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AOGD BULLETIN

Volume 21 I December 2021 I Monthly Issue 8

Dedicated Issue:

"High Risk Pregnancy: Evaluation and Management"

AOGD SECRETARIAT

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AOGD Bulletin

Volume 21 • Monthly Issue 8 • December 2021

Publisher/Printer/Editor
Dr Rekha Bharti on behalf of Association of Obstetricians & Gynecologists of Delhi.

Printed at
Process & Spot C-112/3, Naraina Industrial Area, Phase-1, New Delhi 110 028

Published from
Department of Obstetrics & Gynaecology
Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi -110 029

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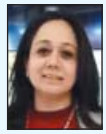

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Foreword

It gives me immense pleasure to write the foreword for this AOGD bulletin dedicated to **High Risk Pregnancy- Evaluation and Management**, further endorsing the AOGD theme of the year 2021-22, **"Promoting Women's Health by Strong Will and Quality Skill"**.

Field of obstetrics in itself is very vast and the possibility that a low risk pregnancy can become high risk at any time during the course of a normal pregnancy has to be always kept in mind. Recent advances focus on prediction, prevention and management of high risk pregnancies along with the need for long term follow up of these women. Woman's body goes through a myriad of changes in order to prepare for and to sustain a pregnancy. These physiological changes can be confused for a pathology if the practitioner is not aware of these changes and doesn't evaluate the woman carefully. This issue throws light on commonly encountered medical disorders in obstetric OPDs and emergencies. Medical disorders are quite prevalent in our country and advances in medical science have also made conception and pregnancy possible in women with complicated medical conditions.

The current issue brings an updated review of common conditions encountered during pregnancy, like anemia, diabetes, epilepsy, thyroid disorders and intrahepatic cholestasis of pregnancy which bring their own set of challenges to the obstetrician. Pregnancies complicated by these medical conditions, if managed appropriately lead to favourable feto-maternal outcome.

I am confident that the readers will find the topics engaging and this bulletin would provide a great learning experience to one and all. I would also like to congratulate the committee members and editorial board for successfully putting forward a very useful lineup this entire year and wish them success for the coming months as well.

Wishing you all a very happy new year. May the coming year be more joyous and successful.

Dr Shubha Sagar Trivedi
Advisor, AOGD

From the President's Pen

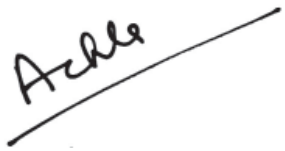
Greetings to all the members of AOGD!

On behalf of the organizing committee of AOGD, I express my heartfelt and sincere thanks to all fellow AOGDIANS for making **43rd Annual Virtual AOGD Conference** a majestic success. With the Holistic efforts and guidance of our seniors and the enthusiasm of our younger members, we were able to successfully hold and accomplish all the conference events. Our team AOGD at Safdarjung hospital, worked really hard to make this academic extravaganza a great success.

The oration by FOGSI Presdient, Dr Shantha Kumari was a treat to our ears and very well appreciated by one and all. The keynote addresses by eminent national and international speakers added glamour and glitter to the conference. We had a total of 12 pre and post conference workshops organized very meticulously by our sub-committees. They were all great hit and relished by all. The interactive quiz and an interesting talent hunt were like cherry on the top. The panel discussions on the burning topics of the day were highly sought. Success of a conference is judged by response of delegates and I'm grateful for the overwhelming participation and response shown by all the delegates ,thus making the conference a huge success.

Our expert Editorial team has brought out this December's E- Bulletin dedicated to **"High risk pregnancy: Evaluation and Management"**. It highlights the tips and tricks in the management of high risk pregnancies which will definitely help our readers in their practices.

"Coming together is a beginning, staying together is progress, and working together is success." – Henry Ford



Dr Achla Batra
President, AOGD (2021-2022)

AOGD General Body Meeting will be held on 7th January, after the Monthly Clinical Meeting. The agenda of the GBM is

1. Passing of AOGD constitution Amendment
2. Call for Nominations for AOGD President and Vice President for the year 2022-23 and Chairpersons of various Subcommittees.
3. Passing of Audit of accounts for financial year 2020-21

From the Vice-President's Pen

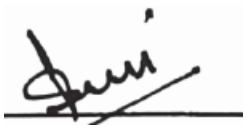
Dear Friends

Wishing you all a very beautiful and blessed 2022.

There has been a very significant fall in MMR of our country in the last decade, but still we have a long way to cover to reach our Goal. This issue brings out an update on **High Risk Pregnancy**, which covers all the current treatment protocols of the high risk conditions. I am sure you will find this very useful in your day to day practice. We also hope that you found our ready reckoners on obstetric emergencies useful.

Hope this year will be full of loads of academics with physical Meetings also, as we are all missing the human touch.

Happy Reading and Take Care



Dr Jyotsna Suri
Vice President, AOGD (2021-2022)

From the Secretary's Desk

Warm greetings to all !

After having witnessed an exhaustive academic bonanza in the month of November in form of our 43rd Annual AOGD Conference, and an anticipating a probable third wave of COVID, we continue in our endeavours to work towards our motto **"Strong Will and Quality Skills- For Woman's Health"**. We continue to bring forth best of programs for our members and masses serving both academic and social purpose so that AOGDIANS don't miss out on the latest developments even if we are not able to meet physically often.

I take this opportunity to thank, from core of my heart, all AOGD members for their overwhelming participation in our annual AOGD conference. The organising team, esteemed faculty, coordinators, delegates and backend technical team left no stone unturned in making the conference a huge success. I sincerely hope that we were able to match up to the expectations of all in bringing forth an amalgamation of knowledge, fun and opportunity for socialisation.

As regards this month's bulletin, I congratulate the editorial team, like always for another interesting and useful issue on **"High Risk Pregnancy: Evaluation and Management"**. It aptly covers all the important aspects viz. intrahepatic cholestasis of pregnancy: newer insights and practical tips for evaluation and management of various important medical disorders of pregnancy like hyperglycemia, anemia, cardiac diseases, epilepsy and thyroid disorders. I am sure these evidence-based articles with practical tips and recent advances in field of high risk obstetrics will be thoroughly useful for our readers looking forward for a better feto-maternal outcome.

Happy reading,

Dr Monika Gupta
Secretary, AOGD (2021-2022)

From the Editor's Desk

Greetings from the editorial board!

We are pleased to release the last bulletin of 2021 and with this we complete three fourth of our one year journey. We are thankful to our advisor, Dr Shubha Sagar Trivedi for writing foreword for this issue of AOGD Bulletin. She is a great academician, teacher of teachers with vast clinical experience.

This bulletin is dedicated to the theme, **"High Risk Pregnancy: Evaluation and Management"**. This issue highlights the controversies associated with the diagnosis of some of the common high risk conditions and update on the management of the conditions that can increase the maternal and/ or foetal morbidity.

"Intrahepatic Cholestasis of Pregnancy" may be associated with adverse foetal outcome and Long term risk of hepatobiliary disease in the mother. "**Hyperglycemia in Pregnancy"** a condition described by different terminologies can affect the pregnancy outcome if not managed appropriately. "**Anemia in pregnancy"** is the most common direct and indirect cause of increased maternal morbidity and mortality. Intensified National Iron Plus Initiative is a stretegy to achieve the goal of *Anemia Mukt Bharat*. "**Cardiac Diseases Complicating Pregnancy"** are a significant cause for admission to Obstetric Intensive Care Units. Improved care starting from preconception period and continued throughout pregnancy can considerably improve the pregnancy outcome in women with "**Epilepsy in Pregnancy"**. Thyroid disorders are considered the most common endocrinological conditions associated with pregnancy. Due to the lack of trimester specific ranges of thyroid function tests, the diagnosis and management of "**Hypothyroidism in pregnancy"** continues to be surrounded by controversies. For optimisation of fetomaternal outcome in women with **"Hyperthyroidism in Pregnancy"** it is imperative to know the effect of thyroid hormones and antibodies on maternal and foetal thyroid glands.

We are grateful to all the authors for providing the abridged updated management of these high risk conditions.

Wish you all a very Happy, Healthy and Prosperous New Year 2022.

Dr Rekha Bharti
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Intrahepatic Cholestasis of Pregnancy: Newer Insights

Nilanchali Singh[1], Nimisha Agrawal[2], Sivalakshmi[3], K Aparna Sharma[4]
[1,2]Assistant Professor, [3]Postgraduate, [4]Additional Professor, All India Institute of Medical Sciences, New Delhi

Intrahepatic cholestasis of pregnancy (IHCP), also known as obstetric cholestasis, is a relatively common gestational disease[1]. In India it is showing an increasing trend and though officially reported as 2%, the actual incidence may be 7-22%. As per studies, IHCP is the most common liver disorder during pregnancy.[2,3,4] Altered bile acid metabolism with accumulation of bile acid is detrimental to the fetus leading to increased perinatal morbidity and mortality in the form of preterm births, meconium stained amniotic fluid, fetal distress and stillbirths or intra uterine fetal death (IUFD).[5]

Also termed idiopathic cholestasis of pregnancy, IHCP is associated with raised bile acids, pruritus and raised transaminases. It is seen mostly in late trimesters and is a reversible cause of cholestasis persisting until delivery. It is a multifactorial disease due to combination of genetic, hormonal and environmental causes. The major concern with IHCP is because of the adverse perinatal outcomes associated with elevated bile acids.[6] Maternal serum bile acid levels of >40 is associated with more adverse perinatal outcomes.[7] There has been increased incidence of fetal distress leading to operative delivery, still births, sudden IUFD, poor CTG tracing, preterm delivery, meconium stained liquor, low APGAR scores of less than 7, prolonged NICU stay and neonatal death. It has also been established that the serum bile acid levels of >100 µmol/L is significantly associated with increased risk of still births.[8] In previous animal studies, it has been observed that elevated bile acids exert toxic effect on fetal myocardium causing anoxic damage, dysrhythmias and sudden intrauterine fetal death in rats.[9] Gorelick et al[10] demonstrated that the addition of glycocholate to an in vitro culture of neonatal cardiomyocytes has a less marked arrhythmogenic effect than the addition of taurocholate at equivalent concentrations using an in vitro model of cardiomyocytes.

Diagnosis of IHCP

There exists wide range of definitions of IHCP or obstetric cholestasis along with absence of agreed diagnostic criteria. Obstetric cholestasis is diagnosed when otherwise unexplained pruritus occurs in pregnancy with abnormal liver function tests (LFTs) and/or raised bile acids and both resolve after delivery. It is a medical disorder of pregnancy characterized by pruritus in the absence of a skin rash with abnormal LFT, neither of which has an alternative cause and both of which resolve after birth. Pruritus is intense and mostly localized to the abdomen, legs, palms, and soles. IHCP usually presents in the second and third trimesters of pregnancy, with the early onset disease usually presenting <33 weeks of gestation.

Diagnosis of IHCP is based on elevated serum bile acids, >10 µmol/L, which is considered the most appropriate laboratory marker for diagnosis. The modified myocardial performance index (MPI) is a pulse wave doppler-based time interval index that enables an assessment of global (both systolic and diastolic) cardiac function, which can be imaged with relative ease in the fetus. Increased MPI has been reported in IHCP fetuses.

Genetic Component in IHCP

While there are known risk factors which makes a woman susceptible to IHCP, the emphasis and research now is on the genetic susceptibility in women especially those with early onset (<33 weeks) and severe (Serum Bile Acid >40 µmol/L) disease. Studies have shown that in these women there is a possibility of 20% mutation in the biliary transporter proteins and 3-5-fold increase in gallstones, pancreatitis, cirrhosis and biliary tree cancer. Clinical significance of finding genetic susceptibility is that these women need long term follow up. Their families are at a higher risk of similar problems.

Role of Biochemical Markers in IHCP

Serum bile acid estimation remains the most sensitive and specific marker and should be used to diagnose and monitor IHCP by weekly estimation. In the Indian context, measurement of serum total bile acid is still expensive. Bile acid measurement should

be done on a random or non-fasting sample (as in fasting samples the level of bile acids is low and those at risk or with severe disease can be missed who have otherwise normal LFT). Bile acid levels can rise significantly after a meal. For the Asian population, normal range of bile acids can be pushed up to 19-20 µmol/L.

Though there is no correlation between transaminases and fetal risk, transaminases should also be measured as they may help in excluding other liver pathologies. In low resource settings, transaminases can be used to monitor pregnant women with the understanding that they are not a good predictor of fetal outcome.

Updates on Clinical Implications of Bile Acids

The levels >100 µmol/L are associated with an increased risk of still birth and this risk significantly increases from 35- 36 weeks. *More important is to note the evidence that if the bile acids recede subsequently on follow up, decision to deliver at 35-36 weeks should not change.* Most women with intrahepatic cholestasis of pregnancy have bile acids below 100 µmol/L, they can probably be reassured that the risk of stillbirth is similar to that of pregnant women in the general population, provided repeat bile acid testing is done until delivery.[12]

Serum Bile acids between 40-100 µmol/L are associated with an increased risk of spontaneous preterm birth, meconium staining of the amniotic fluid, neonatal ICU admissions and fetal asphyxia but do not have a significantly increased risk of still birth and hence with adequate fetal and bile acid monitoring, the woman can be delivered between 37-39 weeks after individualizing each case. The level of Bile acids <40 µmol/L classifies as mild IHCP. These women do not have an increased risk of spontaneous preterm or still birth and can be delivered at 39 weeks. Bile acids are more predictive of stillbirth than other biomarkers. Hence, diagnosis of IHCP depends on these biochemical tests as well as exclusion of other liver disorders in pregnancy.

Differential Diagnosis

IHCP can be differentiated from other types of liver diseases unique to pregnancy that share similar laboratory abnormalities such as preeclampsia, acute fatty liver of pregnancy, and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. Preeclampsia and acute fatty liver of pregnancy are pregnancy-specific causes of abnormal LFT that might form part of the differential diagnosis in atypical or early cases.

In addition, other pruritic skin diseases that cause high transaminase levels in pregnancy must be excluded. Work-up may include carrying out a viral screen for hepatitis A, B, and C, Epstein Barr and cytomegalovirus, a liver autoimmune screen for chronic active hepatitis and primary biliary cirrhosis (for example, anti-smooth muscle and antimitochondrial antibodies) and ultrasonography of liver and biliary tree.

Other evidence of cholestasis should be sought, including pale stools, dark urine and jaundice, and risk factors identified such as a personal or family history of obstetric cholestasis, multiple pregnancy, carriage of hepatitis C and presence of gallstones.

Laboratory Monitoring in IHCP

Raised liver enzymes in IHCP has a diagnostic dilemma. Although a wide variety of cutoff points have been used for defining abnormality in LFTs and bile salts, the upper limit of pregnancy-specific reference ranges should be applied. For transaminases, gamma-glutamyl transferase and bilirubin, the upper limit of normal throughout pregnancy is 20% lower than in the non-pregnant range. Many laboratories use pregnancy-specific ranges for bile salts, but this should not be assumed. Typically, transaminases will range from just above the upper limit of normal to several hundreds. In clinical practice, otherwise unexplained abnormalities in transaminases, gamma-glutamyl transferase and/or bile salts are considered sufficient to support the diagnosis of obstetric cholestasis.

The increase in alkaline phosphatase in pregnancy is usually placental in origin and so does not normally reflect liver disease. A thorough history and examination should be carried out, including a detailed drug history, before abnormal LFTs are determined to be otherwise unexplained. Bilirubin is raised only infrequently and most women will have increased levels of one or more of the remaining LFTs. Isolated elevation of bile salts may occur but this is uncommon; normal levels of bile salts do not exclude the diagnosis.

Some women will have pruritus for days or weeks before the development of abnormal liver function. In these women with persistent unexplained pruritus

and normal biochemistry, LFTs should be measured every 1–2 weeks. Once obstetric cholestasis is diagnosed, it is reasonable to measure regularly LFTs weekly until delivery, along with a baseline coagulation screen, a general review, blood pressure measurement and urine check, allowing monitoring of the condition and exclusion of other diagnoses. If LFTs return to normal in the antenatal period, obstetric cholestasis is not likely to be the correct diagnosis. If LFTs escalate very rapidly, additional diagnoses need to be considered and the frequency of monitoring increased: although this situation can be consistent with obstetric cholestasis, it is not typical.

Pruritus in IHCP

Serum Bile acids do not correlate well with itch scores. Pruritus in pregnancy is common, affecting 23% of pregnancies, of which only a small proportion will have obstetric cholestasis. The pruritus in IHCP is typically worse at night, is often widespread and involves the palms of hands and/or soles of feet. The skin should be inspected and care must be taken to differentiate dermatographia artefacta (skin trauma from intense scratching), which may be seen in IHCP, from other common skin conditions such as eczema or atopic eruption of pregnancy (previously referred to as eczema of pregnancy, prurigo and pruritic folliculitis). If a rash is present, polymorphic eruption of pregnancy or pemphigoid gestations (blisters) should be considered.

Pruritogens associated with itch are autotaxin and sulphated progesterones. They have been found to be 3-4 times higher in IHCP pregnancy as compared to normal pregnancy. Progesterone sulphate doubling is associated with increased itch scores.

The treatment of pruritus comprises of Urso-deoxy cholic acid (UDCA), which causes only a small improvement in symptoms. Rifampicin along with UDCA may have a significant effect; however, the results of TURRIFIC trial are awaited. Antihistaminics and /or topical agents are of limited benefit and at present there is no good treatment for the pruritus associated with IHCP.

Role of Ursodeoxycholic Acid in Management of IHCP

UDCA is a first line drug in the management of IHCP, even though its use is off-label. UDCA acts by stimulating biliary secretion by post transcriptional regulation of BSEP (Bile Salt Export Pump) and the exporters MRP 4 and MRP 3. UDCA also has anti apoptotic effects and reduce mitochondrial membrane permeablity and cyto c expression. It also reduces ethinyl estradiol 17 beta glucuronide expression responsible for cholestasis due to estrogen.

It does not improve the rate of composite adverse perinatal outcomes in a study of all IHCP cases with raised serum bile acids. It protects against spontaneous preterm birth in singleton pregnancies with maternal serum bile acid >40 µmol/L. It does not lower total serum bile acid concentration. It does cause a small improvement in pruritus, a small reduction in maternal ALT concentration and reduces the risk of meconium-stained amniotic fluid.

A study published in Lancet in 2021 evaluated the role of UDCA. Ursodeoxycholic acid treatment had no significant effect on the prevalence of stillbirth in women with intrahepatic cholestasis of pregnancy, but the analysis was probably limited by the low overall event rate. However, when considering only randomised controlled trials, ursodeoxycholic acid was associated with a reduction in stillbirth in combination with preterm birth, providing evidence for the clinical benefit of antenatal ursodeoxycholic acid treatment.[13]

Updates on Management Issues

Management is aimed to reduce the adverse perinatal outcomes associated with IHCP such as sudden IUFD, fetal distress and preterm delivery.

CTG Monitoring

Since there is risk of sudden IUFD associated with IHCP, antepartum fetal monitoring becomes essential. Weekly CTG monitoring from late trimesters around 34 weeks will reduce the perinatal mortality, though there are reports of normal CTG before IUFD in these cases.[1]

Elective Operational Intervention

Most of the elective Cesarean sections are planned between 37 to 38 weeks of gestation. Most of the adverse perinatal outcomes are likely to occur after 37 weeks, so it is preferable to induce at around 37 weeks. The exact gestational age of fetal demise is not clear.

Medical Management

Urso-deoxycholic acid (UDCA) has been proven to reduce the pruritus and the transaminases level,

bilirubin level, bile acid level, but the improvement in fetal effects are not shown. The starting dose of UDCA is 300 mg twice daily and can be increased to 600 mg twice daily when pruritus persists after a week of therapy. UDCA has also shown to normalize the CA: CDCA ratio (cholic acid to chenodeoxycholic acid ratio), Glycine: Taurine ratios and also reduces the urinary excretion of sulphated progesterone metabolites which is associated with the reduction in pruritus. UDCA has shown to reduce toxicity of bile acid to rat cardiomyocytes in some in vitro studies. There are some studies supporting beneficial role of UDCA treatment on perinatal outcome in IHCP, while others did not find any improvement.[11]

Dexamethasone, as a treatment for IHCP is conflicting, though it acts by inhibiting the synthesis of placental estrogen, and thereby providing some improvement both symptomatically and also biochemically by reducing the bile acids. However, studies have shown that repeated use of dexamethasone may result in abnormal neuronal effects and low birth weight babies. This limits its use in IHCP.

Vitamin K, the fat soluble vitamin's absorption is hampered due to the defective enterohepatic circulation of bile acids in IHCP. Vitamin K helps is the synthesis of Factors 2, 7, 9 and 10 and some cases of IHCP are reported with prolonged prothrombin time. Thus, supplementing Vitamin K can reduce the incidence of antepartum and postpartum hemorrhage. Vitamin K is usually given at a dose of 10 mg OD. Kenyon et al found that postpartum haemorrhage was more common in those women who had not taken vitamin K, as compared to those who had received it (45% compared with 12%). There have been no randomized controlled trials in this area. However, the data to support antenatal use of Vitamin K is sparse.

Cholestyramine is a bile acid chelating agent. It binds will bile acid and causes excretion of bile acids in stool thereby exacerbating vitamin K deficiency. Chloestyramine acts by reducing pruritus in IHCP, but has no effects in reducing the laboratory parameters.

SAM (S-Adenosyl Methionone) is the universal methyl group donor used in the synthesis of phosphotidylcholine, thereby, altering the composition and fluidity of hepatocyte plasma membrane and also biliary excretion of hormones. Studies have shown that SAM improves the pruritus and laboratory parameters. In the study, women were given high dose of SAM 800 mg/day intravenously along with UDCA as compared to only UDCA in the placebo group. The double-blinded placebo control trial showed no improvement.

Combination of **rifampicin** with UDCA in 28 pregnancies complicated by IHCP, showed serum bile acid improved in 14 pregnancies. In 10 of 28 pregnancies there was a >50% reduction. Further trials on the use of ripampicin are indicated.

Timing of Delivery

The Society of Maternal Fetal Medicine in their latest guidelines recommends that patients with total bile acid levels of ≥100 µmol/L be offered delivery at 36 0/7 weeks of gestation, given that the risk of stillbirth increases substantially around this gestational age (GRADE 1B); they also recommend delivery between 36 0/7 and 39 0/7 weeks of gestation for patients with intrahepatic cholestasis of pregnancy and total bile acid levels of <100 µmol/L (GRADE 1C).[14]

The SFM also suggests that patients with a diagnosis of intrahepatic cholestasis of pregnancy begin antenatal fetal surveillance at a gestational age when delivery would be performed in response to abnormal fetal testing results or at the time of diagnosis if the diagnosis is made later in gestation (GRADE 2C). It is recommended that administration of antenatal corticosteroids for fetal lung maturity for patients delivering before 37 0/7 weeks of gestation if not previously administered, should be done (GRADE 1A). They also recommend against preterm delivery at <37 weeks of gestation in patients with a clinical diagnosis of intrahepatic cholestasis of pregnancy without laboratory confirmation of elevated bile acid levels (GRADE 1B).

Resolution in Postpartum

After delivery, symptoms of IHCP usually resolve within 48 hours, with laboratory abnormalities normalizing within 2-8 weeks. In normal pregnancy, LFTs may increase in the first 10 days of puerperium. In IHCP, routine measurement of LFTs should be deferred beyond this time, and performed prior to the postnatal follow-up visit or at least should be deferred for 10 days. Postnatal resolution of symptoms of pruritus and abnormal LFTs should be confirmed, in order to secure the diagnosis.

Effects of IHCP on Maternal and Fetal Outcomes

Higher association with GDM and preeclampsia in pregnancy has been reported in women with IHCP. Long term increased risk of subsequent hepatobiliary disease like Hepatitis C, Chronic hepatitis, Fibrosis/ Cirrhosis, Gall stone disease and Cholangitis has been reported.

There is a correlation between the serum bile acid levels and the rate of fetal complications. Adverse perinatal outcomes increases by 1 to 2 % for each additional µmol /L of bile acid. The rate of asphyxia events, preterm delivery and meconium stained liquor was more when serum bile acid level was >40 µmol /L. ECG abnormalities have been reported in IHCP fetuses, bile acid induced arrhythmias and altered cardiac dynamics are seen like atrial flutter, refractory supraventricular tachycardia and prolonged PR interval. Untreated IHCP is associated with fetal cardiac phenotype that is ameliorated by UDCA treatment, also there is risk of increase in fetal PR interval, abnormal heart rate variability, increase in pro BNP concentration.

First-degree relatives have increased risk of gall stone disease, drug induced cholestasis, fibrosis/ cirrhosis, malignancy. IHCP offsprings have raised BMI and dyslipidaemia.

Further Areas of Research

Following studies/trials are ongoing and may through light upon newer arenas.

- TURRIFIC study: Rifampicin treatment can improve serum bile acids in conjunction with UDCA
- UDCA may ameliorate fetal cardiac phenotype associated with untreated IHCP such as:
  - Increase in fetal PR interval length
  - Fetal heart rate abnormality
  - Increase in NT proBNP concentration
- Trial of ileal bile acid transporter inhibitor Volixibat for decreasing adverse outcomes in IHCP is ongoing, results awaited (A Placebo-controlled study of Volixibat in subjects with elevated serum bile acids associated with intrahepatic cholestasis of pregnancy (OHANA)).

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Practical Tips for Management of Hyperglycemia in Pregnancy

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Introduction

GDM is defined as impaired glucose tolerance of variable severity with onset or first recognition during pregnancy. Worldwide, 1 in 10 pregnancies is associated with diabetes, 90% of which are having GDM. Different terminologies are used to define hyperglycemia in pregnancy. Classification as proposed by FIGO is shown in Figure 1.

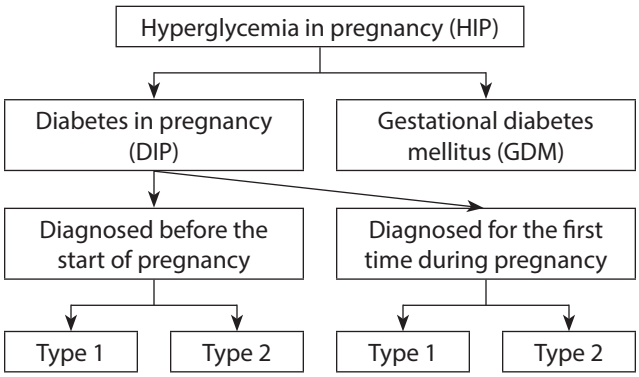

Figure 1: Classification of hyperglycemia in pregnancy[1]

Diabetes in pregnancy (DIP) is defined by WHO criteria of fasting plasma glucose (PG) ≥126mg/dl; random or post prandial PG ≥ 200 mg/dl or HbA1c≥ 6.5%. This is also known as overt diabetes or pregestational diabetes and may be DM Type1 or Type 2. It may be detected before or any time during pregnancy.

GDM is diagnosed if plasma glucose levels range is below this threshold and PG levels are ≥140 to 199 mg/dl. GDM is mostly diagnosed after 24weeks but may also be detected during 1st trimester.

Nearly 90% of all HIP are GDM and already suffer from mild insulin resistance due to chronic beta cell dysfunction of the pancreas. Women with DIP have a more severe form of insulin resistance and are prone to higher grade of fetomaternal complications and progression of diabetic complications like retinopathy, nephropathy, neuropathy.

Prevalence of HIP

HIP has become a pandemic all over the world due to an increased prevalence of obesity, sedentary lifestyle, stress and increasing life expectancy. The prevalence of GDM is directly proportional to prevalence of impaired glucose intolerance (IGT), DM and obesity in any population. Global prevalence of HIP is 16.9%. In India prevalence varies from 3.6 to 17.9% in different parts of the country, depending on the geographical locations and diagnostic methods used.[2] HIP has short and long-term corollaries for the mother and her fetus which are depicted in Table1.

Table 1: Fetomaternal complications in HIP

MATERNAL	**Fetal**
Antepartum	Congenital anomaly
Abortions	Macrosomia
Gestational Hypertension	Prematurity
Preeclampsia	Still birth
UTI and moniliasis	Birth trauma
Polyhydramnios	**Neonatal**
Premature labour	Neonatal death
Intrapartum	Hypoglycemia
Instrumental delivery	Hypothermia
Shoulder dystocia	Polycythemia
Prolonged labour	Hypocalcemia
Traumatic labour	Hypomagnesemia
Cesarean section	Hyperbilirubinemia
Postpartum	Respiratory distress syndrome
Postpartum hemorrhage	Renal vein thrombosis
Subinvolution	Ventricular hypertrophy
Puerperal sepsis	**Long term**
Failed lactation	Obesity
Long term	Overt DM
Recurrence in next pregnancy (33-66%)	Hypertension
Overt DM[3] (50-70%)	Metabolic syndrome

Screening and Diagnosis

Screening for GDM should be done for all pregnant women at first antenatal visit and again at 24-28 weeks of POG, if the first test is negative. There should be a gap of at least 4-6 weeks between the two tests. As maximum glycogenic hormones are produced by the placenta at 24-28 weeks, more number of women develop hyperglycemia at this gestation.

Universal screening by DIPSI criteria is recommended by National guidelines. DIPSI is a simple, feasible, low cost, practical, convenient and acceptable criteria in Indian scenario as nearly two third of Indian population lives in rural areas. Although venous sampling is desirable but as DIPSI can be done as a point of care test by a plasma calibrated glucometer in the periphery, it can provide an immediate report so that patient may be counselled regarding diet, exercise and importance of fetomaternal monitoring at the same visit if the report is deranged.

DIPSI test procedure: 75gram anhydrous glucose is to be given orally after dissolving in approximately 300 ml of water, irrespective of fasting state and is to be consumed within 5-10 minutes. GDM is diagnosed if 2hour plasma glucose ≥140mg/dl. If vomiting occurs within 30 minutes of oral glucose intake, the test has to be repeated next day. If vomiting occurs after 30 minutes, the test continues.

Rationale for non-fasting OGTT is that adequate and brisk insulin response in normal women maintains euglycemic state despite glucose challenge where as women with GDM have an increase in glycemic levels after glucose challenge due to impaired insulin secretion.

As in non-pregnant state, 2 hour plasma glucose value ≥140mg/dl is considered impaired glucose tolerance and is treated as abnormal, the same value is considered abnormal during pregnancy.

Management of Pregnancy with Diabetes Mellitus

Pregnant women with HIP require multidisciplinary team coordination between obstetricians, endocrinologists, neonatologists, nutritionists, physical instructors for optimizing pregnancy outcome.

Preconception counselling: There is a need to optimize health of a woman during preconception period to attain ideal weight, blood pressure, plasma glucose and hemoglobin level before planning pregnancy. Important components include:

- Counselling about impact of glycemic status on maternal outcome:
  a. risk of development or progression of pre-existing complications
  b. types and risks of maternal and fetal outcome
- Life style modification in the form of weight management by diet regulation and daily exercise, cessation of smoking and reduced alcohol intake is advised.
- A thorough medical and obstetric evaluation to assess high risks factors.
- Assess and optimize end organ involvement before pregnancy, including retinopathy, nephropathy, neuropathy, and cardiovascular disease including hypertension.
- Assess and achieve normal thyroid function in women with type 1 diabetes.
- Review all current medications, and change to therapy that is safe for the developing fetus. (Eg-stop statins/ACEI/ARB)
- Woman with DM should ideally conceive when HbA1C level is <6.5% to minimize the risk of congenital anomalies as risk of congenital anomalies increases steadily with rising HbA1c. (If HbA1c≤6, there is 2.8% risk of GCA which increases to 15.8% when HbA1c becomes ≥8)
- Pre conceptional folic acid supplementation of 400mcg/day (minimum of 1 month before conception) to prevent neural tube defects.
- Educate patient and her family about self-monitoring of plasma glucose, target value (ADA recommendations- fasting PG=70-95mg/dl, 2hour PP values 100-120mg/dl, HbA1c<6.5) symptoms and management of hypoglycemia
- Shift the woman on oral antidiabetic drugs to insulin because safety and efficacy of insulin is time tested and well established.
- Provide effective contraception to avoid unwanted pregnancy until glycemic control is achieved.

Antepartum Considerations

Self-monitoring of PG is mandatory (four to seven times per day). The glycemic target during pregnancy is fasting PG level < 90 mg/dl, 1hour PP<140mg/dl, 2 hours PP value < 120mg/dl and 2am> 60mg/dl. Post prandial values are more predictive of fetal risk including macrosomia & fetal demise. Above these levels, there is a risk of occurrence of macrosomia. Morning hyperglycemia occurs frequently due to Somogyi or Dawn phenomena, differentiation can be done by measuring PG at 3 AM.

Somogyi effect: It states that early morning hyperglycemia occurs due to a rebound effect from nocturnal hypoglycemia due to overdose of night dose of insulin. Lowering the night dose of long acting insulin can correct this effect.

Dawn phenomenon: Fasting hyperglycemia not associated with nocturnal hypoglycemia. This can be treated by increasing the night dose of insulin.

Medical Nutrition Therapy[1,4,5]

It primarily involves a carbohydrate controlled balanced meal which is divided into 3 major meals and 2- 3 minor meals. Women should avoid heavy meals or skipping meals.

Goals of MNT

- To provide optimal nutrition for maternal and fetal health.
- To provide adequate energy for appropriate gestational weight gain.
- To help in achievement and maintenance of normoglycaemia.
- To inculcate nutritional patterns that prevent or forestall recurrence of GDM and onset of type 2 diabetes mellitus.
- To provide optimal glycemic control without ketosis.

Constituents of Medical Nutrition Therapy

- Define carbohydrate requirement in terms quantity, quality (glycemic index) and distribution in diet.
- Define the protein, fat and micronutrient requirement and distribution
- Self-Monitoring of Blood Glucose (SBG) and achieve target pre and post meal levels
- Monitoring Ketones

Cochrane meta-analysis of pregnancy outcomes failed to identify any single type of diet plan to be superior than the rest and hence individualizing diet according to patient diet preference and self -monitoring of blood glucose is recommended.

Severe caloric restriction is not recommended in pregnancy and ADA recommends not more than 30-33%% caloric restriction in obese women to prevent ketosis. Reducing carbohydrates to 40% to 45% of total daily calories reduces post-prandial hyperglycemia. Carbohydrate is particularly poorly tolerated in the morning due to diabetogenic hormones which are in higher concentration in the morning. Desirable weight and simplified calculation of caloric requirement and weight gain based on pre-pregnancy BMI are shown in Table 2.

Table 2: Desirable weight and simplified calculation of caloric requirement and weight gain based on pre-pregnancy BMI

Weight Category	BMI (kg/m2)	Calorie requirement in Kcal/kg/day	Total weight gain (Kg)
Underweight	<18.5	upto 40 kcal	12.5-18
Normal weight	18.5-22.9	30	11.5-16
Overweight	23-24.9	22-25	7-11.5
Obese	>25	12-14	5-9

Composition of lunch and dinner thali (National Guidelines): Well-balanced diet including all category of food should be included. One-half thali should contain vegetables (cooked, raw as salad), one-fourth should contain cereals, one-fourth should contain protein rich food, one serving of fruit, one serving of dairy product (Figure 2). Pictorial representations or diet charts may be handed over to the patient for effective understanding.

Figure 2: Thali concept for women with HIP recommended by National Guidelines

Exercise proves a useful adjunct to treatment. Moderate-intensity exercise e.g., brisk walking, easy jogging, or swimming during pregnancy has been associated with lowering of maternal glucose levels. ACOG recommends 30 minutes of moderate-intensity aerobic exercise at least 5 days a week or a minimum of 150 minutes per week.[6] Simple exercise such as walking for 10-15 minutes after each meal can lead to improved glycemic control.

If MNT and exercise fail to achieve plasma glucose targets within 2 weeks in 2nd trimester or within 1 week during 3rd trimester, pharmacotherapy should be started.[1,5]

Oral Antidiabetic Agents

There are some women with GDM requiring medical therapy who, due to cost, language barriers,

comprehension or cultural influences, may not be able to use insulin safely or effectively in pregnancy. Oral agents may be an effective alternative in these women. They are not approved for use in HIP by any regulatory body as they cross the placenta and long-term safety is not well established. They should be used after proper counselling of the parents.[6,7]

Biguanides

Metformin is an insulin sensitizer. It inhibits hepatic gluconeogenesis and glucose absorption and stimulates glucose uptake in peripheral tissues. It has a lower risk of neonatal hypoglycemia and maternal weight gain than insulin. Dosage is 500 mg HS for a week then 500mg BD to a maximum of 2 gm daily. Common side effects are abdominal pain and diarrhea. It is contraindicated in renal disease. Metformin is useful for obese women or for women who are already on high doses of insulin as it improves insulin sensitivity and causes less weight gain during pregnancy. It has a failure rate of 26-50% and patients may eventually need Insulin[4,5,6,7] and is associated with increased incidence of preterm labour.

Following intrauterine exposure to metformin for treatment of GDM, neonates are significantly smaller than neonates whose mothers were treated with insulin during pregnancy. Despite lower average birth weight, metformin-exposed children appear to experience accelerated postnatal growth, resulting in heavier infants and higher BMI by mid-childhood compared to children whose mothers were treated with insulin. Such patterns of low birth weight and postnatal catch-up growth have been reported to be associated with adverse long-term cardio-metabolic outcome.

Sulphonylureas

Glyburide is class B drug. It acts by enhancing insulin secretion and peripheral tissue sensitivity to insulin. The usual starting dose of glyburide is 2.5 mg orally up to a maximum of 20 mg per day. 4-16% women required the addition of insulin to maintain glycemic control. It has fallen into disrepute as is causes macrosomia, neonatal hypoglycemia and has a failure rate of 16%.[6,7]

Insulin Therapy

It is the drug of choice in pregnancy as it does not cross the placenta[1] and tight metabolic control may be achieved. Recommended as first line of therapy by ACOG, ADA, MOHFW if lifestyle modifications fail to achieve control. Table 3 shows profile of insulin which are approved for use in pregnancy currently.

Insulin analogs like aspart and lispro which are rapidly acting insulin, have advantage over regular insulin as they can be injected at the start of a meal and the peak effect corresponds to the highest glucose excursion after a meal and reduce the likelihood of hypoglycemia as their effect lasts for 3-5 hrs.

Absolute indications where Insulin is started simultaneously without waiting for MNT response

Significant diabetes-related morbidity
- High HbA1c
- Ketonuria

Significant medical morbidity
- Associated renal dysfunction
- Associated hepatic dysfunction

Significant obstetric morbidity
- Macrosomia
- Fetal growth restriction
- Hydramnios

Antenatal corticosteroid therapy

During Labour

How to Titrate Insulin?

Insulin dosage should be adjusted according to glycemic trends every 2 to 3 days as assessed by 7 point glucose profile. Insulin needs are highly

Table 3: Profile of insulin safe for use in pregnancy

Insulin name	Type	Onset	Peak effect	Duration	Dosing interval
Aspart	Rapid acting	15 min	60 min	3-5 hrs	At start of each meal
Lispro	Rapid acting	15 min	60 min	3-5 hrs	At start of each meal
Regular	Short acting	60 min	2-4 hr	6-8 hrs	60-90 minutes before meal
NPH	Intermed. Acting	2 hr	4-6 hr	12-20 hrs	Every 8-12 hr
Insulin detemir	Long acting	2 hr	-	24 hrs	Every 24 hr

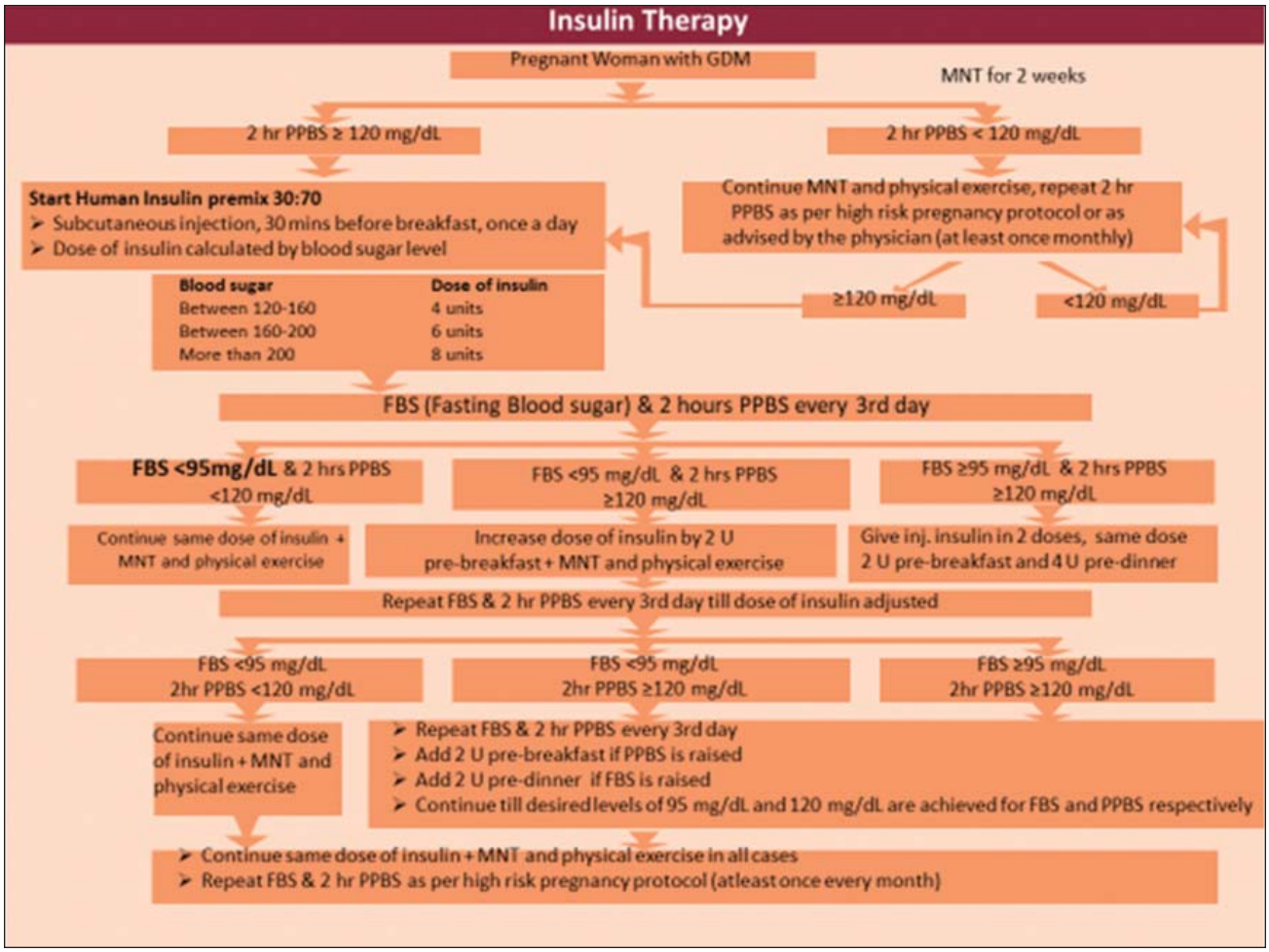

Figure 3: Insulin management in HIP (National Guidelines)

variable during pregnancy. Requirements increase throughout pregnancy and average 0.8units/kg/day in first trimester, 1.0 unit/kg/day in the second trimester, and 1.2 units/kg/day in the third trimester in DIP[1]. In GDM insulin is generally given as pre-meal short or rapid human insulin to control postprandial hyperglycemia along with intermediate insulin at bedtime if there is fasting hyperglycemia. Thereafter, after attaining euglycemia the total requirement may be adjusted as approximately 2/3rd of total dose in the morning (33% rapid acting, 66% intermediate acting) and 1/3rd of dose in the evening (50% as rapid acting insulin before dinner and 50% as intermediate insulin before bed).[5] Glycemic control has been reported to be better with the four times daily regimen than with the twice daily regimen.

If the control is unsatisfactory, potential sources of the problem such as faulty diet, concurrent medication, concomitant illness or infections, stress, lack of exercise and faulty lifestyle need to be explored and rectified. For a single abnormal plasma glucose value, dietary readjustment is advisable.

A simple and practical management algorithm given below has been proposed by National guidelines for management of pregnant women with GDM for initiation and titration of insulin (Figure 3).[4]

Antepartum Fetal Surveillance

Women controlled on MNT (Category A1 as per ACOG) do not require any special fetal monitoring. Daily fetal movement monitoring beginning at 32 to 34weeks gestation is recommended in women who attain euglycemia with only dietary therapy, but randomized trials are lacking.

For women on insulin or oral antidiabetic (category A2 as per ACOG) therapy or those who have poor blood sugar control, more intensive fetal monitoring with non-stress test or biophysical profile assessment should be instituted. Method of fetal surveillance should be in accordance with local practice patterns for high risk pregnancy according to ACOG.

Anomaly scan for congenital fetal anomalies is done at 18-20 weeks, Fetal ECHO at 22-24 week when

indicated. Daily fetal movement count is a simple, cost-effective way to evaluate fetal wellbeing in third trimester. Serial ultrasound scan at 3-4 weeks' interval is indicated to identify fetal macrosomia and polyhydramnios. Fetal non-stress test (NST) or biophysical profile may be done twice a week after 32-34 weeks onwards in women on pharmacotherapy.[1,5,6] Doppler flow studies should only be done in HIP if associated with hypertensive disease, fetal growth restriction or vasculopathy. It is not recommended as a routine method of fetal surveillance.

Macrosomia is diagnosed if fetal weight > 90th percentile or 2 SD above mean for gestational age or birth weight > 4-4.5 Kg in western countries.[5] In India, birth weight of > 3.45 Kg is considered as macrosomia[8]. New methods with better accuracy for prediction are measurement of subcutaneous fat at the mid-humerus, shoulder, abdominal wall, thigh, and peri-buccal area. The best approach for predicting macrosomia may be to combine 3D volumetric measurements (volume of upper arms, thigh, and abdomen) with 2D measurements. Suspected fetal macrosomia is not an indication for early induction of labor, because induction does not improve maternal or fetal outcomes. (Level B). Prophylactic caesarean delivery is planned if estimated fetal weight > 4.5 kg in pregnant women with diabetes (Level C) as macrosomia is associated with increased labour complications for the mother and fetus.[9]

Preterm Labour

In women with HIP, tocolysis if required should be done with Nifedepine 10mg every 20 minutes up to 4 doses followed by 20 mg TDS (maximum 180 mg) as beta mimetic agents like terbutaline, ritodrine cause maternal hyperglycemia and should be avoided.

Antenatal corticosteroids course of dexamethasone 6 mg IM 12 hourly for 48 hours should be given after admitting the patient. PG monitoring is done 4 hourly and insulin dose may be titrated over and above the routine dose according to sliding scale as steroid therapy may precipitate diabetic ketoacidosis.[5] The PG level starts rising within 12 hours of steroid injection and may persist up to 5 days.

Timing of Delivery

The primary goal to time delivery is to prevent stillbirth. The risk of unexplained intrauterine death and stillbirth increases after 36 weeks of gestation in women with HIP. However early elective termination of pregnancy has to be weighed against the risk of delayed lung maturity, respiratory distress syndrome and increases the probability of cesarean delivery due to unfavorable bishops score.

In Indian set up, termination is planned between 38-39 wks. Induction at 38-39 weeks gestation may be slow or unsuccessful due to unfavorable bishops but this has to be balanced against the poorly defined and significantly higher risk of late intrauterine death beyond 38 wks.[5]

Vaginal delivery is preferable unless there is an obstetric or medical contraindication. In case of suspected fetal macrosomia or weight >3.5 Kg, consideration should be given for a primary cesarean section at 38- 39 weeks to avoid shoulder dystocia as it may occur at any weight.

Intrapartum Considerations

As diabetic women are predisposed to infections, strict asepsis is to be maintained during labor and number of per vaginum examination should be restricted. It is essential to carefully watch for progress of labour and maintain a partogram. In case of protracted labour, early decision for cesarean section should be taken.

Table 4: Recommendations for termination of pregnancy by various authorities[1,4,5,6]

Uncomplicated Type 1 & 2 Diabetes	MOHFW	***FIGO***	***ACOG***	***NICE 2015*** *Between 37-38+ 6 weeks*
Class A1GDM	40 weeks	*40-41 weeks*	*39-40 +6*	*40+6*
Class A2 GDM	38-39 weeks	*38-39 wks*	*39-39 +6*	
Controlled			*Between37 &38+6*	
Inadequetly			*34 to 36+6*	
Controlled				
Poorly or associated with other complications				

Glycemic Control During Labour

A strict glycemic control during labor is important to prevent neonatal hypoglycemia after birth. It is important to administer the dose of intermediate acting insulin on the night prior to termination of pregnancy. Morning dose of insulin is withheld on the day of induction/ labour and the patient should be started on 2 hourly monitoring of capillary glucose. Allow woman to take oral fluids during induction and early labour. As the mother has to utilize lot of energy during labour, the requirement of insulin is significantly reduced. Most GDM women will not require insulin. The aim is to maintain a plasma blood sugar level of 70 to 120 mg/dl.

An infusion of 5% dextrose is started @ 125ml/hr if plasma glucose is < 100mg/dl, no insulin is required and Insulin is titrated according to capillary glucose level.

Table 5: Insulin therapy during intrapartum period[4]

Blood sugar level	Amount of insulin added in 500ml NS	Rate of NS infusion
90-120 mg/dl	0	100ml/hr (16 drops/min)
120-140mg/dl	4 U	100ml/hr (16 drops/min)
140-180mg/dl	6U	100ml/hr (16 drops/min)
>180mg/dl	8U	100ml/hr (16 drops/min)

Fetal monitoring during intrapartum period should be done as per high-risk protocol.

Glycemic Management of Diabetes During Cesarean Section

Elective caesarean section should be scheduled as the first case on the morning list. The usual dose of intermediate insulin is given on the night before surgery. The patient is kept fasting after midnight, her usual morning dose of insulin is withheld. In the morning fasting plasma glucose and serum electrolytes are sent.

Regional anesthesia is desired because an awake patient permits earlier detection of hypoglycemia. PG levels are maintained between 70-100 mg/dl during surgery with regular monitoring.

Prophylactic antibiotic is recommended 30 min to 1 hour before surgery after test dose. Strict monitoring of PG after surgery and early resumption of oral intake is recommended.

Pneumatic compression stockings and early mobilization should be encouraged to avoid risk of thromboembolism.

Postpartum Management

While importance of antenatal screening and management of GDM is well recognized, postpartum follow up is often neglected**.** Women with GDM form a high-risk cohort who can be targeted for prevention of Type 2 DM later on in life.

Immediate essential newborn care is given after delivery with emphasis on early breastfeeding within 1 hour to prevent hypoglycemia. Monitoring for hypoglycemia should be started at 1 hour of delivery and continued every 4 hours (prior to next feed) till four stable glucose values are obtained. The cut off capillary blood glucose for hypoglycemia in normal birth weight newborn is <45 mg/dL and <54 mg/dL in case of fetal growth restriction, to initiate treatment[4]. Neonate should also be evaluated for other neonatal complications like respiratory distress, convulsions, hyperbilirubinemia.

As soon as the placenta is delivered, insulin sensitivity improves and need for antidiabetic agent reduces significantly. In women with GDM, stop insulin therapy after delivery In women with Type 2 DM who are breast feeding, they should be advised to resume pre-pregnancy dose of metformin or glibenclamide immediately after birth. For women on insulin, dose is reduced by 20-40% and monitor PG levels carefully to establish appropriate dose.

Objectives of Postpartum Screening are:

- Educate the family regarding high risk of development of DM and emphasize the need for screening at 6 weeks and then annually lifelong through a 75 gm OGTT.
- Discuss the importance of breastfeeding and highlight it's advantages for weight loss, reducing plasma glucose levels and in delaying or preventing onset of DM
- Assessment of cardio-metabolic risk factor should be done in all visits and target weight/BP/lipid/ Plasma glucose levels should be informed to the patient. If these parameters are deranged, multidisciplinary approach to coordinate with physician, nutritionist, physical instructor, pediatrician should be developed.
- Continuation of diet regulation and regular exercise post-delivery is most important for achieving optimal weight loss and prevention of NCDs.

- Patient should be advised regarding the importance of preconception & interconceptional counseling before next pregnancy which should be planned without too much delay.
- Contraception - Risk of unplanned pregnancy overweighs the risk of contraceptive method used. Any contraceptive method is safe for a woman with GDM. Combined hormonal contraceptive containing estrogen and injectable DMPA are category 3 / 4 for women with complicated diabetes or having diabetes with end organ involvement or vasculopathy. Barrier contraceptives and Cu IUCD are category 1, rest of all contraceptive methods are category 2.[10]

Conclusion

Reclassification of maternal glycemic status at least 6 weeks after delivery is a must. It is the best time to detect patients and their offsprings who are at high risk of developing DM or other features of metabolic syndrome later in life. It is important to introduce lifestyle modifications; family planning measures and to ensure optimal glycemic control before next pregnancy to avoid long term complications for the mother and her fetus due to intrauterine programming.

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Anemia in Pregnancy: Evaluation and Management of Iron Deficiency Anemia

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Definition

Anemia is qualitative or quantitative reduction in the oxygen carrying capacity of blood usually resulting from reduced hemoglobin that leads to reduced oxygen supply to peripheral tissues. World health organization (WHO) has defined anemia in pregnant women as hemoglobin (Hb) concentration of less than 11g% and hematocrit (HCT) of less than 33% at any time during pregnancy and in postpartum period as Hb < 10 g%. The **Center** for Disease Control and Prevention (CDC) proposes a cutoff Hb value of 11g% in 1st and 3rd trimesters and 10.5g% during 2nd trimester.

Magnitude of Problem

Anemia is the most common medical disorder during pregnancy, resulting in increased maternal morbidity and mortality. According to National Family Health Survey-4 (2015-2016), prevalence of anemia in pregnancy is 50.3%.

According to WHO, 32.4 million pregnant women suffer from anemia worldwide out of which 50% cases are attributable to iron deficiency anemia (IDA). Globally 5,91,000 perinatal deaths and 1,15,000 maternal deaths occurred due to IDA.

Severity of Anemia in Pregnancy

According to WHO and Indian Council of Medical Research (ICMR), severity of anemia is graded as: mild, moderate and severe, Table 1.

Table 1: Severity of Anemia in Pregnancy

	WHO	ICMR
Mild	10-10.9	10-10.9
Moderate	7-9.9	7-10
Severe	<7	7-4
Very Severe		<4

Etiology

Physiological Anemia: It serves to reduce the blood viscosity which enhances placental perfusion and facilitates transfer of nutrients and oxygen delivery to fetus. It has following characteristics Hb>10g%, HCV>30%, RBC count>3.2 million with normal RBCs morphologically.

Acquired:

Nutritional: Iron deficiency, folate and vitamin B12 deficiency.

Anemia of chronic disease: For example, chronic malaria, TB, chronic renal disease.

Bone marrow insufficiency: Due to drugs, radiation.

Chronic blood loss from any site, e.g. bleeding piles, hookworm infestation

Hereditary: Thalassemia, sickle cell anemia, hemoglobinopathies, hereditary hemolytic anemia

Management and Approach to Anemia (Table 2)

Confirm the diagnosis

Grade the severity

Find out the type of anemia

Investigate for the cause of anemia and treat the cause

Build up the iron stores.

Iron Deficiency Anemia (IDA)

IDA is the most common type of anemia in pregnancy. The nutritional status of women depends on long term iron balance and is favored by ingestion of adequate amounts of iron in the diet and through iron supplementation.

Average iron requirement (Table 3) is 4mg/day throughout pregnancy varying from 0.8 mg/day in 1st, 4 mg/day in 2nd and 6 mg/day in 3rd trimester.

Stages of Iron Deficiency Anemia (Table 4)

Iron stores depletion is the earliest stage in which storage iron is decreased or absent but serum iron concentration, transferrin saturation and blood hemoglobin levels are normal.

Iron-deficient erythropoiesis is characterized by decreased or absent storage iron, usually low serum iron concentration and transferrin saturation, but without frank anemia.

Table 2: Approach to Anemia

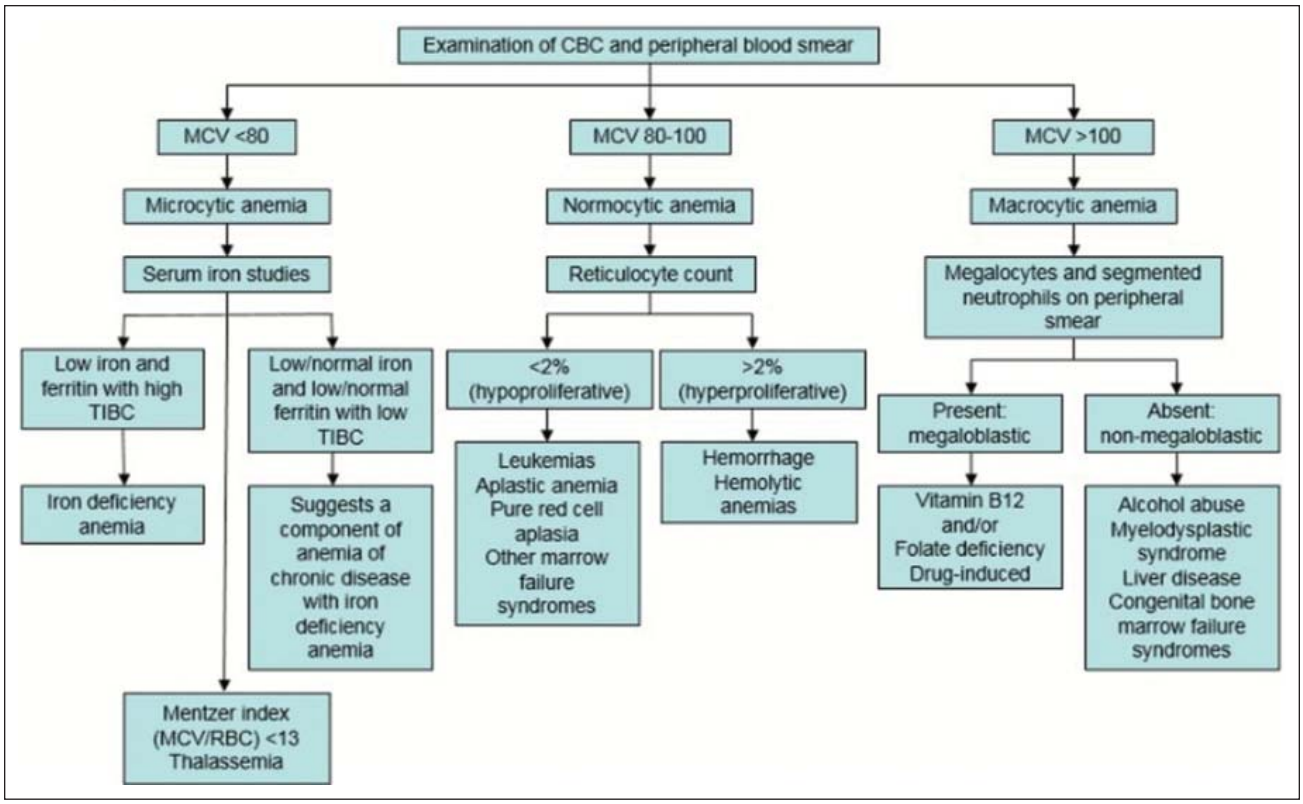


Table 3: Iron Requirement in Pregnancy

	Iron in mg
Fetus and placenta	300mg
Red cell expansion	500mg
External iron loss	200mg
Blood loss at delivery	200mg
Total need	**1200mg**
Iron saved due to amenorrhoea	300mg
Net need in pregnancy	**900mg**

Iron deficiency anemia is the most advanced stage of iron deficiency and is characterized by decreased or absent iron stores, low serum iron concentration, low transferrin saturation and low blood hemoglobin concentration.

Causes of Iron Deficiency Anemia in Pregnancy

Increased demand: Net increase in iron expenditure is approximately 900mg.

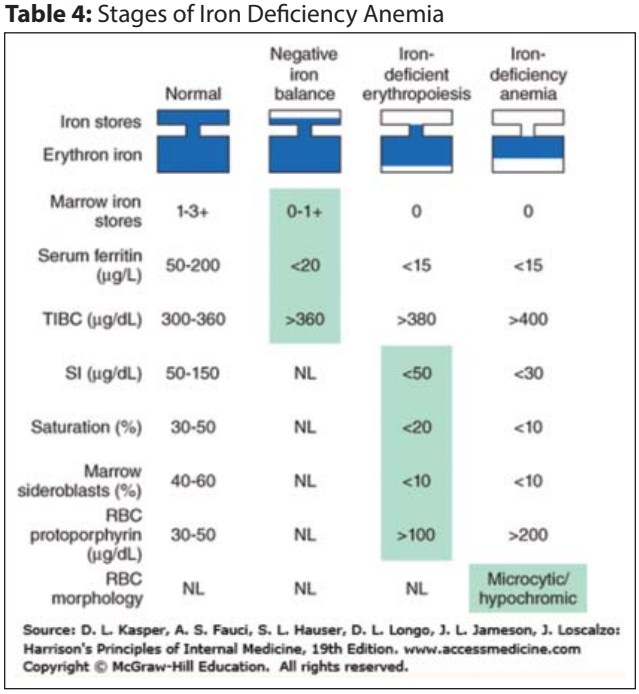
Dietary deficiency: Most common cause of IDA in India.

Impaired absorption

Increased blood loss: Hookworm infestation, Multiple pregnancies.

Effects of Anemia on Pregnancy (Table 5)

Table 4: Stages of Iron Deficiency Anemia



Diagnosis

Complete blood count includes Hb, RBCs indices, reticulocyte counts, platelet count and TLC

Peripheral blood smear

Urine microscopy and culture

Stool for occult blood and ova cyst

Table 5: Effect of Anemia on Pregnancy

Antepartum complications	Intrapartum complications	Postpartum complications	Fetal outcome
Increased risk of preterm delivery Premature rupture of membranes Preeclampsia Intrauterine Death Antepartum hemorrhage Congestive heart failure	Prolonged labor Increased rates of operative delivery and induced labor Fetal distress Abruption Inability to stand even slight blood loss Anaesthesia risk	Postpartum hemorrhage Puerperal sepsis Lactation failure Pulmonary thromboembolism Subinvolution of uterus Postpartum depression	Low birth weight Prematurity Infections Congenital malformation Neonatal anemia Abnormal cognitive development Increased risk of Schizophrenia

Clinical Features of IDA (Table 6)

Table 6: Clinical Features of Iron Deficiency Anemia

General Symptoms	Specific Symptoms
Mild anemia: usually asymptomatic Moderate anemia: weakness, fatigue, lassitude, exhaustion, loss of appetite, indigestion, giddiness, breathlessness Severe anemia: palpitations, tachycardia, breathlessness, generalised edema	Ingestion of non-nutritive materials such as clay, dirt, paper, laundry starch (pica) Lead paint by children, pagophagia (ice craving) Hair loss and restless legs syndrome
General Signs	**Specific Signs**
No signs in mild anemia Pallor, nail changes (depressed nails, koilonychia), cheilosis, glossitis, stomatitis, edema, hyperdynamic circulation as evidenced by short and soft systolic murmur, signs of congestive heart failure (decompensated anemia), fine crepitations at bases of lungs due to congestion	Pallor, decreased papillation of the tongue, cheilosis, and Brittle, fragile and longitudinally ridged nails koilonychia, Platynychia

NESTROFT test

LFTs

Iron studies

Investigations to rule out other causes of anemia

Prevention of Iron Deficiency Anemia (Table 7)

The management starts from childhood.

Dietary modification: consumption of iron rich food, cooking food in iron utensils and avoidance of excessive tea, coffee and overcooking of food

Food fortification with iron (wheat flour, salt): Of various fortifying iron compounds, sodium iron ethylenediaminetetraacetic acid (NaFeEDTA) is most frequently used owing to its effectiveness with a diet rich in phytate such as sugar, curry powder, soy sauce, fish sauce and maize flour. Micronized ground ferric pyrophosphate is another iron salt used for fortification of color-sensitive food vehicles, such as salt in Africa and rice in India.

- Screening of adolescent girls and iron supplementation wherever required
- Hookworm and malaria chemoprophylaxis
- Adequate birth spacing (minimum of two years)

Table 7: Summary of recommendations by WHO and MoHFW.

	During Pregnancy		Postpartum
	Prophylaxis	Treatment	
WHO	Daily 60 mg iron + 400 µg folic acid till term	Daily 120 mg iron + 400 µg folic acid till term	Daily 60 mg iron and 400 µg folic acid - 3 months
MoHFW	Daily 100 mg iron + 500 µg folic acid - for 100 days starting after the first trimester, at 14-16 weeks of gestation	• Mild anemia - 2 IFA tablets/day - 100 days • Moderate anemia - IM iron therapy + oral folic acid	Daily 100 mg iron + 500 µg folic acid - 6 months

Intensified National Iron Plus Initiative (I-NIPI)

Complying with the targets of POSHAN Abhiyaan and National Nutrition Strategy, intensified Iron-plus Initiative (I-NIPI) strategy of the *Anemia Mukt Bharat* Campaign has been designed to reduce prevalence of anemia by 3% per year among six target beneficiary groups through six interventions and six institutional mechanisms (6 x 6 x 6 strategy).

Six Beneficiary Groups Include

1. Children 6-59 months
2. Adolescent girls 15-19 years
3. Adolescent boys 15-19 years
4. Women of reproductive age
5. Pregnant women
6. Lactating women

Six Interventions

1. Prophylactic iron and folic acid supplementation
2. Deworming
3. Intensified year-round behaviour change communication campaign focussing on four key behaviours: a) Improving compliance to Iron Folic Acid supplementation and deworming, b) Appropriate infant and young child feeding practices and c) Increase in intake of iron-rich food and d) ensuring delayed cord clamping after delivery
4. Testing using digital methods
5. Mandatory provision of iron and folic acid fortified foods in government-funded public health programs
6. Intensifying awareness, screening and treatment of non-nutritional causes of anemia.

Six Institutional Mechanisms

1. Intra-ministerial coordination
2. National Anemia Mukt Bharat Unit
3. National Centre of Excellence and Advanced Research on Anemia Control
4. Convergence with other ministries
5. Strengthening supply chain and logistics
6. Anemia Mukt Bharat dashboard and digital portal -one-stop shop for anemia

Prophylactic dose: Daily, one Iron and Folic Acid tablet (red colour: 60 mg elemental Iron, 500 mcg Folic Acid) starting from the second trimester of pregnancy, continued throughout pregnancy (minimum 180 days during pregnancy) and to be continued for 180 days postpartum. IFA tablets available for pregnant and lactating women contain 100 mg elemental Iron and 500 mcg Folic Acid.

Anemia Management Protocol for Pregnant Women

- All pregnant women to be screened at each ANC visits
- *If Hb: 10–10.9 g/dl (mild anemia) or Hb 7–9.9 g/dl (moderate anemia):*

  2 tablets IFA (100 mg elemental Iron, 500 mcg Folic Acid) daily, orally

  OR

  IV Iron Sucrose or Ferric Carboxy Maltose (FCM) late in pregnancy or in case of non-compliance

  Follow up after 2 months

  If Normal Hb– continue IFA Prophylaxis

  If Hb is not improved (< 1g/dl rise in one month) – Investigate / refer
- *If Hb: 5.0–6.9 g/dl (severe anemia)*

  Hospitalization, Evaluation, Blood transfusion

Treatment

The aim of treatment is to raise the Hb levels to near normal followed by restoration of iron stores before she goes into labor. The route of administration of iron depends upon the severity of anemia, duration of pregnancy and any other factors.

Oral Iron Therapy

180-200 mg elemental iron is given daily in divided doses. Iron is absorbed best empty stomach but causes lot of gastric irritation. Alternatively, it can be advised to take before meals or after 1 hour of meals. Vitamin C enhances the absorption of oral iron and tea, coffee, milk and calcium supplements can decrease iron absorption. Compliance is checked by asking the color of stools, which should be black.

A repeat Hb is advised after 3-4 weeks of oral therapy and once Hb reaches normal levels, prophylactic daily iron supplementation is recommended for at least 6 months during pregnancy and should be continued in postpartum period for 6 more months.

Response to Iron Therapy (Table 8)

Patients adequately responding to oral iron will show some clinical improvement with a sense of

improved well-being, lesser palpitations and fatigue, increased effort tolerance, better sleep etc. Optimal response Hb > 2g% increase in 3 weeks

Table 8: Response to Iron Therapy

5-7 days	Reticulocyte count increases (0.2% per day)
2-3 weeks	Hb increases by 0.8-1g% per week RBC indices improve
6-8 weeks	Hb comes to normal range RBCs become normocytic, normochromic on smear S. Ferritin increases

Elemental Iron in Oral Iron Preparations

Percentage of elemental iron is highest in Carbonyl iron preparations followed by Ferrous Fumarate and Ferrous Sulphate, Table 9. Ferrous salts are preferred because they are absorbed (thrice) much more readily. Ferrous

Sulphate is used commonly because it is least expensive and has high elemental iron. Ferrous Fumarate is better tolerated.

Table 9: Elemental Iron in Various Oral Iron Preparations

Various Oral Iron Preparations			
Preparation	**Total Iron (mg/tab)**	**Elemental Iron (mg/tab)**	**% Elemental Iron**
Ferrous Fumarate	200	66	33
Ferrous Sulphate Hydrous Ferrous Sulphate Dessicated	300 200	60 65	20 32
Ferrous Succinate	100	35	35
Ferrous Ammonium Citrate	160	30	18
Ferrous Ascorbate	730	100	14
Carbonyl Iron	100	98	98
Sodium Ferederate	231	33	14
Ferrous-bisglycinate	300	60	20
Ferrous Gluconate	300	36	12

Parenteral Iron Therapy (Table 10 &11)

The rise in Hb after parenteral therapy is 0.7-1.0g% per week which is same as seen with oral iron therapy. The main advantage of parenteral therapy is the certainty of its administration and bioavailability. The indications of parenteral iron are:

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

The contraindications of parenteral iron are:

- History of anaphylactic reactions
- First trimester of pregnancy
- Chronic liver disease
- Active infection.

Oral iron should be stopped 24 hours prior to starting parenteral iron to avoid toxic reactions.

Table 10: Various Parentral Iron Preparations

Preparation	FDA Category	Strength	Route of Administraton
Iron Dextran	C	2 ml/amp 50 mg/ml	IM/IV
Iron Sorbitol	B	1.5 ml/amp 50 mg/ml	IM
Iron Sucrose	B	5 ml/amp 20 mg/ml	IV
Iron Gluconate	N	5 ml/amp 12.5 mg/ml	IV
Iron Carboxymaltose	C	2 ml and 5 ml vials 50 mg/ml	IV

Formulas for Parenteral Iron Dose Calculation

Ganzoni Formula

Required iron dose in mg = 2.4 x (Target Hb – Patient's Hb) x weight in kg + 1000 (for replenishment of stores)

200 mg of iron sucrose is dissolved in 200 ml normal saline and transfused over 20 minutes intravenously. Patient receives 3 doses in a week of 200 mg each.

Management of Severe Anemia in Labour

The hemoglobin levels at the time of delivery should be at least 7 g%, Table 12. Patient requires 1 or more

Table 11: Advantages & Disadvantages of Parentral Iron Preparations

Generic Name	Content	Advantage	Disadvantage
Iron dextran	Colloidal solution of ferric hydrochloride complex with polymerase dextran	Can be given IM or IV, Total dose infusion possible	3-4 weeks for complete absorption Anaphylaxis (test dose required) More systemic toxicity
Iron sorbitol citrate complex	Iron sorbitol citric acid complex	Completely and rapidly absorbed	Only IM Binds transferrin and may saturate it multiple injections required for the total dose
Iron sucrose	Ferric hydrochloride saccharide complex	Minimal risk of anaphylaxis (<.002%), other side effects No test dose required Does not overload transferrin	Only IV Cannot be given as total dose infusion
Ferric carboxy-maltose	Does not contain dextran	Anaphylaxis is rare. No test dose required	Only IV Costly

Table 12: Indications of blood transfusion in pregnancy

Antepartum Period

1. Pregnancy <34 weeks
   a. Hb <5 g/dL with or without signs of cardiac failure or hypoxia
   b. Hb 5-7 g/dL - in presence of impending heart failure
2. Pregnancy >34 weeks
   a. Hb <7 g/dL even without signs of cardiac failure or hypoxia
   b. Severe anemia with decompensation
3. Anemia not due to hematinic deficiency
   a. Hemoglobinopathy or bone marrow failure syndromes
   b. Hematologist should always be consulted
4. Acute hemorrhage
   a. Always indicated if Hb <6 g/dL
   b. If the patient becomes hemodynamically unstable due to ongoing hemorrhage

Intrapartum Period

a. Hb <7 g/dL (in labor)
b. Decision of blood transfusion depends on medical history or symptoms

Postpartum Period

a. Anemia with signs of shock/acute hemorrhage with signs of hemodynamic instability.
b. Hb <7 g% (postpartum): Decision of blood transfusion depends on medical history or symptoms

packed cell volume, each should be transfused slowly over 4-6 hours.

1st Stage

- Counselling and consent
- Propped up position
- Oxygen should be given if required
- Minimizing the number of vaginal examinations
- Monitor for signs of cardiac failure-pulse, BP, Intermittent chest auscultation
- Fluid restriction, blood transfusion under diuretic cover
- Antibiotic prophylaxis

2nd Stage

- Prophylactic ventouse or forceps delivery to cut short the 2nd stage of labor and bearing down
- Strict asepsis to be maintained
- Oxytocin if required should be given in concentrated form to avoid fluid overload
- Restrict intravenous fluids

3rd Stage

- Active management of third stage of labor
- Look for any genital trauma
- Intravenous frusemide given after delivery to decrease cardiac load

Puerperium

- Watch meticulously till 6 hours postpartum for any signs of failure
- Early ambulation is advised
- Prophylactic antibiotics can be considered
- Adequate rest
- Correction of anemia-blood transfusion or iron tablets
- Contraceptive advice

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Cardiac Disease Complicating Pregnancy: Current trends in the management

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Introduction

Cardiovascular diseases are a prominent cause of obstetric intensive care admission and account for significant maternal morbidity and mortality. The worldwide incidence is 0.1-4%. In developed countries the incidence is 0.2-4% whereas in developing countries it is approximately 2%.[1] The prevalence has also been increasing with each passing year, likely causes are higher rates of obesity, hypertension and diabetes; delaying childbirth and increasing number of women with congenital heart disease after surgical treatment becoming pregnant. In developed countries the most common cardiac diseases reported in pregnant women are congenital heart disease but in developing countries Rheumatic heart disease is still the prominent cause. In India, heart diseases contribute to 1/5th of the maternal death. In a study, ICU admission due to heart disease was found to be 6.4 per 1000 deliveries.[2]

Physiological Changes in Cardiovascular System During Pregnancy

Various anatomical and physiological cardiovascular changes come into play during pregnancy making a woman with cardiac disease more prone for complications, Table 1.

Risk Factors

The important risk factors are:

1. Race/Ethnicity: Non-Hispanic black women have a 3.4 times higher risk of dying from cardiovascular disease-related pregnancy complications compared with non-Hispanic white women.
2. Age: Age older than 40 years increases the risk of heart disease related maternal death 30 times the risk for women younger than 20 years.
3. Hypertension: Severe and early - onset hypertension during pregnancy put women at an increased risk of cardiac compromise during or following delivery. In pregnancies complicated by hypertension, the incidence of myocardial infarction and heart failure is 13-fold and 8-fold higher, respectively, than in healthy pregnancies.
4. Obesity: Pre - pregnancy obesity increases maternal death risk due to a cardiac cause, especially if associated with moderate-to-severe obstructive sleep apnea.

The presence of one or more of these risk factors should raise the threshold for suspicion that a patient is at-risk for maternal heart disease and pregnancy-related morbidity and mortality.[3]

Another aspect here to discuss in young women with cardiac disease is its inheritance and risk of passing it to their descendants. The risk is about 1% in babies with parents without any cardiac disease, but its higher if either or both the parents have heart disease. In general, the risk is higher when the mother is affected rather than the father, Table 2. The recurrence risk varies between 3% and 50% depending on the type of maternal heart disease.[4]

Autosomal dominant diseases like Marfan syndrome, hypertrophic cardiomyopathy, or long QT syndrome have an inheritance risk of 50%, regardless of gender of the affected parent. Autosomal recessive and X-chromosomal recessive inheritance are rare.

Diagnosis of heart disease: Diagnosis can be challenging because the overlap of cardiovascular symptoms with those of normal pregnancy may lead to delays in diagnosis and subsequent care. The clinical indicators of heart disease during pregnancy are following- **Symptoms:** Progressive dyspnea/ orthopnea, Nocturnal cough, Hemoptysis, Syncope, Chest pain; **Signs:** Persistent tachycardia/arrhythmia, Cyanosis, Clubbing, Distended neck vein, Splitting of S2, presence of S4, Systolic murmur (>grade3), Diastolic murmur, Cardiomegaly, Pulmonary arteria hypertension.

There is no clinically applicable test that accurately measures functional cardiac capacity. The clinical classification of the New York Heart Association (NYHA) is based on past and present disability and uninfluenced by physical activity.

Table 1: Implications of anatomical and physiological changes of cardiovascular system

Anatomical changes		
Apex beat	Deviated to 4th intercostal space	Elevation of diaphragm Rotation along its long axis
Heart sounds	Loud and splitting of S1, loud S3, presence of S4 occasionally	Increased cardiac output and volume
Physiological changes		
Plasma volume and RBC expansion	Increased by 40- 50%, RBC expansion by 20%.	Hypervolemia essential for utero placental circulation, protection of blood loss at delivery, to counter effect of supine hypotension Physiological anemia essential for good utero placental circulation
Peripheral vascular resistance	Decreases. Nadir in mid trimester	Lower BP in mid trimester Masking of chronic HT in 1&2 Trimester Masking of initial signs of sepsis.
Heart Rate at rest	Increased by 10-20 bpm. Maximum in late 3rd Trimester	Interpretation of tachycardia especially in critically ill patients
Cardiac Output	Increases by 40% Maximum increase at 30-32 weeks; increases exponentially in labour and immediate post partum Significantly reduced by pressure of gravid uterus on IVC.	Deterioration of gravidas with stenotic heart lesions especially in the critical periods
Systemic vascular resistance	Decreased	Masks early signs of sepsis
Arterial blood pressure	Decreased by 10-15 mmHg in mid trimester	Decreased reserve during shock
Venous return	Decreased by pressure of gravid uterus on IVC.	CPR becomes ineffective unless LUD is done
Murmur	Systolic ejection murmur present in 90% Soft diastolic murmur (<grade 3) may be present in 20% Continuous mammary murmur in !0%	Presence of murmur not always signifies heart disease
Pedal edema and varicose vein	Pressure on IVC due to gravid uterus	Physiological edema relieves on foot elevation
ECG changes	Echo changes	
Left axis deviation Deep Q wave Low voltage complex		

NYHA Classification

1. Class I- Uncompromised- No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
2. Class II- Slight limitation- Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
3. Class III- Marked limitation- These women are comfortable at rest, marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20—100 m).
4. Class IV- Severely compromised- Inability to perform any physical activity without discomfort. Angina may develop at rest. If any physical activity undertaken the discomfort increases.

Table 2: Risk of congenital heart disease (CHD) in babies born to women with CHD

Congenital Heart Defect	Neonatal Risk (%)
Any defect	5-6
ASD	4-10
VSD	6-10
Tetralogy of Fallot	3-5
Transposition of the great arteries	0
Aortic coarctation	4
Aortic stenosis	4-18
Pulmonary stenosis	3-4
Ebstein's anomaly	4-6

Table 3: World Health Organization (WHO) risk classification

WHO Pregnancy Risk Classification (Risk of pregnancy by medical condition)	**Cardiovascular Conditions by WHO Risk Class**
WHO Risk Class I No detectable increased risk of maternal mortally and no or mild increase in morbidity.	• Uncomplicated small or mild o Pulmonary stenosis o Patient ductus arteriosus o Mitral valve prolapse • Successfully repaired simple lesions (artrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage) • Atrial or ventricular ectopic beats. isolated
WHO Risk Class II (If otherwise well and uncomplicated) Small increased risk of maternal mortality or moderate increase in morbidity	• Unoperated atrial or ventricular septal defect • Repaired tetralogy of Fallot • Most arrhythmias
WHO Risk Class II or III (Depending on individual) Risk as indicated in Class II (above) or Class III (below)	• Mild left ventricular impairment • Hypertrophic cardiomyopathy • Native or tissue valvular heart disease not considered WHO I or IV • Marfan syndrome without aortic dilatation • Aorta <45 mm in aortic disease associated with bicuspid aortic valve • Repaired coarctation
WHO Risk Class III Significantly increased risk of maternal mortality or severe morbidity. Expert counseling required, if pregnancy is decided upon intensive specialist cardiac and obstetric monitoring needed throughout pregnancy, childbirth and the puerperium	• Mechanical valve • Systemic right ventricle • Fontan circulation • Cyanotic heart disease (unrepaired) • Other complex congenital heart disease • Aortic dilatation 40-45 mm in Marfan syndrome • Aortic dilatation 45-50 mm in aortic disease associated with bicuspid aortic valve
WHO Risk Class IV (Pregnancy contradicated) Extremely high risk of maternal mortality or severe morbidity; pregnancy contraindicated, if pregnancy occurs termination should be discussed. if pregnancy continues, care as for class III	• Pulmonary arterial hypertension of any cause • Severe systemic ventricular dysfunction (LVEF <30%, NYHA III-IV)* • Previous peripartum cardiomyopathy with any residual impairment of left ventricular function • Severe symptomic mitral or aortic stenosis • Marfan syndrome with aorta dilated >45 mm • Aortic dilation >50 mm in aortic disease associated with bicuspid aortic valve • Native severe coarctation

*LVEF = left ventricular ejection fraction; NYHA = New York Heart Association

Different Risk Assessment Scores

WHO risk classification: The Task Force recommends that maternal risk assessment is carried out according to the modified World Health Organization (WHO) risk classification, Table 3.[5]

In women in WHO class I, risk to mother is very low, and cardiology follow-up during pregnancy may be limited to one or two visits. Those in WHO II are at low or moderate risk, and follow-up every trimester is recommended. For women in WHO class III, there is a high risk of complications, and frequent (monthly or bimonthly) cardiology and obstetric review during pregnancy is recommended. Women in WHO class IV should be advised against pregnancy but, if they become pregnant and not willing to consider termination, monthly or bimonthly review is needed.

Several risk scores have been developed for predicting cardiac complications during pregnancy, of which the CARPREG risk score is most widely known and used, Table 4, 5 & 6.[6]

Limitations of Risk Assessment Scores are:

1. Population dependent
2. Dilated aorta and pulmonary artery hypertension population under represented
3. No contraindication for pregnancy is mentioned like mWHO risk classification.

Table 4: CARPREG risk score

Prior Cardiac event (heart failure, transient ischaemic attack, stroke before pregnancy or arrhythmia)
Baseline NYHA functional class >II or cyanosis
Left heart obstruction (mitral valve area < 2 cm^2, aortic valve area <1.5 cm^2, peak LV outflow tract gradient > 30 mmHg by echocardiography).
Reduced systematic ventricular systolic function (ejection fraction <40%).

CARPREG risk score: for each CARPREG predicator that is present a point is assigned. Risk estimation of cardiovascular maternal complications

0 point 5%, 1 point 27%, >1 point 75%

LV = left ventricular, NYHA = New York Heart Association.

Table 5: ZAHARA predictors

History or arrhythmia event
Baseline NYHA functional class >11
Left heart obstruction (aortic valve peak gradient >50 mm Hg).
Mechanical valve prosthesis
Moderate/severe systemic atrioventricular valve regurgitation (possibly related to ventricular dysfunction)
Moderate/severe sub-pulmonary atrioventricular valve regurgitation (possibly related to ventricular dysfucntion
Use of cardiac medication pre-pregnancy
Repaired or unrepaired cyanotic heart disease

Table 6: Khairy predictors

Smoking history
Reduced subpulmonary ventricular function and/or severe pulmonary regurgitation

The CARPREG study included acquired and congenital heart disease, while the ZAHARA study investigated a population with congenital heart disease only. The predictors from the ZAHARA study have not yet been validated in other studies.[7,8]

Investigations

Along with routine antenatal investigation other specific investigations done when indicated:

Non-invasive investigations: Pro BNP: useful in cardiac failure, the cut off value is >100pg/ml; Cardiac troponin: troponin I and T both can be used in myocardial infarction; Chest x ray: can identify cardiomegaly and pulmonary edema; Ambulatory ECG monitoring; Exercise ECG; Ambulatory BP monitoring

Invasive methods: Cardiac catheterisation and Pulmonary artery catheterisation. These are used when continuous and intense monitoring is required.

Management

Here the general aspects of dealing a woman with heart disease since she plans pregnancy till the postpartum period, are discussed in brief. Majority of them are known case of heart disease and rest are diagnosed during pregnancy when have the worsening symptoms. Pre-conceptional counselling is of immense importance when women with known heart disease.

Pre-conceptional Counselling

They should be informed that there is significant worsening of NYHA class as pregnancy progresses. In cases with life threatening cardiac diseases, pregnancy should be planned after corrective surgeries. In women with mechanical valves taking warfarin, switching to other anticoagulants to prevent teratogenicity should be discussed. Risk assessment should be done according to mWHO classification (commonly used), and women with class IV should be counselled against pregnancy and class III after optimizing their cardiac status.

Genetic testing is indicated:

- In cardiomyopathies and channelopathies, such as long QT syndromes
- When other family members are affected
- When the patient has dysmorphic features, developmental delay/ mental retardation, or when other non-cardiac congenital abnormalities are present, in syndromes such as in Marfan, 22q11 deletion, Williams–Beuren, Alagille, Noonan, and Holt–Oram syndrome.

1st trimester screening: Measurement of nuchal fold thickness in the 11 to 13^{+6} week of pregnancy is an early screening test. The sensitivity for the presence of a significant heart defect is 40%, while the specificity of the method is 99%. The incidence of congenital heart disease with normal nuchal fold thickness is 1/1000. Confirmation with invasive test like chorionic villous biopsy can be offered in the 12th week of pregnancy.

2nd trimester screening: All women with congenital heart disease should be offered fetal echocardiography in the 19th to 22nd week of pregnancy.[9,10]

Antenatal Management

Managing a woman with heart disease during her antenatal period requires a multidisciplinary team: cardiologist, obstetrician, fetal medicine specialist,

Table 7: mWHO risk classification and number of antenatal visits

mWHO	1	2	2-3	3	4
No of visits	Once or twice	Once per trimester	bimonthly	Monthly or bimonthly	monthly

paediatrician.

Number of antenatal visits have been specified according to mWHO risk classification, Table 7.

Majority of NYHA class I and II negotiate pregnancy without any morbidity. They should be advised to limit strenuous activities, restrict salt intake in cases of ventricular dysfunction, take adequate rest, iron and vitamin supplementation and undergo regular cardiac and obstetric evaluation.

Early diagnosis and prompt treatment should be started when there is infection, anaemia, hypertension, hyperthyroidism or arrhythmias. All these can cause sudden and rapid decompensation of the cardiac functions in a woman with heart disease. Prevention of bacterial endocarditis is a must in women with specific cardiac disease as recommended by the American Heart Association (AHA). Antibiotic prophylaxis routinely given prior to all cesarean deliveries protects against endocarditis as well. Women undergoing vaginal delivery require antibiotic prophylaxis for selected patients only. In these women antibiotics are administered 30 to 60 minutes before delivery. According to AHA 2007 guidelines, endorsed in 2021, only 4 categories of patients need endocarditis prophylaxis: 1) Prosthetic Cardiac Valve or Prosthetic Material Used for Cardiac Valve Repair or Other Implantable Cardiac Devices; 2) Previous, Relapse, or Recurrent IE; 3) Congenital Heart Disease- Unrepaired cyanotic congenital CHD; and 4) Cardiac Transplant Recipients.[11]

In women with NYHA class III or IV they must be explained about the increased risk of mortality and should be offered MTP. Women who continue pregnancy may need hospitalisation for bed rest, intensive close monitoring and cardiac interventions like corrective surgery.

Indications for cardiac surgery: Type and deterioration of heart lesion and refractory heart failure

Best time for cardiac surgery: For percutaneous therapy 16 weeks and for cardiac surgery with cardiopulmonary bypass 13-28 weeks.[12]

Labour and Delivery

Time of delivery

- Spontaneous labour preferred upto 40 weeks
- Individualization: according to the severity of maternal disease and any associated fetal compromise
- In cyanotic HD significant IUGR may warrant premature termination
- Women with mild unrepaired congenital heart disease and with successful cardiac surgical repair – treated same as normal pregnancy

Mode of delivery

- Vaginal delivery is safer except certain situation & unless there is an obstetric indication of CS
- Induction done for obstetric reasons and is usually safe

Indications for caesarean delivery

- Dilated aortic root >4cm or aortic aneurysm
- Acute severe congestive cardiac failure
- Recent myocardial infarction
- Severe symptomatic aortic stenosis
- Warfarin administration within 2 weeks of delivery
- Need for emergency valve replacement immediately after delivery

Management during labour

- During labor, the mother with significant heart disease should be kept in a semi recumbent position with lateral tilt
- Frequent vitals monitoring
- Encourage oral fluid intake and restrict IV fluids
- Adequate pain relief, continuous epidural analgesia is recommended
- Use of concentrated oxytocin for augmentation
- Delay in 2nd stage of labor to be curtailed by forceps/ventouse application under pudendal and / or perineal block. Ventouse preferred as it can be applied in lateral recumbent position
- Along with conventional management of 3rd stage of labour, it is preferable to administer oxytocin in an IV drip to all cases who are not in failure and simultaneously furosemide 20 mg IV. to relieve volumetric load
- Episiotomy wound repaired early. Pt kept in propped up position, O2 supply throughout
- If PPH occurs should be managed with oxytocin,

Prostaglandin F analogues should be avoided and Methylergonovine is contraindicated because of the risk (10%) of vasoconstriction and hypertension

Danger signs

- Increases in Pulse rate much above 100 bpm or respiratory rate above 24 per min, particularly when associated with dyspnea, may suggest impending ventricular failure
- Cardiac monitoring and pulse oximetry can detect arrhythmias & hypoxia which are indicative of pulmonary edema

Puerperium

Delivery is associated with important haemodynamic changes and fluid shifts, particularly in the first 12–24 h, which may precipitate heart failure in women with structural heart disease. Hence strict monitoring should therefore be continued for at least 24 h after delivery. Meticulous leg care, elastic support stockings, and early ambulation are important to reduce the risk of thrombo-embolism. Appropriate contraceptives should be offered as a basket of choice.

Conclusion

- Physiological changes in pregnancy are not well tolerated in women with cardiac disease especially with stenotic lesions
- Risk assessment is a very important aspect of management
- Counselling and management of women with heart disease should be done according to the risk assessment scores
- These women should be dealt in a tertiary care centre with pregnancy heart team
- Most critical periods for any adverse cardiac event or cardiac failure are around 32 weeks in antenatal, labour and immediate postpartum. Hence they should be closely monitored, appropriate and prompt management should be done when danger signs identified.

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Epilepsy in Pregnancy: Therapeutic strategies

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Epilepsy is one of the most common neurological conditions in pregnancy, with a prevalence of 0.5–1%. Women with epilepsy (WWE), their families and healthcare professionals should be aware of the different types of epilepsy and their presentation to assess the specific risks to the mother and baby. Women with epilepsy (WWE) were once counselled to avoid pregnancy, but epilepsy is no longer considered a contraindication to pregnancy. Over 90% of women with epilepsy will have good outcomes. The risk of death is increased ten-fold in pregnant WWE compared with those without the condition. Most WWE will need to remain on anti-epileptic drugs (AEDs) during their child bearing years and throughout pregnancy. Exceptions include patients with childhood epilepsy, which can remit in adulthood.

Pre-pregnancy Counselling

WWE should be counselled about prenatal screening and its implications, the risks of self-discontinuation of AEDs and the effects of seizures and AEDs on the fetus and on the pregnancy, breastfeeding and contraception. Ideally, women with epilepsy should have access to effective contraception in order to plan their pregnancies. The patient should be jointly evaluated by a neurologist to determine whether she is a candidate for discontinuation of drugs. Individuals who have been seizure free for last 2 years are the potential candidates to stop AEDs. All the alterations in AED dosage and type should be done pre pregnancy and women should embark on pregnancy only when she is well stabilized. In WWE not exposed to AEDs, the incidence of major congenital malformations is similar to the background risk for the general population. In WWE who are taking AEDs, the risk of major congenital malformation to the fetus is dependent on the type, number and dose of AED.

All WWE should be advised to take 5 mg/day of folic acid prior to conception and to continue the intake until at least the end of the first trimester to reduce the incidence of major congenital malformation and AED-related cognitive deficits. The lowest effective dose of the most appropriate AED should be used. Exposure to sodium valproate and other AED polytherapy should be minimised by changing the medication prior to conception, as recommended by an epilepsy specialist after a careful evaluation of the potential risks and benefits.

Pregnancy should be avoided or postponed I women with uncontrolled seizures (particularly tonic-clonic), taking high doses of AEDs, on polytherapy, drug resistant epilepsy, noncompliance with medication, and in presence of other medical comorbidities leading to poor general health.

Choice of antiepileptic drug- Among AEDs, lamotrigine, and carbamazepine monotherapy at lower doses have the least risk of major congenital malformation in the offspring. The most common major congenital malformations associated with AEDs are neural tube defects, congenital heart disorders, urinary tract and skeletal abnormalities and cleft palate. Sodium valproate is associated with neural tube defects, facial cleft and hypospadias; phenobarbital and phenytoin with cardiac malformations; and phenytoin and carbamazepine with cleft palate in the fetus (Table 1).

Monotherapy at the lowest dose that prevents seizure should be the goal. Children exposed to sodium valproate in utero had a significantly lower developmental quotient when compared with those born to WWE who were not taking AEDs, and to those born to women without epilepsy. Hence, Valproate should be avoided in women of reproductive age whenever possible.

For women with epilepsy of childbearing age who are planning pregnancy, lamotrigine or levetiracetam monotherapy are preferred as first line treatment options because they have the most abundant and consistent data for low structural and neurodevelopmental teratogenic risk during pregnancy. In recent years the use of new AEDs has become widespread, however, all these drugs are classified as category C. Also, it is advisable not to change the AED, once the woman conceives, because of risk of increased frequency of fits, which could be detrimental for both mother and her fetus.

Effect of Pregnancy on Epilepsy

Up to 33% of pregnant women will experience an increase in seizure frequency during pregnancy, while the remainder will experience no change or a decrease. The effect of pregnancy on epilepsy may be inferred from the women's seizure frequency before pregnancy. The seizure-free duration is the most important factor in assessing the risk of seizure deterioration. In women

Table 1: AED Specific Congenital Malformation Frequency

AED	Possible congenital malformations	Risk of congenital malformations	Safety in pregnancy and Breastfeeding
No AED		2.0-2.3%	
Carbamazepine	Cardiac defects Facial clefts	2-5% Dose-dependent risk	**Pregnancy:** Considered safest **Breastfeeding:** Safe
Lamotrigine	Cardiac defects Facial clefts	2-5% Dose-dependent risk	**Pregnancy:** Considered safest, may need dose adjustment in the third trimester (check plasma levels) **Breastfeeding:** Safe
Levetiracetam	Cardiac defects Neural tube defects	1-2%	**Pregnancy:** Considered safest **Breastfeeding:** Safe further studies needed
Oxcarbazepine	Cardiac defects Facial clefts	1-3%	**Pregnancy:** Relatively Safe **Breastfeeding:** Safe
Phenobarbital	Cardiac defects	2%	**Pregnancy:** Relatively Safe **Breastfeeding:** Avoid (drowsiness)
Phenytoin	Facial clefts Poor cognition and neurodevelopment	1-2%	**Pregnancy:** Relatively Safe **Breastfeeding:** Safe
Sodium valproate	Neural tube defects Facial clefts Hypospadias Poor cognition and neurodevelopment	6-10% Dose-dependent risk	**Pregnancy:** Avoid if possible **Breastfeeding:** Safe
Topiramate	Cardiac defects Facial clefts Hypospadias	4-6%	**Pregnancy:** Less safe, avoid if possible **Breastfeeding:** Safe
Monotherapy		3-5%	
Polytherapy		6-8%	
Polytherapy with valproate		Up to 10%	

The evidence for the safety profile in breastfeeding

AED = Anti-epileptic drug

who were seizure free for at least 9 months to 1 year prior to pregnancy, 74–92% continued to be seizure free in pregnancy.

Sleep deprivation or noncompliance may play a role in up to 70% of the increase of seizures in some women during pregnancy, and they should be informed about the importance of AED compliance. A number of pregnancy associated complications can result in sub therapeutic levels of AEDs. These include nausea and vomiting, decreased gastrointestinal mobility, antacid use that diminishes drug absorption, an expanding plasma volume, and a reduction in plasma proteins which attach and transport AEDs in the blood.

Besides the sleep deprivation and hyperventilation, pain during labour may decrease the seizure threshold resulting in an increase in frequency. Clearance of most of the AEDs increases during pregnancy, and returns to pre pregnancy levels by 2 to 3 months postpartum. Lamotrigine clearance increases dramatically up to 230% above baseline during pregnancy, and returns to pre pregnancy levels within a few weeks of birth.

Effect of Epilepsy on Pregnancy

The effects of AEDs on the fetus are complex and controversial. The four most commonly used agents i.e. carbamazepine, phenobarbital, phenytoin, and valproate, are known to cross the placenta and are believed to be teratogenic. The rate of congenital malformations is 2-3 times that seen in infants of non-epileptic mothers (i.e. 6-8% in epileptic pregnancies). Thus, more than 90% of mothers taking AEDs during pregnancy will deliver children with no evidence of congenital malformations. However, Valproate may have a dose related adverse effect on long term cognitive potential. It is clear that women with epilepsy who are on AEDs have an increased risk of fetal anomalies, including fetal growth restriction (FGR), major and minor malformations, cognitive disorders,

microcephaly, and infant mortality, all encompassed in the term "fetal anticonvulsant syndrome" which has been associated with most of the currently prescribed AEDs.

FGR affects 7% to 10% of pregnancies of epileptic women on AEDs, and polytherapy seems to be an even more potent cause of reduced fetal growth. Minor anomalies includes distal digital and nail hypoplasia and midline craniofacial anomalies. Major malformations seen are congenital heart defects (ASD, VSD, PDA, pulmonary stenosis, coarctation of the aorta, and tetralogy of Fallot), cleft lip/palate, urogenital disorders (commonly glandular hypospadias), and neural tube defects (NTDs). While the risks of major anomalies vary by AED, multiple studies confirm the greatest risk occurs in the presence of polytherapy. Generalized tonic-clonic seizures during pregnancy have been found to be associated with maternal and fetal hypoxia and acidosis.

Management

Antepartum Management- WWE taking AEDs who become unexpectedly pregnant should be able to discuss therapy with an epilepsy specialist on an urgent basis. It is never recommended to stop or change AEDs abruptly without an informed discussion. Pregnant women on AEDs should have drug levels monitored. *A baseline level prior to pregnancy when the patient is seizure-free with repeat levels at least each trimester and within 4 weeks of the expected date may be adequate for most patients, although monthly levels should be considered for patients with widely fluctuating serum levels of AED.*

Maternal serum screening for NTDs at 16-20 weeks of gestation, and the fetal anomaly scan at 18^{+0}–20^{+6} weeks of gestation can identify major cardiac defects and neural tube defects which are increased due to AEDs**.** However, women with epilepsy are not at increased risk for chromosomally abnormal pregnancies beyond that associated with their chronological age.

In WWE compared with women without epilepsy, the odds of spontaneous miscarriage, antepartum haemorrhage, hypertensive disorders, induction of labour, caesarean section, preterm delivery, fetal growth restriction and postpartum haemorrhage were increased. Given the increased risk in WWE exposed to AEDs, serial growth scans should be offered from 28 weeks of gestation, for detection of growth restriction. There is however no evidence for routine antepartum fetal surveillance with cardiotocography in WWE taking AEDs.

Women who are seizure free for more than 10 years and are not taking AEDs for more than 5 years are considered low risk until complicated by further seizures.

Intrapartum Management- Labor and delivery is usually uneventful and results in a successful vaginal delivery in the majority of women with epilepsy. Epilepsy per se is not an indication for induction of labor and Cesarean section. There are no contraindications to use of labor inducing agents in WWE taking AEDs.

Being fasting and sleep deprived for extended periods of time predisposes women in labor to a lower seizure threshold. Adequate analgesia and appropriate care in labour should be provided to minimise risk factors for seizures such as insomnia, stress and dehydration. AED intake should be continued during labour. If this cannot be tolerated orally, a parenteral alternative should be administered.

When generalized tonic-clonic seizures occur during labor, they should be treated promptly and aggressively to avoid maternal and fetal hypoxia. Hence, an intravenous access should always be established during labour. Continuous fetal monitoring should be done in women at high risk of a seizure in labour, and following an intrapartum seizure. Convulsions in labor may be treated acutely with lorazepam or diazepam intravenously. Seizures in labour may lead to maternal hypoxia due to apnoea during the seizure, and fetal hypoxia and acidosis secondary to uterine hypertonus.

Long-acting benzodiazepines such as clobazam can be considered if there is a very high risk of seizures in the peripartum period. Pain relief in labour should be prioritised in WWE.

Postnatal- WWE should be advised to continue their AEDs postnatally. Mothers should be well supported in the postnatal period to ensure that triggers of seizure deterioration such as sleep deprivation, stress and pain are minimised. Most AED levels gradually increase after delivery and plateau around 10 weeks postpartum with the notable exception of lamotrigine which increases immediately and plateaus within 2 to 3 weeks of delivery.

Hence, if the AED dose was increased in pregnancy, it should be reviewed within 10 days of delivery to avoid postpartum toxicity. These changes necessitate close monitoring of drug levels to avoid toxicity from the increased doses commonly used during pregnancy. Sleep deprivation may increase the incidence of seizures in some postpartum individuals.

New onset seizures in post-partum period require complete evaluation to rule out intra cerebral hemorrhage, cortical vein thrombosis, infection or eclampsia.

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Breastfeeding- Although most AEDs are found in breast milk, breast-feeding is not contraindicated for any of the AEDs used in pregnancy. Most experts believe that benefits of breast feeding outweigh risks of AED. Leviteracetam, Primidone have highest concentration in breast milk followed by Lamotrigine, gabapentin and topiramate. Valproic acid/Carbamazepine/phenytoin/ phenobarbitol amounts in breast milk felt not to be clinically significant. Not many studies done on this do determine if there are any long-term negative effects.

New born Care- All neonates born to women with epilepsy should receive vitamin K 1 mg intramuscularly after birth to prevent coagulopathy. Mothers should be advised to watch for infants who become somnolent before the breasts are emptied, suggesting the possibility of higher than normal levels of AEDs.

Safety strategies include nursing the baby on the floor, using very shallow baby baths, laying the baby down if there is a warning aura, not bathing the baby unaccompanied, wearing identification tags, and avoiding sleep deprivation, and alcohol if prone to myoclonic jerks. Postnatal mothers with epilepsy at reasonable risk of seizures should be accommodated in single rooms only when there is provision for continuous observation by a care taker, partner or nursing staff.

Differential Diagnosis of Seizures in Pregnancy

In pregnant women presenting with seizures in the second half of pregnancy which cannot be clearly attributed to epilepsy, immediate treatment should follow existing protocols for eclampsia management until a definitive diagnosis is made by a full neurological assessment. Other cardiac, metabolic and intracranial conditions should be considered in the differential diagnosis. Neuropsychiatric conditions including non-epileptic attack disorder should also be considered.

Contraception

WWE should be offered effective contraception to avoid unplanned pregnancies. Copper intrauterine devices (IUDs), the levonorgestrel-releasing intrauterine system (LNG-IUS) and Depot medroxyprogesterone acetate injections should be promoted as reliable methods of contraception that are not affected by enzyme-inducing AEDs.

Women taking enzyme-inducing AEDs e.g. carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine, topiramate and eslicarbazepine should be counselled about the risk of failure with some hormonal contraceptives e.g. combined hormonal contraception, progestogen-only pills, transdermal patches, vaginal ring and progestogen-only implants, which should be avoided.

WWE taking enzyme-inducing AEDs should be informed that a *copper IUD is the preferred choice for emergency contraception because emergency contraception pills with levonorgestrel and ulipristal acetate are affected by enzyme-inducing AEDs*. Women taking lamotrigine monotherapy and oestrogen-containing contraceptives should be informed of the potential increase in seizures due to a fall in the levels of lamotrigine.

All methods of contraception may be offered to women taking non-enzyme-inducing AEDs e.g. sodium valproate, levetiracetam, gabapentin, vigabatrin, tiagabine and pregabalin. The risks of contraceptive failure and the short- and long-term adverse effects of each contraceptive method should be carefully explained to the woman. Effective contraception is extremely important in WWE, with regard to stabilisation of epilepsy and planning of pregnancy to optimise outcomes.

Status Epilepticus (SE)

SE is defined as ongoing seizure activity lasting greater than 30 minutes or recurrent seizures without full recovery of consciousness between episodes. The actual incidence during pregnancy is unknown. Predisposing factors include poor compliance with AEDs, central nervous system infections, trauma, and illicit drug use. SE represents a medical emergency and majority seizures are generalized tonic-clonic. Trauma from recurrent seizure activity can result in preterm labor, rupture of membranes, abruptio placenta, and fetal death.

Diagnostic and therapeutic interventions should be performed simultaneously. A patent airway must be secured and supplemental oxygenation given. Intravenous benzodiazepines are used acutely and Lorazepam is the drug of choice and it is given in 2-mg boluses every 5 minutes. In refractory cases in which barbiturates or a continuous infusion of benzodiazepines is needed, an elective intubation is required to protect the airway.

Conclusion

Pregnancy in WWE is a “high risk” with small but significant increased obstetric risks especially in women exposed to AEDs, needing multidisciplinary team approach involving a neurologist, fetal medicine specialist and an obstetrician. WWE should be reassured that most mothers will have normal healthy

babies and the risk of congenital malformations in the fetus is dependent on the type, number and dose of AEDs. Pre conceptional, counselling and use of Folic acid is the cornerstone of management.

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Hypothyroidism in pregnancy: Still an Enigma

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Thyroid disorders are common endocrinological disorders in pregnancy and affect up to 5% of all pregnancies. Overt hypothyroidism affects 0.3-0.5% of all pregnant women; subclinical hypothyroidism and hyperthyroidism affect 2-3% and 0.1-0.4% of all pregnancies, respectively.[1] An optimal thyroid hormone balance is indispensable to normal fetal development.

Autoimmune disorders of the thyroid are an important cause of both hypo and hyperthyroidism in pregnancy. While Graves' disease comprises all 85% of hyperthyroid cases, Hashimoto thyroiditis is the most common cause of overt hypothyroidism. Postpartum thyroiditis affects nearly 4-10% of all mothers and may occur anywhere between the first twelve months of delivery and may lead to permanent hypothyroidism. Autoimmune thyroid diseases may improve during pregnancy with uncommon post-delivery exacerbations secondary to the altered immune status of pregnancy.

Embryology of the Thyroid Gland

The first endocrine gland to develop in a foetus is the thyroid gland. The rudimentary lateral thyroid arises from the neural crest cells, while the median thyroid (forming the major bulk of the organ) develops from the primitive pharynx. The gland is functionally mature by twelve weeks. The fibroblast growth factor plays an important part in the development of the thyroid gland.[2]

Thyroid Physiology in Pregnancy

The normal physiological thyroid function changes during pregnancy can be summarized as follows:

- Iodine requirements increase during pregnancy due to increased renal clearance and losses to the fetoplacental unit. However, a higher than the recommended intake may lead to fetal hypothyroidism and goitre. The WHO and American Thyroid Association (ATA) recommend an intake of 250 mcg (max 500 mcg) of iodine per day during pregnancy and lactation.[3,4]
- Thyroid gland size increase by 10-30% during the third trimester secondary to increased extracellular fluid and blood volume.[5]
- Thyroid hormone production increases during the pregnancy by 50%.
- During the first trimester, the human chorionic gonadotropins (hCG) directly and weekly stimulate the pituitary thyroid-stimulating hormone (TSH) receptors due to a fair homology between the beta subunits of their receptors. This causes an increased thyroid hormone production and a fall in TSH levels through a negative feedback loop mediated by an increasing free thyroxine (FT4) level. The TSH and hCG changes mirror each other i.e. with an increase in hCG, the TSH decreases (Gestational thyrotoxicosis). In a fraction of women (one to two in ten women) TSH levels may be low or undetectable during the first trimester. This transient subclinical hyperthyroidism may be considered a normal physiological finding.[6]
- High estrogen levels cause an increase in thyroid binding globulins (TBG) production and sialyation leading to decreased clearance and increased levels (two folds) during the pregnancy. The TBG levels plateau during the mid-trimester up to several days post-delivery.
- A rise in TBG levels and increased renal clearance of iodine leads to an increase in the thyroid pool of total and bound T3 and T4 levels (not FT3 and FT4) very early in the course of pregnancy. This rise approximates 50% of the total non-pregnant value during the first half of pregnancy. The levels plateau by twenty weeks of gestation when a new steady state is reached returning the overall production to non-pregnant levels.

Fetal Thyroid Function

Maternal TSH cannot cross the placenta. Maternal T4 (not T3) can cross the placenta throughout the pregnancy and is important in fetal neurological development especially during the period when the foetal thyroid gland is functionally immature (before twelve weeks of gestation). Thereafter the placental thyrotropin-releasing hormone (TRH) stimulates the fetal pituitary and produces fetal thyroid hormones. However, the fetal thyroid hormone production is meagre up to eighteen to twenty weeks of pregnancy. Thereafter, it increases gradually.

Thyroid Function Tests During Pregnancy

Serum TSH Reference Range During Pregnancy

In 2011, the ATA recommended that the reference range of TSH should be population-specific and trimester-specific. If a reference TSH range was not available for a particular subpopulation base, a range of 0.4- 4.5 mIU/L was to be taken as reference for non-pregnant women, 0.1-2.5 mIU/L for the pregnant women in their first trimester, 0.2-3.0 mIU/L in their second trimester and 0.3-3 mIU/L in their third trimester.[7] In line with the ATA 2011 guidelines the Ministry of Health and Family Welfare, Government of India (MOHFW-GOI) in 2014 gave similar trimester-specific TSH values ranges for pregnant women i.e 0.1-2.5 mIU/L for the first trimester, 0.2-3.0 mIU/L for second and 0.3-3.0 mIU/L for the third trimester.[8]

Later, the ATA 2017 guidelines emphasised that for regions where pregnancy specific reference ranges are not available, a reduction in the maternal TSH levels, lower limit by 0.1–0.2 and upper limit by 0.5–1.0 mU/L, as compared to nonpregnant values should be considered for diagnosis of hypothyroidism. It also mentioned that studies from India and other countries have demonstrated only a modest reduction in the upper reference limit of TSH as compared to non pregnant values.[4]

In Indian context, the controversy of a reference TSH range in pregnancy continues. Marwaha et al in 2008, used 5th and 95th percentiles to determine the reference ranges for TSH. According to them the trimester-specific values in the first, second, and third trimesters of pregnancy were 0.6–5.0, 0.44–5.78, and 0.74–5.7 IU/mL, respectively.[9] In 2018, Kalra et al suggested that the upper limit cut-off TSH value of 4.0 mIU/L as proposed by the revised ATA 2017 criteria was too high for the Indian population. They recommended using a cut-off value of 3.00 mIU/L instead.[10] A systematic review published in the same year and utilizing pooled data from eight Indian studies recommended a cutoff value of 5–6 mIU/L (similar to non-pregnancy values) for all trimesters of pregnancy.[11] They further urged not to use strict criteria of 2.5 mIU/L as cut off during the first trimester of pregnancy.

In the guidelines published by Federation of Obstetric and Gynaecological Societies of India -Indian Thyroid Society (FOGSI-ITS) in 2019, TSH upper reference range of less than 4.0 mIU/L TSH was recommended. The trimester-specific upper limit TSH cut-off values recommended by them were 2.5 mIU/L for the first trimester and 3.0 mIU/L for the second and third trimester.[12] Hence, well-designed local population-based studies are needed to obtain local and trimester-wise TSH reference ranges and to study the overall maternofetal implications of the reference ranges for Indian population.

Total T4- Upper limit increases by 5% per week starting at seven weeks. At sixteen weeks, total T3 and T4 are 1.5 times higher than non-pregnant levels (Non-pregnant range: 5–12 µg/dL).

FT4 levels: Measurement of free T4 in the dialysate or ultrafiltrate of serum samples using liquid chromatography/tandem mass spectrometry is considered most reliable. Due to increase in TBG and decrease in albumin concentrations in the third trimester, measurement of FT4 concentration by automated immunoassays which are used by most of the laboratories provide lower values of measured serum FT4 concentrations. Population-based, trimester-specific reference ranges if available can overcome this issue. Where unavailable or when there is a question of their reliability, total T4 may be used in place of FT4.

Thyroid Hormone Testing During Pregnancy[13]

TSH: It is the most reliable indicator of thyroid status. Hence it is the first-line screening tool to assess thyroid disorders in pregnancy.

T4: Where TSH levels are greatly reduced or increased, FT4 levels should be done. In cases of hyperthyroidism and women on anti-thyroid drugs, drug titration is based on FT4 levels measurement. Accurate estimation of the FT4 concentrations can also be done by calculating a FT4 index.

T3: In cases of suspected hyperthyroidism total T3 is also measured (used preferentially over FT3). With T3 thyrotoxicosis, total T3 should be measured.

Thyroid autoantibodies: Anti-thyroid peroxidase (TPO) and thyroglobulin autoantibodies may be seen in 20% of the females of the reproductive age. Most of these women remain euthyroid. In cases of subclinical hypothyroidism (even euthyroid cases) and positive TPO antibodies, there is a high risk of adverse pregnancy outcomes in terms of pregnancy loss and preterm delivery.

According to the ATA, routine testing for TPO antibodies in euthyroid women is not recommended

as thyroid hormone replacement for anti-thyroid peroxidase antibodies in these women does not improve pregnancy outcomes.[4] In contrast to the ATA guidelines FOGSI-ITS recommends measurement of TPO antibodies in all pregnant women at least once.[12]

Diagnosis of Hypothyroidism in Pregnancy

The symptoms of hypothyroidism during pregnancy may overlap with the normal physiological complaints during this period such as fatigue, constipation, weight gain, muscle cramps, edema, dry skin, and hair loss. Additionally, there may be cold intolerance and findings of the prolonged relaxed phase of deep tendon reflexes.

Primary hypothyroidism is diagnosed by the presence of raised TSH levels during pregnancy. Overt hypothyroidism is defined as an elevated serum TSH with decreased FT4 levels. Subclinical hypothyroidism is the presence of elevated TSH with normal FT4 levels.

Maternofoetal and Neonatal Effects of Hypothyroidism in Pregnancy

Untreated maternal hypothyroidism is considered to promote miscarriages, recurrent pregnancy loss, anaemia, pregnancy-induced hypertension, gestational diabetes, abruption, postpartum, haemorrhage, increased caesarean rates (due to fetal distress), myopathy, and in severe cases congestive heart failure in the mothers. Subclinical hypothyroidism is a risk factor for placental abruption (three-fold rise) and preterm delivery (two-fold rise). Adverse fetal outcomes due to hypothyroidism may include low birth weight, cognitive impairment, developmental abnormalities, and congenital hypothyroidism. Neonates may develop hyperbilirubinemia and respiratory distress.[15]

Screening of Asymptomatic Pregnant Women for Hypothyroidism

The role of 'universal' screening of symptomatic pregnant women during the first trimester is controversial. India falls under a relative iodine sufficient belt, however, iodine deficiency is still prevalent in the foothills and hilly areas. A high incidence of iron deficiency anaemia in the country also promotes hypothyroidism. Autoimmune thyroiditis contributes to a large number of cases of hypothyroidism in iodine sufficient areas in the country. Universal screening has not been recommended till now in any country due to the paucity of data. However, the recent FOGSI-ITS guidelines recommend that all pregnant women should be screened at the their first antenatal visit by serum TSH levels.[12] The American College of Obstetrics and Gynaecology (ACOG), the Endocrine Society, and the American Association of Clinical Endocrinologists recommend against universal screening for thyroid diseases in pregnancy.[13] They support a 'targeted' approach to screening for hypothyroidism for pregnant women at high risk for overt hypothyroidism. These include women residing in an iodine-deficient belt, symptomatic women, women with a positive family history of thyroid disease, and a positive personal history (pre-existing thyroid disease, positive TPO antibodies, goitre, age more than thirty years, type 1 diabetes, history of head and neck irradiation, recurrent miscarriage/preterm delivery, class 3 obesity, history of infertility, prior thyroid surgery, lithium/amiodarone/recent iodinated radiological contrast intake and hypothyroidism in prior pregnancies). However, one-third of women with subclinical or overt hypothyroidism may be missed using the targeted approach. The ATA neither supports nor negates the approach of universal screening.[4]

Treatment of Hypothyroidism in Pregnancy

The MOHFW-GOI Guidelines (2014) Recommendations

- If TSH levels are <2.5 mIU/L in the first trimester and <3 mIU/L in the second and third trimester, no further management is required.
- If TSH levels are between 2.5/3 to 10 mIU/L, 25 mcg of levothyroxine should be started per day. No treatment is needed after delivery.
- If TSH levels are >10 mIU/L, treatment is started with levothyroxine 50 mcg per day. The recommended dose is continued post-delivery.
- If the woman is already on levothyroxine (pre-existing illness) treatment is planned as per similar targets. Post-delivery treatment is continued with pre-pregnancy dosages. A repeat TSH is advised after six weeks of delivery for guiding further treatment.
- TSH is repeated 6 weekly and dosages of

levothyroxine should be adjusted accordingly in multiples of 25 mcg/day. At all times TSH is never allowed to reach below 0.1 mIU/L.[8]

ATA and the American Association of Clinical Endocrinologists recommend T4 replacement therapy starting with levothyroxine dosages of 1–2 mcg/kg daily or approximately 100 mcg daily for overt hypothyroidism. Higher dosage may be required in women without thyroid function (post-surgery or thyroid radioablation). T3 preparations are avoided during pregnancy as these lead to very high levels of maternal T3 and very low levels of T4 (T3 doesn't cross placenta). Therapy is guided using TSH levels done every 4-6 weeks to maintain a goal of TSH between the normal pregnancy range (lower limit of the reference range and 2.5 mIU/L). In women with pre-existing hypothyroidism, an increase in demand of up to 25% of the existing dose may be anticipated.[4]

The FOGSI-ITS 2019 Recommendations

Overt hypothyroidism during pregnancy- Treatment includes administration of levothyroxine in dosages of 1.6-2.0 mcg/kg/day maintaining target levels of ≤ 2.5mIU/L. It recommends increasing the dose of levothyroxine by 30% as soon as pregnancy is diagnosed in cases of pre-existing hypothyroidism. Further dose titration should be done by TSH level measurement every 4 to 6 weeks until mid-pregnancy and at least once near twenty-eight weeks of gestation.

Women who are TPO antibody positive and euthyroid in early pregnancy are at risk of developing hypothyroidism and TSH estimation should be done for them at least once and in every trimester at least up to the second trimester. In these women (euthyroid with positive TPO antibodies) with a positive history of pregnancy loss, levothyroxine therapy can be started.[12]

Subclinical hypothyroidism- For the management of subclinical hypothyroidism 50-100 mcg levothyroxine is started based on TSH levels. Levothyroxine is recommended with TSH levels of >10 mIU/L or with TSH between 4 to 10 mIU/L with positive TPO antibodies. Levothyroxine can be considered in TPO antibodies negative women with TSH in the range of 4 to 10 mIU/L or TPO antibodies positive women with TSH in the range of 2.5 to 4 mIU/L.[12]

Post-partum

For post-partum women with the pre-existing disorder, the FOGSI-ITS recommends that dosage should be revised to pre-pregnancy levels. A repeat TSH at 6 weeks post-partum is warranted. In newly diagnosed hypothyroidism levothyroxine may be discontinued especially with dosages of ≤50 mcg/day. In these cases of levothyroxine discontinuation, TSH levels should be evaluated at 6 weeks. With positive TPO antibodies, annual monitoring with TSH is recommended post-delivery.[12]

Conclusion

An optimal thyroid hormone balance is necessary for fetomaternal well-being. Maternal thyroid hormones play an important role in fetal growth and development. This is especially true before twelve weeks of gestation when the fetal thyroid gland is functionally immature. However, a full-fledged fetal thyroid gland functionality is achieved only after eighteen to twenty weeks of gestation.

Hypothyroidism is a condition of high levels of serum TSH and low levels of circulating maternal thyroid hormones with/without positive TPO antibodies. As of now, no standardized upper limit cut-off range for pregnant TSH values exists for Indian women. Numerous studies and guidelines have given various trimester-specific reference ranges. Hence, the definition of hypothyroidism will vary according to the respective guideline preferred by a pregnant woman's treating obstetrician.

In general, levothyroxine should be started for overt hypothyroid pregnant women in dosage of 1 to 2.0 mcg/kg/day while maintaining a TSH level greater than 0.1 mIU/L at all times. A higher incremental dose of 25-30% may be required for women with pre-pregnancy hypothyroidism. Women with subclinical hypothyroidism may be started on levothyroxine based on their TSH values and TPO antibody status. Therapy is guided by TSH value estimation every four to six weeks in all women.

Women with pre-pregnancy hypothyroidism will require continuation of pre-pregnancy dosages post-delivery. In those with new-onset hypothyroidism, levothyroxine therapy may be continued or discontinued depending upon the last levothyroxine dose strength received. A repeat TSH is required after six weeks post-partum and annually if the woman is TPO antibody positive.

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Hyperthyroidism in Pregnancy: Optimizing Feto-maternal Outcome

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Introduction

Hyperthyroidism, a condition characterized by low levels of serum thyroid-stimulating hormone (TSH), is an important cause of adverse maternal and fetal outcomes during pregnancy. It is seen in 0.2-0.7% of all pregnancies.[1,2] The majority (95%) of hyperthyroidism cases are accounted by autoimmune Graves' disease. Hyperthyroidism may be subclinical or overt. Overt hyperthyroidism is defined as suppressed (<0.1 mIU/L) or undetectable (<0.01 mIU/L) levels of serum TSH values in the presence of an elevated thyroid hormone level which is well above the pregnancy-related cutoffs.

The causes of hyperthyroidism during pregnancy can be broadly classified into two categories: Intrinsic thyroid diseases (toxic adenoma, subacute thyroiditis, iatrogenic) and Gestational thyrotoxicosis (hyperemesis gravidarum, multiple pregnancies, hydatiform mole). Autoimmune thyroiditis complicates 10% of all pregnancies and can present as the hyperthyroid phase of Hashimoto's thyroiditis or silent thyroiditis.

Gestational transient thyrotoxicosis/Physiological hyperthyroidism is a non-immune thyroid disorder seen in the late first or mid-trimester with hyperemesis and molar pregnancy secondary to raised hCG levels. Classic symptoms of hyperthyroidism are absent or minimal, except for weight loss. It can be differentiated from Graves' disease by the absence of diffuse goitre and absent serum TSH receptor (TR) antibodies. It is not reported to be associated with poor pregnancy outcomes. The American College of Obstetrics and Gynecology (ACOG) does not recommend the measurement of thyroid function and treatment of these women unless they show signs of overt hyperthyroidism.[3]

Effect of Hyperthyroidism on Pregnancy

Maternal hyperthyroidism is a risk factor for toxemia, preterm delivery, abruption, congestive cardiac failure, anemia, infection, and thyroid crisis. It is a risk factor for small for dates fetuses, intrauterine growth retardation/IUGR, intrauterine fetal demise, low birth weight infants, and prematurity.[4-7] The fetal risk is raised to two-fold in well-controlled maternal hyperthyroidism as compared to nine-fold in uncontrolled hyperthyroidism.

Effect of Pregnancy on Graves's Disease

In women with Graves' disease, symptoms of hyperthyroidism may exacerbate during the first trimester. Disease severity usually reduces during the second half of pregnancy only to finally exacerbate post-partum.

Screening for Hyperthyroidism During Pregnancy

Universal screening for hyperthyroidism during pregnancy is not recommended. Symptomatic women, those with diabetes mellitus or with a family history of thyroid disorder and diabetes should undergo screening. Women with goiter and thyroid nodules should also be screened.

Routine screening of all women for post-partum thyroiditis is also not recommended. Women with Type 1 diabetes, positive first-trimester thyroid peroxidase (TPO) antibodies test, or postpartum depression should undergo serum TSH evaluation at 3 and 6 months post-delivery.

Diagnosis of Hyperthyroidism in Pregnancy

Clinical diagnosis of Graves' disease in pregnancy is difficult as the symptoms may be confounded by normal physiological pregnancy changes. Findings of insomnia, shortness of breath, heat intolerance, elevated pulse rate, and decreased exercise tolerance may be normally seen during pregnancy. In addition to these palpitations, nervousness, tremors, frequent stools, excessive sweating, weight loss, neck swelling, and raised blood pressure may also be seen. Ophthalmopathy (lid lag, lid retraction) and dermopathy (pretibial myxedema) may also be noted along with a goiter.

In established cases of Graves' disease planning pregnancy, the risk of anticipated maternofetal morbidity and mortality should be explained along with the teratogenic potential of certain anti-thyroid drugs.

Laboratory Tests for Diagnosing Hyperthyroidism During Pregnancy

- TSH: TSH is the most reliable indicator of thyroid status in a pregnant woman.
- T3, T4: When the TSH levels are abnormally low, measurement of FT4 levels is necessary. Total T3 measurement is also done (preferable to FT3) in all cases of hyperthyroidism and especially in cases suspected of T3 thyrotoxicosis. Monitoring of pregnant women on thioamides for hyperthyroidism is done using FT4 levels.
- TR antibodies and thyroid-stimulating immunoglobulins: Routine testing is not recommended in absence of strong evidence. However, identification of these antibodies may result in increased antenatal fetal surveillance.[3]

Diagnosis of hyperthyroidism is usually made using Free thyroxine (FT4) estimation or FT4 Index. A suppressed TSH level with raised FT4 level is pathognomic of hyperthyroidism. In 15% of normal pregnancies, TSH levels may be suppressed during the first trimester, which later returns to the normal range gradually. In yet another normal variant, serum FT4 may be in the upper normal or slightly elevated range. However, FT3 levels remain grossly normal in such cases. *TPO antibodies and thyroid anti microsomal antibodies* may also remain elevated in Graves' disease. Most women with Graves' disease will have detectable *TR antibodies*. Raised TR antibodies and the presence of diffuse goiter are characteristic of Graves' disease.

General Management Options for Overt Hyperthyroidism During Pregnancy

Antithyroid drugs: Thioamides (propylthiouracil, methimazole, carbimazole) are the drug of choice. They block the iodination of tyrosine and prevent thyroid hormone production. Since the release function of the hormone is unaffected the effect of the drug is appreciated only when the existing thyroid colloid stores are depleted. Usually, the effect starts to appear within one week and it becomes fully evident by 4-6 weeks of starting therapy.

The choice of thioamides depends upon the period of gestation and the type of thyrotoxicosis (predominantly T3 or T4). Methimazole may be associated with cutis aplasia, choanal atresia, gastrointestinal and facial abnormalities in fetuses when used during the first trimester.[8] Propylthiouracil is the preferred drug in the first trimester. Treatment is immediately started with propylthiouracil on reaching a diagnosis of hyperthyroidism. In case of allergy or intolerance to propylthiouracil, carbimazole/methimazole may be given. It should be switched to methimazole or carbimazole at the beginning of the second trimester. Since propylthiouracil blocks the conversion of T4 to T3, it is predominantly used in T3 thyrotoxicosis. Thioamides should be started at the lowest possible dosages and guided by maternal T4 levels (which should be kept in high normal levels).

The ACOG recommends using either of the drugs (methimazole or propylthiouracil) after the first trimester. It reports a rare association of hepatotoxicity with propylthiouracil. A period of transition from propylthiouracil to methimazole may lead to poor thyroid control. Hence it recommends that both these medicines must be used after weighing their adverse effects against each other. The decision regarding drug transition should involve endocrinologists or maternal-fetal medicine specialists. A dose ratio of 20:1 propylthiouracil to methimazole is recommended when switching the drugs.[3]

Monitoring of treatment is done by assessment of maternal pulse, weight gain, thyroid size, and measurements of total T4 or FT4 and TSH (recommended therapeutic target levels for total T4 12-18 µg/dL, fT4 2-2.5 ng/dL, and TSH 0.1-0.4 mIU/L). In cases of thyrotoxicosis, the dosage of propylthiouracil should be slowly reduced to the lowest possible dose. During treatment, fetal hypothyroidism should be ruled out by examining the fetal growth pace and heart rate patterns.

Post-partum use of antithyroid drugs can be continued in breastfeeding mothers. Antithyroid drugs may be stopped if the patient was receiving lower dosages during pregnancy (methimazole <5–10 mg/day or propylthiouracil <100– 200 mg/day). Maternal and fetal thyroid status should be monitored every 1-2 weeks in these women.

Beta-blockers: These inhibit the conversion of T4 to T3 and can be used as an adjunct to antithyroid drugs for tachycardia, palpitation, and tremors. Long-term use is discouraged due to its adverse fetal effects.

Iodide: Low doses may be used but it may lead to fetal goitre.

Surgery: Subtotal or total thyroidectomy may be done in the second trimester when antithyroid drugs fail to bring clinical response (propylthiouracil used up to 300 mg or 40/mg per day of methimazole or carbimazole).

Radioactive iodine: ^{131}I use is contraindicated in pregnancy due to its teratogenicity. Patients are counselled not to conceive for at least three months (up to twelve months) of stopping the therapy. Inadvertent administration of radionuclide during the organogenesis period may lead to fetal hypothyroidism in 3% of fetuses. When used after twelve weeks of gestation, it can cause fetal thyroid ablation which requires intrauterine and thereafter lifelong thyroid hormone replacement.

Management of Graves' Disease During Pregnancy

a. Pre-existing active Graves' disease: Continue with anti-thyroid drugs. TR antibody titers can estimate the risk of fetal hyperthyroidism. Titres should be done in the third trimester (when the disease is in the remission phase) preferably by bioassay to establish the receptor stimulating nature of the antibodies.
b. Newly diagnosed Graves' disease: Start treatment as soon as a diagnosis is made.
c. Early pregnancy relapse with a history of Graves' disease: Remember to differentiate it from the normal physiological rise of serum T4 levels during the first trimester. Restart medications.
d. History of prior surgery or radioiodine treatment (ablative procedures): Reassess TR antibodies status at the start of pregnancy and then at 18-22 weeks of gestation if found elevated. Since maternal TSH and T4 levels remain normal on levothyroxine replacement therapy, TR antibody estimation is the only way to determine fetal hypo/hyperthyroidism. In the presence of TR antibody in the mother, the foetus is at risk of hyperthyroidism despite the mother being euthyroid. If fetal tachycardia is found add propylthiouracil to levothyroxine replacement. Propylthiouracil controls fetal hyperthyroidism.
e. Women with Graves' disease whether they required or not required antenatal anti-thyroid therapy or who underwent ablative procedures before pregnancy may have circulating antibodies in their neonates who are at risk of neonatal Graves's disease. The pediatrician must be informed beforehand about maternal Graves' disease so that the neonate can be followed accordingly.[9]

Management of Subclinical Hyperthyroidism

Subclinical hyperthyroidism complicates 1.7% of all pregnancies and is characterized by an elevated serum FT4 in the presence of low TSH levels. Treatment of subclinical hyperthyroidism is not required since it is not associated with adverse maternofoetal outcomes.

Management of Thyroid Storm and Thyrotoxic Heart Failure During Pregnancy

These are acute life-threatening emergencies. A thyroid storm is a condition of hypermetabolism

Table 1: Drugs, Dosing Schedule, and Adverse Effects

Drugs	Dosage	Side effects
Antithyroid drugs-Thioamides The goal of treatment is maintaining FT4 levels slightly above or in the high-normal range with the lowest possible dose.	Propylthiouracil- 100-200 mg three times a day (average 200-400/day) Methimazole- 5-30 mg is divided into two doses initially. Later once a day dosage on maintenance. Carbimazole- 15 mg in divided doses	Purpuric rash, drug fever, nausea (2%). Transient leucopenia (10%) Agranulocytosis (1%)- Serial leucocyte count is not recommended due to acute onset. In case the patient develops a fever, sore throat they are immediately asked to stop the drug and report back with a leucocyte count. Agranulocytosis is not related to drug strength
Beta-blockers	Propranolol- 10-40 mg orally twice/ thrice a day Atenolol-50-100 mg/day	Small placenta, FGR, neonatal respiratory distress, neonatal hypothermia, hypoglycaemia, and bradycardia
Iodide	Low dose potassium iodide 6-40 mg/day	Fetal goitre

characterized by severe thyrotoxicosis and systemic failure presenting as fever, tachycardia, cardiac dysrhythmia, and central nervous system dysfunction. Diagnostic scoring by Burch-Wartofsky Point Scale is widely available.

Thyrotoxic heart failure results from myocardial effects of T4 hormones in women with uncontrolled hyperthyroidism and it is characterized by reversible cardiomyopathy, pulmonary hypertension, and heart failure. It may be incited by preeclampsia, anemia, or sepsis. It is seen in 9% of women with uncontrolled hyperthyroidism (more common than thyroid storm).

On the first suspicion of thyroid storm or thyrotoxic heart failure, an urgent serum TSH, FT4, and total T3 level estimation should be done. Treatment is initiated immediately in an intensive care unit. The incipient cause should also be treated side by side. Delivery is not planned until the storm settles.

Management includes the use of agents inhibiting thyroid release of T3 or T4 (high dosage of propylthiouracil with iodine administration in form of sodium iodide/potassium iodide/Lugols solution or Lithium carbonate in cases of iodine allergy), blocking the peripheral conversion of T4 to T3 (dexamethasone or hydrocortisone), beta-blockers (propranolol, labetalol, esmolol should be used with caution in heart failure) and supportive measures (temperature control).

Fetal Thyroid Function and Fetal Hyperthyroidism

The fetal thyroid gland attains functional maturity by 12 weeks of gestation however it reaches its full potential only after 20 weeks of gestation. The fetal thyroid is stimulated by its pituitary TSH levels under the placental-thyrotropin releasing hormone action. Maternal TSH cannot cross the fetoplacental barrier however T4 can. Methimazole and propylthiouracil can cross the fetoplacental barrier and are useful in the treatment of maternal as well as fetal hyperthyroidism.

Immune-mediated fetal hypo/hyperthyroidism may be caused by the transplacental passage of maternal thyroid immunoglobulins. Mothers with Graves' disease can have *thyroid-stimulating immunoglobulin* and *TSH-binding inhibitory immunoglobulins* (or *thyrotropin-binding inhibitory immunoglobulins*) that may stimulate or inhibit the fetal thyroid, respectively. 1-5% of cases of neonates born to women with Graves' disease (with circulating TSH-binding inhibitory immunoglobulins) develop fetal hyperthyroidism or neonatal Graves' disease. Development of neonatal Graves' disease in some neonates may be delayed when their mothers were on thioamides therapy during the antenatal period because of delayed clearance of maternal immunoglobulins than the thioamides from the neonatal blood. Some of these neonates may have a transient rise in TSH levels (hypothyroidism).

Fetal hyperthyroidism typically presents as IUGR and fetal tachycardia. It may be associated with craniosynostosis, premature skeletal maturation, cardiac failure, hydrops, and fetal goiter. Fetal hyperthyroidism in maternal Graves' disease becomes more pronounced at the end of the second trimester. Maternal thyroid-stimulating immunoglobulin levels of ≥35% and TSH receptor binding inhibitory immunoglobulin levels of ≥40% are associated with fetal thyrotoxicosis.[10] The role of cordocentesis in establishing a diagnosis of fetal hyperthyroidism in presence of maternal active/treated Graves' disease and fetal tachycardia is controversial. In cases where the mother was on anti-thyroid drugs and antenatal fetal evaluation was not suggestive of fetal thyroid disorder but the neonate is born with a goiter, umbilical cord blood sampling should be considered to diagnose neonatal hypo/hyperthyroidism.

Treatment for fetal hyperthyroidism is by maternal propylthiouracil in dosage of 100-400 mg/day or methimazole 10-20 mg/day. The foetus is followed up by clinical improvement in heart rate and resolution of goitre by ultrasound planned after two weeks of starting treatment. Further dose adjustments are done accordingly. Propylthiouracil and methimazole doses should be reduced at the first hint of normal fetal heart tracings. Close fetal monitoring is required to maintain fetal heart rate in the normal range.

In mothers with no thyroid hormone production after ablative procedures for hyperthyroidism and who are on levothyroxine replacement, fetal hyperthyroidism may develop. This will require antithyroid drug administration to the mother in addition to levothyroxine replacement. In these cases, if the foetus develops hypothyroidism after antithyroid drug administration, maternal levothyroxine dose should be increased accordingly. Hence it is very clear that a very close fetal monitoring and drug titration is required in such women.[10]

Postpartum Thyroiditis

It is characterized by clinical evidence of hypothyroidism or hyperthyroidism or both post-delivery. Postpartum thyroiditis also occurs in up to 10% of all pregnancies. It is seen between 6 weeks to 6 months (or twelve months in certain cases) after delivery or within 6 weeks of miscarriage. The hyperthyroid phase of thyroiditis in this disease is often followed by a hypothyroid phase which may be permanent in up to 1/3rd of cases (especially in women with high antibody titers) with an annual progression rate of 3.6%.[8]

The higher the levels of thyroid antibodies (even before conception), the more is the risk of developing postpartum thyroiditis. The thyrotoxic phase is self-limiting and mildly symptomatic usually not requiring treatment. Antithyroid medications are ineffective. Beta-blockers may be used in cases of severe symptoms.

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Pregnancy Outcome in Women with Cardiac Diseases: Experience at Tertiary Care Centre

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Abstract

Background: Multiple cardiovascular, hematological, and metabolic adaptations occur during pregnancy. A preexisting cardiac lesion can worsen the already burdened hypervolemic cardiovascular system of a pregnant woman. Such women are at increased risk for cardiac decompensation and failure. Literature on characteristics of cardiac diseases in pregnancy in developing nations is scarce. This study was conducted to assess the prevalence and outcomes of cardiac diseases in Indian pregnant women.

Methodology: This retrospective observational study was conducted over a period of one year at a tertiary care center in Northern India. Medical records of women with cardiac disease delivered at the institute were retrospectively studied. Prevalence rates, clinical characteristics, and maternofetal outcomes of women with cardiac diseases were noted.

Results: Out of a total of 28,564 deliveries at the institute during one-year duration, 146 women were diagnosed with cardiac disease. The majority of these women were in the 25-20 years age group (52.73%), unbooked (84.93%), primigravida (65.06%), had a normal range body mass index (>75%) and were educated till grade eight (53.42%). Rheumatic heart disease (RHD) was reported as the most common cardiac disease (69.86%) followed by congenital heart disease (CHD) (15.06%), cardiomyopathies (13.01%), and aortoarteritis (2.05%). Mitral valve was the most common valve involved (>65.47%) in women with RHD. Two women (1.36%) with RHD developed infective endocarditis. Among CHDs, uncorrected CHD was the most common (10.27%). It was also inclusive of three cases of Eisenmenger syndrome. Cardiac failure, arrhythmia, and pulmonary artery hypertension were the major cardiac complications that were observed in the study. Majority of women (54.79%) were delivered by cesarean section. The observed maternal mortality rate was 12.32%. The neonatal mortality and stillbirth rates were 3.42% and 9.58%, respectively.

Conclusion: Rheumatic heart disease accounts for majority of the women with cardiac diseases in pregnancy. Cardiac failure, arrhythmia, thromboembolic events, pulmonary artery hypertension, pregnancy-induced hypertension, gestational diabetes, and postpartum hemorrhage are important causes of maternal morbidity in these women.

Introduction

An increase in the prevalence rate of cardiovascular disease during pregnancy has been reported in recent years throughout the world. Advancing maternal age, obesity, rising rates of essential hypertension, and diabetes have reportedly led to this rise. The overall reported prevalence rate of cardiac disease during pregnancy is between 0.3 to 3.5%.[1]. After hypertensive disorders of pregnancy (prevalence rate 5-10%), congenital heart disease/ CHD (75-82% of all cardiovascular diseases)) is the most common cardiovascular disease encountered during pregnancy in the western world and rheumatic heart disease/RHD (56-89%) in the developing world.[2] Cardiomyopathies comprise yet another severe form of cardiovascular disease in pregnancy with a reported incidence rate of 1 per 3000 to 1 per 4000 live births and a mortality rate of 18 to 56%.[3]

Pregnancy is a state of increased physiological stress characterized by an increase in cardiac output, plasma volume, heart rate, increased atrial and ventricular diameters, hypercoagulability, and atherogenesis. Physiological changes in the hepatobiliary and renal systems, further predispose to altered pharmacokinetics of numerous cardiac drugs. In a woman with cardiac disease, the ventricular adaptions to pregnancy are not optimal and the woman is at the risk of sudden cardiac decompensation and heart failure. Furthermore, these women are at risk for preterm labor, preeclampsia, postpartum hemorrhage, fetal growth retardation, stillbirths, and neonate loss. A rising trend in maternal mortality is being witnessed

in these groups of women in the western world. However, the data from the developing world on the characteristics of cardiac disease in pregnancy is still not robust. This study was hence conducted to determine prevalence rates, risk factors, and fetomaternal outcomes of cardiac diseases in Indian pregnant women.

Material and Methods

This retrospective observational study was conducted at a tertiary care center located in Northern India over one year duration. Medical case records of women with cardiac disease delivered at the institute were retrieved. Women's age, Body mass index (BMI), parity, period of gestation at the first antenatal visit, the total number of antenatal visits, presenting complaints, gestational age, and mode of delivery were noted. The prevalence rates of acquired and congenital cardiac diseases were calculated. Maternal outcomes which were noted were maternal mortality (primary outcome), presence of preeclampsia, preexisting hypertension, gestational diabetes, mode of delivery, postpartum hemorrhage, obstetric critical care unit/CCU admission, duration of CCU, and in-patient hospital stay (secondary outcomes). Neonatal outcomes which were noted were neonatal mortality (primary outcome), prematurity, low birth weight, fetal growth restriction, and neonatal intensive care unit (NICU) admission (secondary outcomes).

The data were tabulated in an excel sheet and analyzed using Statistical Package for the Social Sciences version 20.0.

Results

There were a total of 28,564 deliveries during the study period. A total of 146 women were diagnosed with cardiac disease (0.51% of total deliveries). 95 women (65.06%) of those with cardiac disease first presented to the institute in their third trimesters (>28-weeks of gestation). 80 women (54.79%) with cardiac disease belonged to New York Heart Association (NYHA) functional Class I, 29 women (19.86%) to NYHA class II, and 37 women (25.34%) to NYHA class III or IV. Most (n=77; 52.73%) of the women with cardiac disease belonged to the age group of 25-30 years and were unbooked (n=124; 84.93%). A majority of them were nulliparous (n=95; 65.06%), had their BMI in the normal range (n=111; 76.02%) and were educated till eighth grade (n=78; 53.42%), Table 1.

Table 1: Clinical profile of women with cardiac disease

Age	**n (% of women with cardiac disease)**
20-25 years	77 (52.73%)
25-30 years	40 (27.39%)
30-35 year s	21 (14.38%)
>35 years	8 (5.49%)
Booking status at the institute	
Booked	12 (8.21%)
Unbooked	124 (84.93%)
Registered	10 (6.84%)
Parity	
P0	95 (65.06%)
P1	35 (23.97%)
≥P2	16 (10.95%)
Body mass index (Kg/m²)	
<18.5	48 (32.87%)
18.5-24.9	64 (43.83%)
25.0-29.0	30 (20.54%)
≥30.0	4 (2.73%)
Education level	
Illiterate	12 (8.21%)
Primary school passed	35 (23.97%)
Eighth grade passed	78 (53.42%)
High school passed	12 (8.21%)
Intermediate grade passed	9 (6.16%)

RHD was the most common (n=102; 69.86% of all cardiac disease; 0.35% of all deliveries) cardiac disease in the study. This was followed by CHD (n= 22; 15.06% of all cardiac disease; 0.07% of all deliveries). Three women (2.05% of all cardiac disease) presented with aortoarteritis and severe hypertension. One among them went into left ventricular failure. 19 women (13.01%) presented with cardiomyopathy, Table 2.

Among women with RHD, combined mitral stenosis (MS) + mitral regurgitation (MR) (n=54; 36.98% of cardiac disease) was the most common valvular involvement followed by MS alone (n=42; 28.76%), combined MR + tricuspid regurgitation (TR) (n=4;2.73%) and MR + aortic regurgitation (AR) (n=2; 1.36%). 18 women (12.32%) with RHD had single valve replacement (mitral valve) and 3 (2.05%) women had double valve replacement (mitral valve + aortic valve). 2 women (1.36%) with RHD presented with infective endocarditis, Table 2.

Out of the 22 women with CHD, 7 women (4.7%) had corrected lesions. While the rest 15 (10.27%) had uncorrected CHD. Three women (2.05%) with CHD presented with Eisenmenger syndrome (all three of them had uncorrected CHD), Table 2.

40 women (27.39%) delivered before term. While

Table 2: Prevalence rate and types of cardiac diseases in the study population

Prevalence rate of cardiac disease	51.11 cases/ 10,000 deliveries (0.51%)
NYHA grades at initial presentation (n, %)	
Grade I Grade II Grade III Grade IV	80 (54.79%) 29 (19.86%) 25 (17.12%) 12 (8.21%)
RHD (n, %); MS+MR MS MR+TR MR+AR Infective endocarditis	102 (69.86%) 54 (36.98%) 42 (28.76%) 4 (2.73%) 2 (1.36%) 2 (1.36%)
CHD (n, %) Corrected CHD Uncorrected CHD	22 (15.06%) 7 (4.7%) 15 (10.27%); 3 among these were Eisenmenger syndrome with pulmonary artery hypertension requiring cesarean delivery.
Aortoarteritis (n,%)	3 (2.05%)
Cardiomyopathy (n,%)	19 (13.01%)

27 women (18.49%) developed pregnancy-induced hypertension, 21 (14.38%) had preexisting hypertension. Postpartum hemorrhage was seen in 32 women (21.91%).

80 women (54.79%) with cardiac disease underwent cesarean section. The rest 66 (45.2%) underwent vaginal delivery. Instrumental vaginal delivery was done in 32 women (21.91%) women. The majority (n=138; 4.52%) of cesarean sections were done for obstetrics indications. All women with NYHA grading class ≥3 underwent cesarean delivery, Table 3.

32 women (21.91%) required obstetric CCU admission. The average duration of stay in CCU was 96±15 hours. The duration of total inpatient hospital stay in women with cardiac disease was on average 14±3days, Table 3.

27 women (18.49%) underwent cardiac failure, 6 women (4.10%) developed an arrhythmia, and 5 women (3.4%) pulmonary artery hypertension. The observed mortality rate was 12.32% (n=18). 83.33% (n=15) of the women who succumbed to cardiac disease were unbooked. Causes of death were attributed to cardiogenic shock (n=10;55.55% of total mortality), arrhythmia (n=3), thromboembolic events (n=2), and septic shock (n=3).

The average birth weight in women with cardiac disease was 2205±264 grams. 52 women (35.61%) delivered newborns with low birth weight. 45 women (30.82%) delivered growth retarded babies. The mean Apgar score at 1 minute was 6.45±2.42 and 5 minutes was 8.03±1.83. 27 (18.49%) neonates required NICU admission. A total of 15 (9.58%) intrauterine deaths and 5 (3.42%) neonatal deaths were reported. The most common cause of neonatal mortality was prematurity followed by birth asphyxia, Table 3.

Table 3: Maternal and fetal outcomes of cardiac diseases in pregnancy

Maternal outcomes	**n(%)**
Preterm delivery	40 (27.39%)
Pregnancy induced hypertension	27 (18.49%)
Postpartum hemorrhage	32 (21.91%)
Gestational diabetes	26 (17.80%)
Mode of delivery Cesarean delivery Vaginal delivery Instrumental vaginal delivery	80 (54.79%) 66 (45.2%) 32 (21.91%)
CCU stay (mean±SD) Average duration of CCU stay	32 (21.91%) 96±15 hours
Length of total stay in hospital	14±3days
Cardiac failure	27 (18.49%)
Arrhythmia	6 (4.10%)
Pulmonary artery hypertension	5 (3.4%)
Mortality rate	18 (12.32%)
Fetal outcomes	
Low birth weight	52 (35.61%)
Fetal growth restriction	45 (30.82%)
NICU admission	27 (18.49%)
Intrauterine death	15 (9.58%)
Neonatal mortality rates	5 (3.42%)

Discussion

Women with cardiac disease are at an increased risk for clinical deterioration during pregnancy. This study aimed to find out the prevalence rates and maternofetal and neonatal outcomes of cardiac lesions in pregnant women of India.

The reported prevalence rate of cardiac disease in pregnancy varies between 0.3 to 3.5%.[1,4] We reported a prevalence rate of 0.51% for cardiac disease in pregnancy in our study. This was well under the above-reported range.

The incidence of cardiac disease in pregnant women further varies according to the geographical area and socioeconomic strata. In developing countries, the majority (80%) of cardiac diseases are accounted for by RHD, while in the developed world it is the CHD that occupies the top place. Furthermore,

RHD may be encountered for the first time during pregnancy.[5] We reported a prevalence rate of 70% for RHD in our study. Poor hygiene, low socioeconomic status, ignorance, low education level, and delayed presentation to health care facilities are some of the reasons for high prevalence rates of RHD in the Indian pregnant population. In our study, many pregnant women (65.06%) with cardiac disease presented very late in their third trimester. This clearly emphasizes the ignorance towards prenatal checkups and early antenatal bookings in these women.

Mitral valves are the most commonly involved valves in RHD during pregnancy.[5] This was very true in our case, where the majority of women with RHD were found to have combined MR and MS. It is a fact that stenotic valvular lesions are less well tolerated in pregnancy as compared to the regurgitant lesions (provided cardiac function is preserved in the latter group). Aortic stenosis (AS) is rare during pregnancy (usually associated with congenital bicuspid aortic valve) and so is isolated AR (usually associated with MR or bicuspid aortic valves), isolated TR, and isolated Pulmonary regurgitation (PR). An enlarged left atrium with MS/MR/AS increases the risk of left atrial thrombus formation, arrhythmia, and sudden cardiac arrest. We reported one such case of a massively dilated left atrium with mitral regurgitation and left atrial thrombus formation. The patient went into arrhythmia post-cesarean (done for obstetric indications) and had a sudden cardiac arrest.

In recent years, the developing world has also seen a rise in the incidence of pregnancy with CHD. This change is due to advances in medical sciences which have allowed numerous infants (>%85) with CHD to reach adulthood. To note infants of these women with CHD usually possess a higher risk of inheriting CHD (%12-3) as compared to the general population (0.8-1%).[6]

We reported a prevalence rate of 15% for CHD in our study. Such a high prevalence rate of CHD was in line with that reported by Gahlot et al and Pandey et al.[7,8] However, it was a little lower than that reported by Konar et al (21.3%).[1] We also reported three cases of Eisenmenger syndrome (reversal of shunt in septal defects) that roughly comprised 14% of CHD cases in our study. Pandey et al in their study reported an almost similar prevalence rate of Eisenmenger syndrome in their study (10%).[9]

A majority (55%) of women in our study belonged to class I of NYHA functional classification for cardiac disease which was almost similar to that reported by other authors (>50%).[8,10] It is important to realize that almost 20% of pregnant women will develop diastolic dysfunction and dyspnoea on exertion normally which may take almost up to a year after delivery to return to normal.[11,12] However, irrespectively all women presenting with atypical complaints and disproportionate dyspnea during pregnancy should be evaluated for an underlying cardiac disease.

The reported percentage of women with cardiac disease undergoing cesarean delivery in our study was 55% (n=80). This was higher than that reported by previous authors (between 30-45%).[1,7,8,14-16] Such rates could be explained by the fact that, majority of the women had a history of at least one cesarean delivery in the past and did not give consent for trial of labor after cesarean or had poor bishops score. This is concerning considering the rising rates of morbidly adherent placentas in recent years and the grave maternofetal consequences associated with them.

Pregnancy with cardiac disease can be complicated by excess weight gain, preeclampsia, preterm births, fetal growth restriction, hemorrhage, abruption, gestational diabetes, progressive cardiac failure, and maternal death.[4] We noted cardiac failure, arrhythmia, thromboembolic events, pulmonary artery hypertension, pregnancy-induced hypertension, gestational diabetes, and postpartum hemorrhage as important causes of maternal morbidity in our study.

More than a quarter of women with cardiac disease required obstetric CCU admissions in our study. The average duration of CCU stay was 96±15 hours. This was almost similar to that reported by Mohan et al. We also reported a prolonged hospital stay of 14±3days in women with cardiac disease overall. Of note, two women with RHD who were diagnosed with infective endocarditis in our study had a prolonged hospital stay and CCU stay. They required high-spectrum antibiotics for at least three weeks. These findings figure out an increased risk of maternal morbidity in these women. Even the maternal mortality rates are substantially high. We reported a maternal mortality rate of 12.32% in our study. This figure was almost comparable to the rates reported by Mohan et al (12%).[17] However, it was much higher than that reported by other authors (between 1-5%).[1,8,13] This disparity could be secondary to differences in the population characteristics, high rates of unbooked

deliveries, last-minute visits to health facilities, and an overall poor general wellbeing of this group of pregnant women. The reported cause of death in the majority of women in our study was a cardiogenic shock.

The reported live birth rate in our study was approximately 90%. This was almost similar to the live birth rates achieved by Mohan et al. and Patne et al.[10,17] Also the reported neonatal mortality rates of 3.4% and NICU admission rates of 18.4% in our study were comparable to other authors.[8,10,15,17] Of note both the women with infective endocarditis delivered prematurely and had poor fetal outcomes. One of them delivered a still-born baby while the other woman had an early neonatal death. There were no reports of neonatal CHD in our study although the reported neonatal congenital anomalies rate and neonatal death rates in women with CHD have been reported to be 1-4% and 3-50%, respectively.[18] In very similar findings, Konar et al and Mohan et al reported no instance of neonatal CHD in their study.[1,16]

Conclusion

Most of the women with heart disease are not registered until late pregnancy. Pregnancy induced hypertension, gestational diabetes, cardiac failure, arrythmias and postpartum hemorrhage are main causes of maternal morbidity in these women. Maternal mortality, low birth weight babies, fetal growth restriction, NICU admission and intrauterine death rates are high in these women.

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Feto-maternal Outcome in Women with Obstetric Cholestasis

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Abstract

Aim: To study feto-maternal outcome in pregnant women with Obstetric Cholestasis. **Material & Methods:** Cross-sectional study was conducted in Tertiary care Hospital in Delhi. Pregnant women presenting with pruritus and diagnosed as Obstetric Cholestasis after meeting the inclusion/exclusion criteria were included in the study group. Age, parity and gestation matched women were taken as controls. Women were started on medical management and were followed with weekly LFT and Coagulation profile and termination of pregnancy was carried out at 38 weeks or earlier in case of deteriorating LFT (>4-fold rise in titre) or foetal compromise. **Results:** Most of the patients in the study and control groups were in the age group 21-30 years and were primigravida. Pruritus over palms and soles was the main symptom seen in all women diagnosed with obstetric cholestasis. Recurrence of cholestasis was seen in 63.16%. Postpartum haemorrhage was observed in 23.3% (7/30) patients in the study group as compared to 3.3% (1/30) in the control group. Higher incidence of premature delivery (23.3%), fetal distress, meconium staining of amniotic fluid, (46.7%) NICU admission (35%) and stillbirths (3.3%) was seen in the study group as compared to the control group. All women became asymptomatic and LFT became normal 2 weeks after delivery. **Conclusion:** Adverse pregnancy outcome was more common in patients with obstetric cholestasis than in normal antenatal women. Early diagnosis and timely follow up is necessary to prevent adverse perinatal outcome.

Introduction

Obstetric Cholestasis (OC), earlier known as Intrahepatic Cholestasis of Pregnancy (ICP), is the most common liver disorder peculiar to pregnancy. It usually manifests in the third trimester of pregnancy as skin itching and as elevation of serum levels of bile acids and liver enzymes[1,2]. This condition worsens as pregnancy proceeds and resolves completely after delivery[3]. It may recur in 40-60% cases in subsequent pregnancies[1,4].

Obstetric cholestasis has been observed in almost all ethnic groups, but there is relevant geographical variation in its incidence. It is very common in Chile (6%-27%) and in Sweden (1%-1.5%)[2]. In India, figures varying from 1.2% to 9.3% have been reported.[5,6] The cause of obstetric cholestasis is thought to be a combination of genetic, hormonal and environmental factors, although the exact etiology is unknown[7]. Studies have reported poor fetomaternal outcomes in women with obstetric cholestasis. There is significant maternal discomfort related to intense pruritus and consequent sleep deprivation. Increased rates of caesarean section[5,8], risk of maternal coagulopathy[9] and postpartum haemorrhage[10] have also been observed with cholestasis of pregnancy. Major perinatal consequences of this disease are premature delivery (19%-60%)[11], fetal distress (22%-33%)[12], meconium staining of amniotic fluid[5,8] and stillbirths (1%-2%)[13]. The aim of our study was to determine feto-maternal outcome in pregnant women having Obstetric Cholestasis visiting tertiary care hospital.

Material & Methods

Cross sectional study was conducted in the Department of Obstetrics & Gynaecology at a tertiary care hospital. Thirty pregnant women meeting all the inclusion criteria (Pruritus, Serum transaminases raised above 35 IU/L, Gestational age 28-40 weeks and willing to comply with the study protocol were included in the study group. Women with any of the following criteria were excluded Dermatological and/or allergic pruritus, Viral Hepatitis, Cholelithiasis, Preeclampsia/ HELLP Syndrome or Chronic Liver Disease. Thirty age, parity and gestation matched women were taken as controls. All participants underwent a detailed evaluation and complete information regarding history (personal, family, medical) was recorded on a proforma. Women in the study group were started on medical management

(Urosodeoxycholic acid) and were followed with weekly LFT and Coagulation profile and termination of pregnancy was carried out at 38 weeks or earlier in case of deteriorating LFT (>4 fold rise in titre) or foetal compromise. Mode of delivery, pregnancy outcome (normal vaginal delivery or caesarean section), maternal and perinatal outcome and postpartum resolution period were recorded.

The analysis was carried out using SPSS software vr.16. Chi square test/Fisher's exact test was used for qualitative data. The p value of less than 0.05 was considered to be statistically significant.

Results

Majority of the patients in the study and control groups were in the age group 21-30 years and gestational age group of 31^{+0} – 36^{+6} weeks. 67% women in the study group were primigravida. Age and Obstetric profile of both study and control group is shown in Table 1.

Table 1: Age and Obstetric profile of both study and control group

Age (Years)	**Study Group (n=30)**		**Control Group (n=30)**	
	No.	%	No.	%
≤20	1	3.3	1	3.3
21-25	18	60	19	63.4
26-30	10	33.4	9	30
>30	1	3.3	1	3.3
Gravidity				
	No.	%	No.	%
G1 (Primigravida)	20	66.7	19	63.3
≥ G2	10	33.3	11	36.7
Gestational Age at Enrolment (Weeks)				
	No.	%	No.	%
28^{+0} – 30^{+6}	2	6.6	2	6.6
31^{+0} - 33^{+6}	8	26.7	8	26.7
34^{+0} - 36^{+6}	11	36.7	10	33.3
≥37	9	30	10	33.3

Postpartum Haemorrhage was observed in 23.3% (7/30) patients in the study group as compared to 3.3% (1/30) in the control group. There was no maternal mortality in our study. Caesarean section rate in women with obstetric cholestasis in our study was 26.6% (8/30) compared to 6.7% (2/30) in normal pregnant women (Table 2).

Table 2: Comparison of Maternal Outcome in Study and Control Group

PPH	**Study Group (n=30)**		**Control Group (n=30)**	
	No.	%	No.	%
Yes	7	23.3	1	3.3
No	23	76.7	19	96.7
Mode of Delivery				
Normal Vaginal	20	66.7	27	90
Instrumental Vaginal	2	6.7	1	3.3
Caesarean section	8	26.6	2	6.7

The complications like preterm delivery, meconium staining of amniotic fluid, low5 min APGAR and NICU admissions were more commonly seen in study group as compared to those in control group (Table 3).

Table 3: Comparison of Fetal Outcome in Study and Control Groups

Test	**Study Group (n=30)**		**Control Group (n=30)**	
	No.	%	No.	%
Meconium Staining				
Present	14	46.7	4	13.3
Absent	16	53.3	26	88.7
Preterm Delivery				
<37 weeks	7	23.3	2	6.7
>37 weeks	23	76.7	28	93.7
Low 5 min APGAR				
<7	9	30	2	6.7
≥7	21	70	28	93.3
NICU Admission				
Yes	10	33.3	2	6.7
No	20	66.7	26	93.3

Meconium staining of amniotic fluid was seen in 46.7%. In the study group, fetal asphyxia (low 5 min APGAR) was observed in 30% and NICU admissions 33.3% were significantly more (p<0.001) compared to 6.7% in the control group. There was one (3.3%) stillbirth in the study group while none in the control group. The stillbirth occurred in unbooked women who had presented to us late gestation in labor.

Discussion

Obstetric cholestasis, earlier known as Intrahepatic Cholestasis of Pregnancy, is the commonest liver disease that is unique to pregnancy. It was first described by Ahlfeld in 1883 as recurrent jaundice in

pregnancy that resolved following delivery. Pruritus was added to the definition in subsequent case reports in 1950's.[14] In our study pruritus was seen in all women who were diagnosed with obstetric cholestasis. Obstetric cholestasis usually presents in third trimester and frequently recurs in 60-90% of subsequent pregnancies.[15,16] The recurrence rate of pruritus in our study was found to be 63.16% and majority (90%) women presented after 28 weeks.

Studies have shown higher incidence (25-44.5%) of caesarean section has been observed in women with Obstetric cholestasis.[6,12] Ray et al[6] (2005) reported 31.2% (10/32) caesarean section rate. Majority were emergency caesareans being done for fetal distress and meconium stained liquor. In our study also, there were significantly higher number of caesarean section and 80% were done for fetal distress.

Obstetric cholestasis has been associated with increased risk pf are premature delivery (19%-60%)[11], fetal distress (22%-33%)[12], meconium staining of amniotic fluid [5,8,15] and stillbirths (1%-2%).[13] In our study significantly, higher number of adverse fetal outcomes were seen in study group than in control group: preterm deliveries (23.3% vs 6.7%), meconium staining (46.7% vs 13.3%), and NICU admissions (33.3% vs 6.7%). In the study group, there was one stillbirth. No perinatal death occurred in the control group. The women who had still birth was not taking antenatal care and was not on medical management for obstetric cholestasis. Older studies have reported a perinatal mortality rate of 10%-15%[17,18]. This has been reduced to 3.5% or less because most women are delivered by 38 weeks of gestation. A large cohort study was conducted in Australia reported reported a higher incidence of gestational diabetes, preeclampsia and/or spontaneous preterm labour in women with obstetric cholestasis compared to the general population but found no increase in still birth rate in women who were medically managed.[19] Authors have argued that no increase in stillbirth rate was secondary to timely start of medical management. The American College of Obstetricians and Gynaecologists also endorses active management protocols for women with Obstetric Cholestasis.[20]

Conclusion

Obstetric cholestasis usually presents in third trimester of pregnancy with pruritus as a main symptom and has high recurrence rate subsequent pregnancies. Adverse fetal outcome are more common in women with obstetric cholestasis than in normal antenatal women hence early diagnosis and medical management with timely follow up is necessary.

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Events Held in October 2021

S.No.	Date	Event	Time
1	01.10.2021	AOGD Symposium with Elite Club West Delhi "Progesterone in RPL"	3:00 - 5:00 pm
2	01.10.2021	Module-1 "Hyperglycemia in Pregnancy: Preconceptional care and Screening" by Safe Motherhood Subcommittee	5:00 - 7:00 pm
3	02.10.2021	"Conservative Management of Pelvic Organ Prolapse & Urinary Incontinence" by Urogynae Subcommittee	11:00 - 1:00 pm
4	05.10.2021	"PPH Preparedness – Road to Maternal safety" by AOGD	5:00 - 7:00 pm
5	08.10.2021	"Endometriosis and Infertility" by Endometriosis Subcommittee	3:00 - 5:00 pm
6	09.10.2021	Webinar on Theme: "PGT India- A Dream Come True" by Fetal Medicine & Genetics Subcommittee	7:00 - 9:00 pm
7	16.10.2021	"Luteal Phase Defect" by AOGD (Physical Meet)	3:00 - 5:00 pm
8	21.10.2021	"Fertility Preservation Theme" by Adolescent Subcommittee with DGF-SW	5:00 - 7:00 pm
9	21.10.2021	Public Forum by Outreach Subcommittee	4:00 - 5:30 pm
10	22.10.2021	Twins Pregnancy- Are we doubling the trouble? Let's double the joy", with DGF-S	
11	23.10.2021	"Fertility Special CME" by Seeds of Innocence	1:00 onwards
12	28.10.2021	"Tubal Corrective Surgeries; The Use Of Endoscopy" by Endoscopy Subcommittee	6:00 - 8:00 pm
13	28.10.2021	Breast Cancer and Breast Cancer Prevention and Awareness	7:00 - 8:00 pm
14	29.10.2021	AOGD Monthly Clinical Meeting at ESI Hospital	4:00 - 5:00 pm
15	30.10.2021	"Management of Cervical Cancer: Nuances and Changing Perspectives" by Oncology Subcommittee	5:00 - 7:00 pm
16	30.10.2021	"Adolescent PCOS & POI" by IMA Outer West Branch Delhi, in Association with Adolescent health committee	3:00 - 5:00 pm

Events Held in November 2021

S.No.	Date	Event	Time
1	5.11.2021	Module -2 "Hyperglycemia in Pregnancy: Intervention for Glycemic control" by Safe motherhood committee	5:00-7:00 pm
2	11.11.2021	WS on "Progress in Fetal Diagnosis & Therapy- New Concept" by Fetal Med & Genetics subcommittee (Apollo Hospital)	2:00-7:00 pm
3	12.11.2021	WS on "Care Bundle for Stillbirth: Making every baby count" by Safe Motherhood committee (LHMC)	2:00-7:00 pm
4	13.11.2021	Pre Conf WS "E-PICSEP" by AOGD with FOGSI (SJH)	2:00-7:00 pm
5	14.11.2021	Quiz on "Adolescent Health" for Yuva members by AOGD	2:00-7:00 pm
6	14.11.2021	Medico Legal Conference in Obstetrics & Gynaecology " (MAMC & LNJP Hospital)	2:00-7:00 pm
7	15.11.2021	"A TO Z OF Post-Partum Haemorrhage" AOGD Multidisciplinary Subcommittee, (DDUH)	2:00-7:00 pm
8	16.11.2021	"Hyperandrogenism- Evidence Based Methodology", Reproductive Endocrinology Subcommittee (Max Saket)	2:00-7:00 pm
9	17.11.2021	"Dealing with Myomas Endoscopically ", by Endoscopy Committee, Fortis & SGRH	2:00-7:00 pm
10	18.11.2021	"Protocols & Procedures for Cervical Cancer Prevention (Video session)" Oncology Committee & ISCCP (SJH)	2:00-7:00 pm
11	19.11.2021 20.11.2021 21.11.2021	43rd AOGD Annual Conference	10:00-18:00 hrs
12	22.11.2021	WS on "Revisiting Basic Infertility Practices" by Infertility Committee (SJH)	2:00-7:00 pm
13	23.11.2021	"Fighting The Fright: Non Hemorrhagic Maternal Collapse", (UCMS & GTB Hospital)	2:00-7:00 pm
14	24.11.2021	WS on "Episiotomy & Obstetric Anal Sphincter Injury (OASI)" by Urogynae Committee (SGRH)	2:00-7:00 pm
15	25.11.2021	WS on "Safe Abortion Values Evidence and Respect" by QI & Safe Motherhood committee (AIIMS)	2:00-7:00 pm
16	3.12.2021	AOGD Monthly Clinical Meeting at MAMC & LNJP Hospital	4:00-5:00 pm

Events to be Held in December 2021

S.No.	Date	Event	Time
1	02.12.2021	"Tubal Corrective Surgeries; The Use of Endoscopy" by Endoscopy Committee	6:00 - 8:00pm
2	03.12.2021	AOGD Monthly Clinical Meeting at MAMC & LNJP Hospital	4:00 - 5:00 pm
3	20.12.2021	PG Forum "Diabetes in Pregnancy by LHMC and VMMC & Safdarjung Hospital	7:00 - 8:30 pm
4	30.12.2021	"Chronic Pelvic Pain" by AOGD in Association with FEPPA"	5:00 - 7:00 pm
5	07.01.2022	AOGD Monthly Clinical Meeting at Sir Ganga Ram Hospital	4:00 - 5:00 pm

Events Held under the Aegis of AOGD in October 2021

Progesterone in RPL

"Hyperglycemia in Pregnancy:
Preconceptional Care and Screening"

"Conservative Management of Pelvic Organ Prolapse
& Urinary Incontinence"

"PPH Preparedness - Road to Maternal Safety"

"Endometriosis and Infertility"

"PGT India - A Dream Come True"

"Luteal Phase Defect"

"Fertility Preservation Theme"

Online Training on Menstrual Hygeine

Twins Pregnancy- Are We Doubling The Trouble?
Let's Double The Joy"

"Fertility Special CME"

"Tubal Corrective Surgeries; The Use of Endoscopy"

Breast Cancer and Breast Cancer Prevention and Awareness

AOGD Monthly Clinical Meeting at ESI Hospital

"Management of Cervical Cancer: Nuances and Changing Perspectives" by Oncology Committee, 30th October

"Adolescent PCOS & POI"

Events Held under the Aegis of AOGD in November 2021

"Progress in Fetal Diagnosis and Therapy- New Concept"

"Care Bundle for Stillbirth: Making Every Baby Count"

"FOGSI- JOGI- E-PICSEP"

Quiz on "Adolescent Health"

"Medico Legal Conference in Obstetrics & Gynaecology"

"A TO Z of Post-partum Haemorrhage"

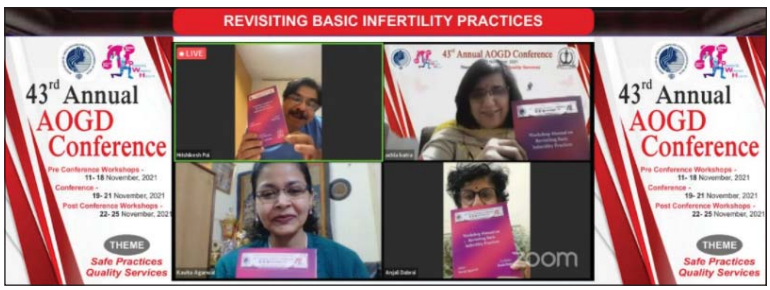
"Hyperandrogenism- Evidence Based Methodology"

"Dealing with Myomas Endoscopically"

"Protocols & Procedures for Cervical Cancer Prevention"

AOGD 43rd Annual Conference
19th, 20th & 21st November

AOGD 43rd Annual Conference
19th, 20th & 21st November

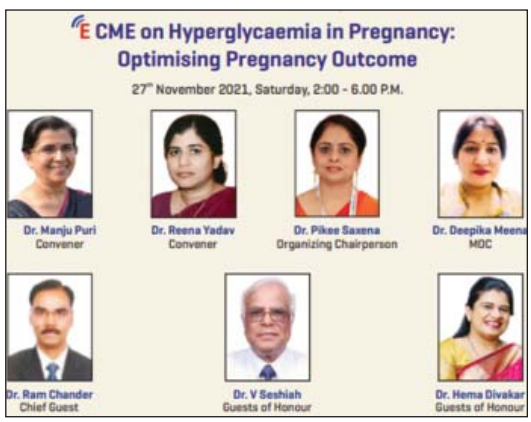


"Revisiting Basic Infertility Practices"

"Fighting the Fright: Non Hemorrhagic Maternal Collapse"

"Episiotomy & Obstetric Anal Sphincter Injury"

"Safe Abortion Values Evidence and Respect"



Hyperglycemia in Pregnancy: Optimising Pregnancy Outcome

Journal Scan

Saumya Prasad[1], Sheeba Marwah[2]
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Effects of Iodine Supplementation During Pregnancy on Pregnant Women and Their Offspring: A systematic review and meta-analysis of trials over the past 3 decades

Nazeri P, Shariat M, Azizi F

Eur J Endocrinol. 2021 Jan;184(1):91-106.

Objective: The current systematic review aimed to provide comprehensive data on the effects of iodine supplementation in pregnancy and investigate its potential benefits on infant growth parameters and neurocognitive development using meta-analysis.

Methods: A systematic review was conducted on trials published from January 1989 to December 2019 by searching MEDLINE, Web of Science, the Cochrane Library, Scopus, and Google Scholar. For most maternal and neonatal outcomes, a narrative synthesis of the data was performed. For birth anthropometric measurements and infant neurocognitive outcomes, the pooled standardized mean differences (SMDs) with 95% CIs were estimated using fixed/random effect models.

Results: Fourteen trials were eligible for inclusion in the systematic review, of which five trials were included in the meta-analysis. Although the findings of different thyroid parameters are inconclusive, more consistent evidence showed that iodine supplementation could prevent the increase in thyroglobulin concentration during pregnancy. In the meta-analysis, no differences were found in weight (-0.11 (95% CI: -0.23 to 0.01)), length (-0.06 (95% CI: -0.21 to 0.09)), and head circumference (0.26 (95% CI: -0.35 to 0.88)) at birth, or in cognitive (0.07 (95% CI: -0.07 to 0.20)), language (0.06 (95% CI: -0.22 to 0.35)), and motor (0.07 (95% CI: -0.06 to 0.21)) development during the first 2 years of life in infants between the iodine-supplemented and control groups.

Conclusion: Iodine supplementation during pregnancy can improve the iodine status in pregnant women and their offspring; however, according to our meta-analysis, there was no evidence of improved growth or neurodevelopmental outcomes in infants of iodine-supplemented mothers.

A Longitudinal Study of Thyroid Markers During Pregnancy and The Risk of Gestational Diabetes Mellitus and Post-partum Glucose Metabolism

Tang L, Li P, Zhou H, Li L

Diabetes Metab Res Rev. 2021 May;37(4):e3441.

Aims: To determine the relationship between thyroid markers during pregnancy and gestational diabetes mellitus (GDM) or post-partum glucose metabolism.

Materials and Methods: Based on pregnancy 75-g oral glucose tolerance test (OGTT) results, 1467 subjects were grouped into normal glucose tolerance (NGTp; n = 768) and GDM (n = 699) groups. Furthermore, based on post-partum 75-g OGTT results, 286 GDM subjects, screened for glucose metabolism after delivery, were grouped into NGTd (n = 241) and abnormal glucose tolerance (AGT; n = 45) groups.

Results: Maternal age, family history of diabetes, acanthosis nigricans, previous adverse pregnancy outcomes and caesarean section incidence, and thyroid positive antibody rates were higher in the GDM group than in the NGTp group. In the first trimester, free triiodothyronine (FT3), thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) levels were higher in the GDM group than in the NGTp group. In the second trimester, free thyroxine (FT4) levels were lower and TPOAb and TgAb levels were higher in the GDM group than in the NGTp group. After adjusting for confounding factors, FT3, TPOAb and TgAb (first trimester), and FT4, TPOAb and TgAb (second trimester) were risk factors for GDM. TPOAb and TgAb levels were higher in the AGT group than in the NGTd group and were potential predictors of abnormal post-partum glucose tolerance.

Conclusions: GDM risk significantly increased with increased FT3 (first trimester), TPOAb and TgAb (first and second trimesters) or with decreased FT4 (second trimester). Presence of thyroid antibodies predicted post-partum glucose abnormalities in subjects with GDM.

Intrahepatic Cholestasis of Pregnancy: Are in vitro fertilization pregnancies at risk?

Alemdaroğlu S, Yılmaz Baran Ş, Durdağ GD, Yuksel Şimşek S, Yetkinel S, Alkaş Yağınç D

J Matern Fetal Neonatal Med. 2021 Aug;34(15):2548-2553.

Aim: Single pregnancy patients with intrahepatic cholestasis of pregnancy (ICP) were divided into two groups according to the conception method, as spontaneous and *in vitro* fertilization (IVF). We aim to compare the maternal, laboratory and perinatal characteristics of both groups.

Materials and Method: The records of 10,929 patients who gave birth in the center between October 2011 and July 2019 were analyzed retrospectively from the data processing system records. Maternal, laboratory and perinatal characteristics of 109 single pregnancies (spontaneous *n*: 91; IVF *n*: 18) diagnosed with ICP were compared.

Findings: The maternal demographic data of both groups were similar (*p*: .05). In both groups, gestational week, gestational age at birth, birth weight, neonatal intensive care admission rate, meconium-stained amniotic fluid, umbilical cord pH, the 5-minute APGAR score, and the presence of pregnancy complications were similar ($p > .05$).

Result: Although ICP is reported with a higher incidence in IVF pregnancies, ICP findings and prognosis are similar to those of spontaneous pregnancies.

Valproate Usage in Pregnancy: An audit from the Kerala Registry of Epilepsy and Pregnancy

Seshachala BB, Jose M, Lathikakumari AM, Murali S, Kumar AS, Thomas SV

Epilepsia. 2021 May;62(5):1141-1147.

Objective: This is an audit of the use of valproate (VPA) during pregnancy in women with epilepsy (WWE).

Methods: We identified all pregnancies exposed to VPA in the Kerala Registry of Epilepsy and Pregnancy between January 2010 and December 2019. Subjects' past usage of antiepileptic drugs (AEDs), seizure count before and during pregnancy, fetal outcome, and major congenital malformations (MCMs) were abstracted from the registry records. The presumed reason for usage of VPA was deducted from the clinical records.

Results: There were 221 pregnancies (17.75%) exposed to VPA (monotherapy, n = 149) during the audit period. The MCM rate for the completed pregnancies exposed to VPA was higher (n = 20, 10.36%) than that of VPA-unexposed pregnancies (n = 39, 4.96%). The relative risk for MCM with VPA exposure was 2.1 (95% confidence interval = 1.24-3.48, number needed to treat with VPA to result in MCM = 19). Reasons for using VPA during pregnancy (some women had more than one reason) were (1) VPA was the first AED prescribed and was effective (68, 29.06%), (2) other AEDs were ineffective (128, 54.70%), and (3) other AEDs were discontinued due to adverse effects (17, 7.28%). Other reasons (21, 8.97%) were (1) VPA was selected after the epilepsy classification was revised (3, 1.28%), (2) other AEDs were expensive (2, .85%), and (3) patient switched to VPA from other AEDs for unspecified reason (16, 6.83%). VPA was discontinued during pregnancy for 6 (2.71%) persons. Less than 10% of women were tried on lamotrigine or levetiracetam before switching to VPA.

Significance: Nine MCMs per thousand pregnancies can be avoided if VPA is not used in WWE. Safe and effective AEDs as alternatives to VPA are the need of the hour. Professional bodies and regulatory authorities need to implement updated guidelines on AED usage in girls and women.

Keywords: antiepileptic drug; birth defect; guidelines; malformation risk; shared decision-making.

Proceedings of AOGD Monthly Clinical Meeting held at ESIC PGIMSR and Model Hospital, Basaidarapur, New Delhi on 29th October, 2021

A Mullerian Anomaly with Associated Rare GI Anomaly Masquerading as Hydrosalphinx

Divya Solanki, Taru Gupta, Sunaina Aggrawal, Sangeeta Gupta

Mullerian duct anomalies, MDA are estimated to occur in 5.5% of all women. Renal anomalies occur in 29% of MDA and are associated with unicornuate uterus (40%), renal agenesis is most common reported anomaly (67% of cases). Incidence of associated skeletal anomalies is 10% & GI anomalies are very rare. We report a case who had uterus didelphys with a huge enteric duplication cyst and mild kyphoscoliosis. Enteric duplication cysts are rare congenital malformation with incidence of 1 in 4500 births. The clinical presentation is extremely variable depending upon its size, location and structural configuration. GI anomalies are very rare and only few cases reported in literature to be associated with MDA.

A 17 year old unmarried female was referred from surgery department with c/c of abdominal distension which she noticed from past 20 days, generalized pain abdomen and constipation followed by spurious diarrhoea. On examination she had a suprapubic mass equivalent to 28-30 weeks size of gravid uterus, tense cystic consistensy arising from pelvis with a tubular extension upto the left hypochondrium, smooth surface, well defined margins, with slightly restricted mobility, lower margins of mass could not be reached. In ultrasound a huge convoluted cystic mass with internal echoes, arising from the pelvis extending upto left hypochondrium. Two widely divergent uterine horns were seen on extreme right and left sides of pelvis s/o didelphys uterus. Endometrium thickness of right horn was 4.5mm and left horn wass 5mm, both ovaries were visualized and were normal. Moderate bilateral hydroureteronephroiss was noted possibly due to pressure from pelvic mass. Liver, gall bladder, pancreas, kidney, spleen are normal. Ultrasound impression of huge hydrosalphinx was given. On CECT abdomen and pelvis a grossly dilated convoluted tubular structure arising from pelvis and extending superiorly up to the left lumbar region (adjacent to inferior pole of spleen) with hyperdense material displacing and compressing the adjacent bowel loops. Mass seems to be densely adhered to sigmoid colon. Diagnosis of Hydrosalpinx & ?enteric duplication cyst, EDC was given.

Surgery opinion was taken in view of CECT report. Patient was planned for exploratory laparotomy with surgeons. A large tubulo-cystic mass of size 30x20 cm filled with greenish brown thick fluid of volume nearly 2 liters was found. Uterus was didelphys and bilateral tubes and ovaries were normal. Mass was adherent to sigmoid colon and posterior wall of rectum. Resection of part of sigmoid colon followed by end to end anastomosis was done. Diversion ileostomy (loop) from apparently normal ileum was done. The patient was discharged on day 15 and post operative period was uneventful. Patient is under follow-up and is planned for stoma closure and re-anastomosis.

Our patient had an enteric duplication cyst that was densely adhered to serosa of sigmoid colon and anteriorly over first part of rectum and had tubular configuration. The cyst was not communicating with the lumen of bowel. Spinal defects, cardiac or urinary malformations, are reported associated with EDC with an incidence rate of 16–26%. Other digestive anomalies are present in about 10% of cases. Therefore, once an EDC is found, a search for other anomalies should be done.

On reviewing literature only a few cases have been reported where there is an associated mullerian anomaly with GI anomaly. Our patient had uterus didelphys with a huge enteric duplication cyst and mild kyphoscoliosis. It is important that a case with mullerian anomaly should be evaluated for other associated anomalies. Associated GI anomalies are very rarely reported so high index of suspicion is required.

A Rare Case of Degenerated Fibroid Presenting as Secondary PPH

Deepshikha Jaiswal, Nila Surendran Pratiksha Gupta, Nupur Gupta

Leiomyoma or fibroid is the most common benign pelvic tumour ofuterus. Its presentation during pregnancy and postpartum period may vary. Its incidence in pregnancy is approximately 1.5-2% and is associated with increased risk of complication during pregnancy including abortions, preterm labor, red degeneration, malpresentations, increased cesarean section rates, postpartum hemorrhage. In our case, a 26 years old woman presented as bleeding per vaginum of post operative day 16 of Em LSCS for primi with breech in labor not willing for vaginal delivery. Intraoperatively there was ?degenerated ?infarcted hybrid type of fibroid of 7 X 5 cm size. Post operatively patient had normal post partum period till day 16 of Em LSCS, when she presented with secondary PPH. USG confirmed endometrial cavity filled with an echogenic material with thick ET (35mm) with multiple echogenic foci showing twinkling artifact. On taking her up for evacuation, friable fibroid like tissues felt and it was removed with ovum forceps. The mass removed was sent for histopathological examination which confirmed it later on to be aninfarctedmyoma tissue.

Usually leiomyomas regress spontaneously, but a differential diagnosis of degenerative fibroid should be considered with the aforesaid clinical picture. Patient with fibroid uterus in antenatal period should be kept in regular follow up in post natal period and progesterone containing contraceptive should be avoided or used with caution.

Keywords: leiomyoma, post natal fibroids, degenerating fibroid, progesterone contraceptive

A Rare Case of PID Associated with Endometriosis after Transvaginal Oocyte Retrieval

Neelam Meena, Sanjana wadhwa, Leena Wadhwa, Sonam Singh, Kamta Prasad

Ultrasound-guided transvaginal oocyte retrieval is a standard procedure for ovum pick up (OPU) during *in vitro* fertilization and can be associated with complications. Endometriosis is a potential risk factor for PID following transvaginal oocyte retrieval. A 21 year old female with secondary infertility with Grade 4 endometriosis with peritoneal and bladder endometriosis (cystoscopic fulgration done twice) underwent IVF during COVID pandemic in view of OHSS, was lost to follow up, presented with pain abdomen and abdominal swelling after 3 month of transvaginal oocyte retrieval (TVOR) with ultrasound showing Complex cystic mass 12*8*9 cm in left adnexal region. There was no history of fever or discharge. On examination vitals stable, afebrile, there was 18 week size firm mass with restricted mobility. Investigations revealed TLC WNL. MRI revealed hugely dilated oviduct with left Tubo-ovarian mass. Laparoscopy was performed withderoofing of TO mass followed by drainage and fulgration of cystic wall. Intraop loculi of pus and hemorrhage were present. Post op she received Doxycycline for 3 weeks and monthly inj. Leuprolide. On follow up Ultrasound after two months, her left adnexal mass regressed and now plan is for Frozen Embryo transfer

Inoculation of vaginal bacteria and anaerobe opportunists is suggested to be the cause of PID following oocyte retrieval.In cases with endometriomas, complications, such as PID, tubo-ovarian abscess, can occur even long after the completion of transvaginal oocyte retrieval in assisted reproductive technology (ART) cycle, indicating that women with endometriosis are prone to develop infectious complications. More vigorous antibiotic prophylaxis, better vaginal preparation using povidone iodine followed by saline are recommended when TVOR is performed in endometriosis case. Surgical treatment preferably by laparoscopy should be considered in severe case of PID following endometriosis.

Quiz Held at Monthly Clinical Meeting

Rekha Bharti[1], Niharika Guleria[2]
[1]Professor, [2]Senior Resident, VMMC & Safdarjung Hospital

1. **In WHO 90-70-90 targets for elimination of cervical cancer, 70 is for percentage of**
   a. Women screened by high performance test by 25 yr & again by 40 yr
   b. Women screened by high performance test by 25 yr & again by 45 yr
   c. Women screened by high performance test by 30 yr & again by 45 yr
   d. Women screened by high performance test by 35 yr & again by 45 yr
2. **Follow-up for women after treatment of endometrial cancer**
   a. Every 3-6 mths for 1 yrs, then 6-12 mths thereafter
   b. Every 3 mths for 1 yr, then 6 mths thereafter
   c. Every 3-6 mths for 2 yrs, then 6-12 mths thereafter
   d. Every 3-6 mths for 5 yrs, then 6-12 mths thereafter
3. **Progression of Complete Molar and Partial Molar pregnancy to GTN occurs in**
   a. 15%–20%, and 0.5%–5% of cases, respectively
   b. 15%–20%, and 10%–15% of cases, respectively
   c. 15%–20%, and 5%–10% of cases, respectively
   d. 15%–20%, and 1%–2% of cases, respectively
4. **Serum HE4 levels are increased in**
   a. Ovarian, lung, breast, stomach, bladder and endometrial cancers
   b. Ovarian, lung, breast, colon, bladder and endometrial cancers
   c. Ovarian, lung, breast, pancreas, bladder and endometrial cancers
   d. Ovarian, lung, breast, thyroid, bladder and endometrial cancers
5. **Hereditary basis for endometrial cancer (EC) is present in**
   a. 5% cases and rest are sporadic
   b. 10% cases and rest are sporadic
   c. 15% cases and rest are sporadic
   d. 20% cases and rest are sporadic

Answers

Q. 1- d	Q. 2- c	Q. 3- a
Q. 4- c	Q. 5- b	

Winners of the Monthly Clinical Meeting Quiz October 2021

Dr Yukti Bhardwaj
DNB (BPSGMC) Obstetrics & Gynaecology, Senior Resident, VMMC & Safdarjung Hospital

1st Position

Dr Sukanya Sanapala
Resident, Obstetrics & Gynaecology, VMMC & Safdarjung Hospital

2nd Position

Proceedings of AOGD Monthly Clinical Meeting held at MAMC & Maulana Azad Medical college and Lok Nayak Hospital, New Delhi on 3rd December, 2021

Diaphragmatic Hernia in Pregnancy

Anjali Tempe, Devender Kumar, Vedika Bali

The majority of diaphragmatic hernias are diagnosed in the antenatal period or within the first few years of life. Diaphragmatic hernias complicating pregnancy is extremely rare with only 56 cases reported in literature and is frequently misdiagnosed. Maternal diaphragmatic hernias pose significant management challenges with regards to timing and mode of both delivery and hernia repair. Here we describe a patient at 31 weeks period of gestation diagnosed with traumatic diaphragmatic hernia.

A 23 year old lady, G2P1L1 at 31 weeks period of gestation presented with multiple episodes of vomiting, 12-15 per day for 3 days. This Vomitous consisted of food particles but was non bilious/not blood tinged. It was associated with epigastric pain. There was history of a similar episode at around 28 weeks for which conservative treatment was undertaken. There was no complaint of fever, cough, chest pain, bladder/bowel symptoms, outside food intake, itching or yellowish discoloration of body. The patient was perceiving adequate fetal movements with no history of any leaking/bleeding per vagina. The patient's first and second trimester history was uneventful and as reported her complaints started at 28 weeks in third trimester. Her first pregnancy was uneventful, and she delivered a full-term female child vaginally of birthweight 3kg at GTB hospital. There was no significant past medical, surgical history or family history. Upon further review, the patient recalled a robbery at home two years back which resulted in a stab injury in her left subcoastal region. However, no treatment was undertaken for it and records were not available.

During physical examination the patient showed stable vital signs with saturation of 99 percent on room air, respiratory rate of 18 per minute and pulse rate of 86 per minute. Her systemic examination including respiratory, cardiovascular and central nervous system was unremarkable. Upon abdominal examination, uterus was distended, dextro rotated with fundal height, symphysiofundal height and abdominal girth of 32 weeks, 32 cm and 30 inches respectively and corresponding to period of gestation. We observed a single life fetus at 31 weeks period of gestation in cephalic presentation.

The patient was admitted and laboratory tests ordered revealed elevated liver function tests with deranged sugar profile and positive urinary ketones, suggesting a probable case of hyperemesis/ starvation/ diabetic ketosis. A medicine consultation was taken and ultrasound whole abdomen with serum amylase and lipase as advised were reported normal. Patient was managed conservatively with intravenous fluids, injectable antacids and antiemetics but no improvement was observed. Suspecting a possibility of intestinal tuberculosis or sub acute intestinal obstruction, a chest x-ray and abdominal x-ray were ordered and to our surprise the radiologist reported left diaphragmatic hernia. For confirmation computed tomography was done which revealed left sided diaphragmatic hernia with herniation of stomach, jejunal loops, transverse colon, splenic flexure and descending colon with mesenteric and omental fat and vessels with organo-axial gastric volvulus and passive atelectasis of left lower lobe, but there were no ischemic intestinal signs.

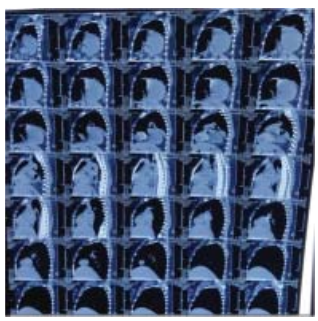

Figure 1: *sagittal section of CT chest*

Figure 2: *coronal section of CT chest*

As the condition of the mother and fetus was stable, we decided to continue expectant management. Four doses of dexamethasone were given for fetal maturation. Adequate intravenous hydration was given, antiemetics, proton pump inhibitors and aprepitant was given. As the patient was not tolerating orally, a nasogastric tube was inserted

but the patient refused so, we started her on total parenteral nutrition in order to meet nutritional requirements of pregnancy. At 34 weeks cesarean section was performed (infraumbilical midline vertical incision). Male baby weighing 1670 grams was born. Baby was admitted in nursery in view of low birth weight. The patient was followed up in gastrointestinal surgery and laproscopic intraperitoneal mesh hernioplasty was performed after 6 weeks postpartum. The surgery went uneventful and the patient was discharged on post operative day four.

The presentation of maternal hernia for the first time in pregnancy is rare and poses a management dilemma regarding timing of delivery and repair. A pregnant patient with diaphragmatic hernia can remain asymptomatic until advancing pregnancy. As the pregnancy progresses, abdominal pressure increase, further herniation is produced and gastrointestinal symptoms develop. The main life-threatening complications are severe dyspnea and visceral strangulation, which may cause maternal or fetal death. Diagnosis in pregnant patients is quite difficult because its symptoms like heartburn, nausea and vomiting are extensive during pregnancy. The key test for diagnosis is chest X-ray, showing air-fluid levels or gas in the herniated part of intestinal tract (over diaphragm) (sensitivity 70%) with Computerized tomography and magnetic resonance imaging to confirm the diagnosis. The management of a pregnant patient with symptomatic diaphragmatic hernia is a challenge. Expectant management with Gastric decompression (nasogastric tube) and antenatal corticosteroids (24-34 weeks) till fetal maturity followed by hernial repair. The most appropriate way to end pregnancy in these patients remains unclear. It has been demonstrated that uterine contractions without Valsalva do not increase intraabdominal pressure and so, they are unlikely to cause hernia incarceration or repaired hernia rupture.

Therefore, a patient with a repaired diaphragmatic hernia can deliver vaginally, without bearing down. But in case of non-repaired diaphragmatic hernia most authors accept elective cesarean section; hernia repair can be done at the same time, but it is not mandatory

Anaphylaxis to Iron Sucrose

Y M Mala, Poonam Sachdeva, Shakun Tyagi, Shalini, Uma, Anuradha, Vijeta, Vandana

Incidence of serious life threatening anaphylaxis with iron sucrose is 0.002%. We report two cases of severe hypersensitivity reaction to iron sucrose, because it is commonly used drug and such reactions are rare but potentially life threatning

Case 1: G3P2L2 with 34 weeks+3 days POG presented to LNH with severe anemia not in failure not in labor. On investigations diagnosis of severe iron deficiency anemia was made and plan of I.V iron sucrose infusion was made. 10 minutes after completion of iron sucrose patient had severe anaphylaxis reaction starting with tingling in arms,chest tightness and difficulty in breathing. Patient was initially managed with I.V pheneramine, hydrocortisone, I.V fluids and beta agonist but patients condition deteriorated and went into cardiac arrest. Patient was revived back with injection adrenaline 0.5mg 1/1000 given i.m and was kept in ICU for 3 days and had complete recovery.

Case 2: G2P1L1 33 weeks +6 days POG with moderate Iron deficiency anemia not in labour was given i.v iron sucrose infusion immediately after which patient had severe anaphylaxis reaction with which was managed with i. V pheneramine, hydrocortisone, I.V fluids and beta agonist and i.m adrenaline 0.5mg 1/1000. Patient was observed in ICU for 24 hours and had full recovery.

Conclusion: I.V iron should be given in a tertiary care well equipped centre. High index of suspicion is the key for detection of anaphylaxis. Injection adrenalin 0.5ml 1:1000 dilution is the drug of choice. All the reactions should be reported to higher authorities, drug store and pharmacovigilance: NCC-PvPI

Perimortem Cesarean Section- Every Second Counts!

Nalini Bala Pandey, Deepti Goswami

Perimortem cesarean section (PMCS), sometimes referred to as resuscitative hysterotomy, is cesarean delivery in the setting of maternal cardiopulmonary arrest, primarily used to assist maternal resuscitation and good fetal outcomes.

We presented two case report of PMCS performed in the setting of maternal cardiac arrest. In both the cases, mother had an underlying cardiac disease

and cause of cardiac arrest is pulmonary embolism in first case and arrhythmia in another. Maternal cardiac arrest team (anesthetist, obstetrician and pediatrician) activated, the patient made supine, left uterine displacement done and cardio-pulmonary resuscitation (CPR) started. Decision for PMCS was taken when there was no return of spontaneous circulation (ROSC) by 5 minutes of resuscitation. The PMCS was done concurrently by obstetrician with the ongoing CPR at the place of the cardiac arrest, with a scalpel. The abdomen and uterus was opened via a midline vertical incision. Baby handed over to pediatrician. The CPR was continued while the surgery was taking place. The mother could not be revived in either of the cases, but babies' resuscitated well and discharged in healthy condition.

In Women over 20 weeks of gestation, if there is no ROSC to correctly performed CPR within 5 minutes of maternal cardiac arrest, consider PMCS as per AHA 2020 guidelines. During Maternal cardiac arrest, the gravid uterus impairs venous return cardiac output (60%) secondary to aorto-caval compression. Delivery of the fetus and placenta by PMCS reduces oxygen consumption, improves venous return, cardiac output, and facilitates chest compressions and improved respiratory mechanics. Despite being an invasive procedure, in the emergency setting, PMCS should not be delayed in an attempt to obtain consent.

Thus providers of maternal care should be aware about the need of PMCS in case of cardiac arrest in pregnant women at or above 20 weeks of gestation. All centers that provide care for obstetric patients must have PMCS tray readily available.

Calendar of Virtual Monthly Clinical Meetings 2021-22

28th May, 2021	B L Kapoor Hospital
25th June, 2021	All India Institute of Medical Sciences
30th July, 2021	Sitaram Bhartia Hospital
3rd September, 2021	Army Hospital (Research & Referral)
24th September, 2021	Deen Dayal Upadhyay Hospital
29th October, 2021	PGIMSR & ESI Hospital
19th - 21st November, 2021	43rd Annual Conference
26th November, 2021	MAMC & Lok Nayak Jai Prakash Narayan Hospital
7th January 2022	Sir Ganga Ram Hospital
28th January, 2022	ABVIMS & Dr Ram Manohar Lohia Hospital
25th February, 2022	UCMS & Guru Tek Bahadur Hospital
25th March, 2022	VMMC & Safdarjung Hospital
29th April, 2022	LHMC & Smt. Sucheta Kriplani Hospital
27th May, 2022	Apollo Hospital

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