold standard test for H1N1. It has 97% sensitivity and 98% specificity. Viral culture is used for research and antibody testing is for epidemiological purpose.[39]

Treatment

H1N1 in pregnancy must be detected and antivirals must be started as early as possible to avoid complications. Antivirals of choice are oseltamivir (Tamiflu) oral capsules and zanamivir (Relenza) inhaler. Dose schedules are discussed below.[39] Table 3 shows dose schedules.

The most common complication of A H1N1 influenza is pneumonia.

The plan of management in such cases has been summarized:[40]

- Early involvement of obstetric anesthetist, respiratory physician, hematologist and a microbiologist
- Rule out other associated pregnancy-related complications such as chorioamnionitis, severe urinary tract infection, malaria etc.
- Exclude complications of pregnancy: such as pre-eclampsia, venous thromboembolism and pulmonary embolism
- Be prepared to deal with: DIC, post-viremia encephalitis
- Antimicrobial therapy should be based upon bacteriological sensitivities
- Maternal pyrexia should be treated with paracetamol
- Antenatal steroids for preterm labor.

The decision to deliver will be made for an obstetric indication. In the event of a critically ill woman close to term, it is not unusual to deliver her baby, usually by cesarean section, to help with mechanical ventilation of the lungs to improve her recovery. This should be done once her clinical condition is stabilized and other potential complications such as coagulopathy have been excluded or corrected. The decision is made in conjunction with the obstetric, critical care and neonatal teams.[40]

TABLE 3: Dose schedule according to symptoms of H1N1 symptoms[39]

Condition	*Drug regimen*
URTI only, no pneumonia	Oseltamivir 75 mg for 5 days
Symptomatic at day 5	Above treatment for 10 days
Pneumonia, no tachypnea	Oseltamivir 150 mg BD for 10 days
Pneumonia, tachypnea, ventilator	Oseltamivir 150 mg BD and Zanamivir 10 mg for 10 days
Multiorgan dysfunction	Titrate as per creatinine clearance
Persistent chest X-ray shadow >10 days	Zanamivir for 21 days

Prevention

The CDC currently recommends influenza vaccine for all pregnant women in any trimester during flu season. FDA has approved the H1N1 monovalent vaccine as intramuscular injection (inactivated) and an intranasal spray (Live). Live intranasal vaccine should not be administered to pregnant women.[41] The virus is highly contagious and is contracted by aerosol transmission from inhaling the droplets from an infected person coughing and sneezing, so good respiratory hygiene by covering the mouth and nose must be followed and good hand hygiene by washing hands frequently with soap and water. Infant must be isolated from mother until mother has received antiviral medications for at least 48 hours, is without fever for 24 hours without antipyretics and can control cough and respiratory secretions.[41]

ZIKA VIRUS[42]

With the emergence of zika infection in India, although it causes mild symptoms in humans, it results in transmission from mother to fetus leading to congenital infection leading to microcephaly. As the vector for transmission of zika virus (ZIKAV), the *Aedes* mosquito are present in abundance in India, the vulnerable pregnant population with zero immunity, is at risk for getting infected and delivering a malformed baby. ZIKAV is a single-stranded RNA virus of genus *Flavivirus*, family *Flaviviridae*. It is related to dengue, yellow fever, Japanese encephalitis and West Nile viruses. The disease course is not severe, does not require hospitalization and deaths have not been reported. Most common symptoms are a maculopapular rash, fever, arthralgia, conjunctivitis, myalgia, and headache. Fatalities are rare, typically only with comorbidities. However, an increase in cases of fetal microcephaly, Guillain-Barré syndrome and other neurological and autoimmune syndromes has been reported in areas where ZIKV outbreaks have occurred. Although these associations cannot yet be said to be causal, emerging evidence suggests that they may be. The mainstay of detection of ZIKAV in maternal serum is reverse transcriptase polymerase chain reaction (RT- PCR) assay in serum and urine collected ≤7 days after illness onset. Serological assays to detect either IgM or IgG in serum collected ≥4 days after illness onset can also be done.

ZIKAV can cross the placental barrier, and it is likely that Zika infection in early pregnancy poses the greatest risk. Congenital ZIKAV infection leads to fetal microcephaly, fetal loss (in the first trimester), fetal growth restriction, placental insufficiency, fetal death, ocular involvement—macular atrophy and optic nerve abnormalities and hydrops fetalis. There is no evidence of increased susceptibility to Zika infection during pregnancy. Tools for fetal evaluation of ZIKAV infection are maternal serial ultrasound examinations and amniocentesis. There is no vaccine or any specific antiviral treatment. Treatment is mostly supportive rest, fluids, and use of analgesics and antipyretics. Fever is treated with acetaminophen. Aspirin and other nonsteroidal anti-inflammatory drugs are avoided.

Guidelines by Ministry of Health and Family Welfare and Directorate General of Health Services of India for international travelers to zika infected areas:

- Nonessential travel to the affected countries to be deferred/cancelled
- Pregnant women or women who are trying to become pregnant should defer/cancel their travel to the affected areas
- Travelers to the affected countries should follow individual protective measures, to prevent mosquito bites
- Travelers having febrile illness within two weeks of return from an affected country should report to the nearest health facility

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