JABALPUR OBSTETRICS & GYNAECOLOGICAL SOCIETY

Jigyasa

The Curiosity..

HIGH RISK PREGNANCY
BEYOND THE HORIZON

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DR KAWITA BAPAT
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Dear all,

Greetings from FOGSI 2021-2022I hope and wish all of you are safe in this pandemic times.Please take care.I am very pleased to write a message to readers of quarterly journal of JOGS which is based on important topic of HIGH RISK PREGNANCIES,BEYOND THE HORIZON, In this era of medico legal implication and violence against doctors, we should know all the complications and should believe in team work.I congratulate all the authors for sharing their knowledge and editors for bringing it together.I hopethis edition of the journal will update the readers and improve their skills of management.

PROF. DR. GITA GUIN
President
(JOGS 2021-22)

प्रिय एवम सम्मानीय JOGS बंधु

सर्वप्रथम मेरा हृदय आभार एवम शुभेच्छा स्वीकारें।

मैं नतमस्तक होकर इस भीषण कठिन माहामारी में, आपने मानवता के लिए किए गए निस्वार्थ सेवा का जो अप्रतिम उदाहरण पेश किया , उसके प्रति स्वयं के एवम JOGS के तरफ से पुनः आभार वयक्त करती हूं।

अतुलनीय चेष्टा, समर्पण की जो रूपरेखा मेरे सखिद्वय अनुराधा एवम कावेरी ने बांधी एवं असम्भावनाओं से सराबोर, हिचकते, सकुचाते मैंने जबलपुर स्त्री एवम प्रसूति रोग संघ का बागडोर संभाला। मन में अनिश्चितता के भाव यूँ उभरे जैसे समाज के भावों से डांवाडोल मेरा अंतर्मन भी कई बार उद्वेलित होता रहा, असुरक्षा के भाव उभरते रहे कि किस प्रकार मैं आप लोगो की अपेक्षाओं को पूरा कर पाऊंगी।

पर आपके सहयोग से आज मैं समाज के विभिन्न तबको तक अपनी सोच को पहुंचा पा रही हूं। साथ ही साथ, आप थक जरूर गए होंगें वेबीनार के मकड़जाल में फंस कर, पर हम चेष्टा कर रहें हैं कुछ थोड़ा बहुत सकारात्मक वैज्ञानिक गतिविधि बनाये रखने की।

बहुत सारी खामियां रहेंगी, कहानियां भी मस्त बनेंगी, पर जब आप साथ हैं, तो सोच को मैंने आपकी सोच पर भरोसा कर, अपनी अनिश्चितताओं को सोने भेज दिया है और हमसब किसी भी मुकाम को हासिल करने का हौसला लिए निकल पड़े हैं।

आइए, दिल से दिल मिलाएं, हाथ से हाथ बांधे हम स्वयं एवम समाज की बेहतरी की दिशा में एक कदम और बढ़ाते हैं। आशा है बहुत जल्द हम एक दूसरे से स्वछंद वातावरण में मिल पाएंगे एवं एक दूसरे के सानिध्य से इन विगत दिनों के एकाकीपन को मिटा देंगें।

ईश्वर से आपकी सार्वभौम प्रार्थना एवं शुभेच्छा संग

DR SONAL SAHNI
Secretary
(JOGS 2021-22)

Dear friends,

Greetings from Team JOGS 2021-22

“The beginning is the most important part of the work” -Plato

Foremost, a big applause to all fraternity members for their sheer dedication towards the service of patients amidst the Covid pandemic. As we assume office, and take upon this mammoth task of fulfilling our academic and social pursuits, teamwork and hardwork will be our motto.

We will weave our thoughts around women-welfareand execute our plans for strengthening the roots of women healthcare .We intend to reach out to the masses through our social connect campaigns encompassing vital issues like Safe Motherhood, Contraception, Save The Girl Child, Adolescent Health, Sexually Transmitted Diseases, Cancer Screening & Prevention, Save The Uterus ,Healthy Diet And Nutrition etc.

To quench our unending thirst for knowledge and pursuit of excellence, we plan to organise Continuous Medical Education programs throughout the tenure, utilizing both online and offline modes circumstantially. We intend to rope in eminent speakers from all corners to deliver valuable insights about recent advances and engage in fruitful discussions on burning topics.

Benchmarks have been set by our extremely efficient predecessors and we shall strive hard to prove ourselves worthy of the heritage. Looking forward to your gracious presence and participation in all our endeavors.

With heartfelt thanks

DR JIGYASA DENGRA
Editor
(JOGS 2021-22)

Hello all,

Hope and wish you all are doing well in these pandemic times.

“I believe in being strong when everything seems to be going wrong. I believe that happy girls are the prettiest girls. I believe that tomorrow is another day, and I believe in miracles.” – Audrey Hepburn

I believe and hope all of you will agree with me that women are epitome of strength from “womb to tomb.” Although, we are residents of male dominated society where women are considered as soft, subtle and helpless but when it comes to being strong then women are the one to be considered, we all know that female fetuses are very strong and when it comes to situations like IUGR where survival is difficult it is the female fetuses who come out well, when it comes to changing environment in their lives it is the women who have to change and adjust, as of in India after marriage, it is women who have to consider halt in their careers for their family, as of during pregnancy and delivery…but I have always seen women standing strong in spite of whatever they have to go through. I feel blessed and privileged to be chosen by HIM to serve this part of society who cares, stands for All.

We have decided the theme of this edition of our quarterly journal, JIGYASA….the curiosity as HIGH RISK PREGNANCIES…BEYOND THE HORIZON as we know that some or other times the complications occur which are never thought of and we get stuck. In this era of medico-legal implications we hope that this edition of our journal will help you to update your knowledge.

I thank to all the contributors for sharing their knowledge with us.

I thank our president (JOGS) DR GEETA GUIN madam and secretary (JOGS) DR SONAL SAHNI madam who believed in me and gave me the opportunity.

I also am very much thankful DR BHOOMIKA, my co-editor who always stood with me.

Happy reading.

Peripartum Cardiomyopathy

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Introduction

Peripartum cardiomyopathy (PPCM) is a form of heart failure with reduced ejection fraction (<45%)which strikes women of childbearing age during last months of pregnancy or in the months following delivery in the absence of an identifiable cause of heart failure. PPCM has considerable overlap with extreme hemodynamics of normal pregnancy, thereby posing diagnostic challenge to obstetricians and cardiologists involved in care of such patients. Early diagnosis and aggressive management with special emphasis on long-term follow up and prevention of recurrence are prerequisites for optimal outcomes in this subset of patients of heart failure with reduced ejection fraction.

Epidemiology

The global estimates for incidence of PPCM vary by region. The incidence is highest in Nigeria (1 in 100 deliveries) while it is found to be lowest in Japan (1 in 20,000 deliveries) (1,2). In the Indian scenario, Pandit et al have reported an incidence of 1 in 1374 live births (3). With increasing awareness regarding this disease entity leading to early and timely diagnosis, the incidence of PPCM is expected to be higher than the reported numbers.

Etiology and Pathophysiology

PPCM is an idiopathic cardiomyopathy with no known definite etiology. However, multiple risk factors have been found to have statistical association with PPCM, but cause-effect relationship between these risk factors and PPCM remains unproven. Pre-eclampsia and hypertension are found to have the strongest association with PPCM and are prevalent in up-to 42% of all cases of PPCM (5% for pre-eclampsia and 37% for other hypertensive disorders). Multiple gestation is the next common risk factor for PPCM and is reported in 9% of women. In addition, high parity, high gravidity, extremes of reproductive age, malnutrition, selenium deficiency,maternal smoking, genetic predisposition (TTN, TNNC1 mutations) and various ethnic and socioeconomic risk factors have been associated with PPCM. These are tabulated in table 1.

Table 1: Associated risk factors for PPCM

1. Hypertension
2. Pre-eclampsia
3. Ethnic factors (African ancestory)
4. Multifetal pregnancy
5. High parity/gravidity
6. High maternal age (>30 years)
7. Malnutrition
8. Selenium deficiency
9. Maternal smoking
10. Genetic predisposition (TTN, TNNC1 mutations)

Various pathogenic mechanisms have been proposed for the development of PPCM including nutritional deficiencies, autoimmune process, viral myocarditis, catecholamine excess, and increased myocyte apoptosis. Likely, the pathophysiology entails multiple mechanisms. Recently, in a murine model of STAT 3 gene knockout mutation,oxidative stress led to cleavage of prolactin hormone. The resultant 16 kDa N-terminal fragments of prolactin have been shown to have vasculotoxic and pro-apoptotic properties and have emerged as key initiatingmechanismsof PPCM in a susceptible heart harbouring multiple risk factors. Mice treated with bromocriptine (which suppresses prolactin secretion) led to reversal of heart failure and ventricular dysfunction. However, human prolactin may be more resistant to such cleavage. Vascular endothelial growth factor deficiency (VEGF) deficiency along with 16 kDa prolactin fragments have also been implicated in another mouse model. Additionally, soluble Fms-like tyrosine kinase 1 (sFlt1), which is markedly elevated in pre-eclampsia, strongly antagonizes VEGF. Addition of VEGF supplementation to bromocriptine helped in complete recovery against a partial recovery with bromocriptine alone.

Clinical features and diagnosis

Most of the cases of PPCM are diagnosed after delivery (93%). Elkayam et al reported that 75% of the cases were diagnosed in first month postpartum, with more than half diagnosed in the first week postpartum (4). With increasing awareness, the proportion of patients with this cardiomyopathy being diagnosed antepartum is expected. Delayed diagnosis results in acute decompensated heart failure and is consequent worse outcomes.

Patients typically present with symptoms consistent with heart failure that include dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, fatigue, atypical chest pain, and abdominal discomfort. Physical examination usually reveals tachypnea, tachycardia, elevated jugular venous pressure, pulmonary crepitations, hepatomegaly and pedal edema. Acute presentations such as hemodynamically unstable ventricular tachycardias, cardiogenic shock and thromboembolic manifestations are well known but fortunately occur only in a minority of these patients.

Differential diagnosis

PPCM is a diagnosis of exclusion. Various differential diagnoses need to be excluded by careful evaluation. The differential diagnoses of PPCM include conditions that can predispose to heart failure during pregnancy, such as severe anemia, severe sepsis, pre-existing dilated cardiomyopathy, valvular and congenital heart disease, coronary artery disease, spontaneous coronary artery dissection, ventricular arrhythmias, pulmonary embolism and other cardiomyopathies. These are summarised in table 2.

Table 2: Differential diagnoses of PPCM

1. Pre-eclampsia
2. Hypertensive heart disease
3. Pre-existing cardiomyopathy
4. Ischemic heart disease
5. Tachycardia induced cardiomyopathy
6. Chemotherapy related cardiomyopathy
7. Left ventricular non-compaction
8. Arrhythmogenic cardiomyopathy
9. Recurrent PPCM
10. Takotsubo cardiomyopathy
11. Myocarditis
12. Pulmonary embolism
13. Congenital heart disease
14. Valvular heart disease

Investigations

- Echocardiogram plays a pivotal role in diagnosis of PPCM. A cut-off of <45% left ventricular ejection fraction (LVEF) is required for diagnosis of PPCM. It also provides information on valvular regurgitation, ventricular dilatation, intracardiac thrombus and helps rule out other etiologies of heart failure.
- Electrocardiogram may show non-specific abnormalities but a normal ECG doesn't rule out PPCM.
- Chest radiographs can be performed postpartum and may provide vital clues regarding cardiothoracic ratio, pulmonary venous hypertension and heart failure response to treatment.
- Cardiac magnetic resonance imaging may provide additional information like accurate estimate of LVEF, cardiac volumes, myocardial edema and clues to various cardiomyopathies based on late gadolinium enhancement imaging.
- Endomyocardial biopsy is reserved for those cases with a high suspicion of heart muscle disorder.

Prognosis and Outcomes: Mortality and Recovery

There are multiple parameters which portend poor prognosis in patients with PPCM. Concomitant preeclampsia, obesity, severe left ventricular systolic dysfunction with LVEF <30%, LV dilatation, LV thrombus, right ventricular dysfunction and biomarkers such as sFlt1, elevated troponin and NT-proBNP have all been associated with higher mortality rates. One-year mortality in patients with PPCM varies from 4-11%, while 2-year mortality ranges from15-28%. Extended follow up studies (>5 years) suggest mortality rates of 7-20%.(5)

PPCM is an important cause of heart failure with recovered ejection fraction as this form of cardiomyopathy shows higher rates of recovery in LVEF as compared to other etiologies of heart failure with reduced ejection fraction.Time and degree to which LVEF recovers depends on the patient population and the definition of recovery. Recovery typically occurs within the first 6 months after diagnosis; however, recovery up-to 2 years have been reported. IPAC study prospectively studied 100 patients with PPCM and found that 72% of them recovered to an LVEF >50% at 12 months.(6)Mahowald et al in his retrospective analysis of 59 women with PPCM reported a recovery rate of 43% by 12 months. The median time of recovery in these patients was 8 months.(7)

LVEF at the baseline is the best predictor of recovery. In the IPAC study, only one third of patients with LVEF < 30% recovered at 1 year. In contrast, 90% of the patients with LVEF > 30% recovered completely. However, LVEF is not the only predictor, and a low LVEF should not prematurely prompt for a mechanical assist device or enlisting for cardiac transplant before allowing recovery to occur. In few studies, pre-eclampsia is associated with a better recovery rate as resolution of hypertension with delivery may accelerate recovery. The evidence base is however small, to draw definite conclusions regarding this relationship.

Management

❑ ***Medical Management***

Acute management of heart failure in patients with PPCM is on the same lines of those patients with acute decompensated heart failure seen in patients of heart failure with reduced ejection fraction due to other causes. In patients with acute pulmonary edema/congestion, intravenous loop diuretics constitute the main stay of treatment. Oxygen saturation less than 90% warrantscorrection of hypoxemia with oxygen supplementation to maintain saturation >90%. Non-invasive positive pressure ventilation should be considered early if oxygen supplementation does not suffice.Systolic blood pressure above 110 mmHg in such patients warrants vasodilators such as nitroglycerine, while a non-vasodilating inotrope should be started in patients with systolic blood pressure <85 mmHg or those in

cardiogenic shock. Re-evaluation should guide further management. If patient is persistently having saturation <90%,endotracheal intubation with invasive ventilation should be considered. Maintenance of adequate urine output (>20 ml/hr) by increasing dose of loop diuretics, adding a thiazide diuretic or low dose dopamine is to be done. Patients in refractory heart failure require consideration for advanced heart failure therapies such as mechanical circulatory support or cardiac transplantation. Results of cardiac transplant in such setting is however inferior than in other diseases. Patients with PPCM have higher tendencies for developing thromboembolic events due inherent hypercoagulable state of pregnancy, left ventricular dilatation, left ventricular dysfunction, and immobilization especially after patient undergoes caesarean section. Hence,anticoagulation should be started immediately in patients with severely decreased LVEF (<30%) and continued for6-8 weeks. While warfarin and low molecular weight heparin are considered safe during lactation, warfarin needs to be avoided during pregnancy. Use of novel oral anti coagulants (NOACs) has not been tried in PPCM, and should thus be avoided.

Bromocriptine in dose of 2.5 mg daily for 7 days (for 6 weeks in severe cases) may be considered in the management of acute PPCM. In a randomized controlled trial, bromocriptine was found to have higher rates of recovery of LVEF at 6 months when compared to placebo.If bromocriptine is used, oral anti coagulation is mandatory irrespective of the LV function.

The management for acute PPCM can be remembered as BOARD therapies- bromocriptine, oral HF drugs after stabilization, anticoagulation, relaxants (vasodilators) and diuretics.

Longer duration therapy is advised in severe cases. Oral heart failure medications such as beta blockers, ACE-inhibitors/ARB/ARNI and mineralocorticoid receptor blockers (Renin angiotensin aldosterone pathway blockers, RAAS blockers) should be continued till the left ventricular ejection fraction improves. RAAS blockers need to be avoided during pregnancy, however ACEI and ARB's can be used during lactation. ARNI secretion in breast milk has not been documented and hence can be considered compatible with breast feeding. There are no guidelines for deciding timing of implantation of implantable cardiac defibrillator (ICD) for primary prevention of sudden cardiac death. However, it should be avoided in first 6 months after diagnosis of PPCM, since a large proportion of patients recover to an LVEF >35%. Wearable external defibrillators may be considered in the intervening period in patients thought to be at high risk for sudden cardiac death.

Patients with PPCM should be on 6 monthly follow up till the LVEF recovers to >50%. Patients with recovered ejection fraction should also be on close follow up as up-to 44% of patients with PPCM may need to be restarted on medications within 6 months of discontinuation of heart failure therapies. The management options in PPCM are summarized in table 3.

Table 3: Management options for PPCM Acute management for hemodynamically unstable patients

1. Oxygen supplementation – mask, NIV, invasive mechanical ventilation
2. Non-vasodilating inotropes
3. Mechanical circulator support devices – IABP, Impella, ECMO, LVAD
4. Diuretics – Loop, thiazide
5. Anti-coagulation – warfarin, low molecular weight heparin

Diuretics – loop, thiazideAcute management of hemodynamically stable patients

1. Oxygen supplementation – mask, NIV, invasive mechanical ventilation
2. Diuretics – Loop, thiazide
3. Vasodilators – nitrates, hydralazine, isosorbidedinitrate
4. Anti-coagulation – warfarin, low molecular weight heparinChronic management

1. Routine heart failure drugs –
    - RAAS blockers (ARNI, ACEi, ARB) [*Avoid during pregnancy*]
    - Beta blockers
    - Mineralocorticoid receptor antagonists [*Avoid during pregnancy*]
    - Digoxin
    - Diuretics
2. Bromocriptine
3. Anti-coagulation in patients with severe LV dysfunction (LVEF <30%)
4. Discuss contraception
5. Sudden cardiac death prevention – wearable external defibrillator, implantable cardiac defibrillator
6. Heart transplant

❑ ***Labor and Delivery***

Timing and mode of delivery is a joint decision that has to be made with the involvement of cardiologist, obstetricians, paediatricians, patient and family members. Every attempt to stabilize mother prior to delivery is a prerequisite for optimal maternal and fetal outcomes. Hemodynamically stable patients should undergo vaginal delivery unless caesarean section is warranted based on obstetric indications. The second stage of the labor should be shortened to reduce the cardiovascular stress. In hemodynamically unstable patients, maternal stabilization may prevent potential fetal complications pertaining to prematurity. However, ifhemodynamics remain unstable, early delivery should be promptly considered. It has been noted that neonates born to mothers with PPCM have lower birth weights, lower Apgar scores and a higher chance of stillbirth. Thus, early delivery needs to be weighed against the risks to the newborn.

❑ ***Discharge Advice: Lactation and Contraception***

Benefits of breast feeding to both mother and neonate are numerous. Majority of heart failure medications are safe during lactation and should be continued and escalated to the target doses to achieve maximum benefit. A small study suggested that women who breast fed their new-borns had higher rates of recovery(8). The IPAC investigators also reported no adverse outcomes when breast feeding was continued (9).

Counselling for contraception should begin as early as PPCM is diagnosed. The contraceptive options include intrauterine contraceptive devices, combined or progestin only pills, diaphragm,tubal ligation, hysteroscopic tubal ligation for women and condom and vasectomy for males. The type of contraceptive method is decided by multiple factors such as failure rates of contraception, prothrombotic effects of oral contraceptives, and individual preferences. In general, estrogen based contraceptives should be avoided. Progesterone based contraceptives (subcutaneous implants or Mirena intra uterine devices) remain the preferred modes.

❑ **Subsequent Pregnancy**

Prognosis of future pregnancy in a patient with prior history of PPCM depends largely on the LVEF prior to the next conception. Patients who continue to residual LV dysfunction should be counselled against future pregnancies due to prohibitively high maternal and fetal complication risks. More than 50% of these patients show further deterioration in LV function during/after next pregnancy. In patients who recover to a normal LV function, future pregnancy carries a better prognosis but recurrence risk of PPCM still persists (up to 15-20%), with no guarantee to an uncomplicated course. There are no definitive guidelines on advise on future pregnancies in such a scenario and an individual case to case based decision needs to be taken by a team of experts. If a patient with PPCM in the past conceives, she

should be closely followed up in regular clinical visits with serial echocardiograms and NT-proBNP levels. A team based approach is essential to manage such a case.

Conclusion

PPCM is a diagnosis of exclusion. Early diagnosis and treatment with guideline directed medical therapy for heart failureare the keys for obtaining optimal fetal and maternal outcomes. Experimental therapies like Bromocriptine hold promise but need to be studied further before routine clinical application. Contraception plays an important role in preventing future pregnancies and subsequent insult on an already diseased heart. The risk of recurrence in subsequent pregnancies in patients with recovered LV function is known and patients should be cautioned regarding the same. Gaps in knowledge exist regarding the complex pathogenetic mechanisms, anticoagulation strategy and duration, timing of ICD for primary prevention and management strategies for subsequent pregnancies in PPCM.

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Diabetic Complications and its association with Pregnancy

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Introduction

The prevalence rate of lifestyle diseases, obesity and diabetes in particular has been steadily rising globally. Traditionally viewed as low risk groups, women in their reproductive prime are also increasingly afflicted. There is a rising incidence of type 1 diabetes, type 2 diabetes and gestational diabetes in pregnant women.

Advent of various fertility options have changed the demographics and are helping women conceive in their late reproductive years. With newer drugs and insights about significance of glycemic control, more and more diabetic women with complications are also able to give birth to a healthy offspring.

Fetal and neonatal complications among women with pre-gestational diabetes range in severity from potentially mild (large for gestational age infant) to lethal (higher risk of miscarriage and some congenital malformations).

One of the most important things for us clinicians is to counsel all women of childbearing age with type 1 or type 2 diabetes about the potential effects of diabetes and their medications on maternal and fetal outcomes as well as the potential impact of pregnancy on their diabetes control and any existing complications. Preconception care can improve glycemic control in early pregnancy and, in turn, reduce the risk for some adverse pregnancy outcomes, such as congenital anomalies.

It is important to educate the women to defer pregnancy and encourage the use of contraception till target glycemic control is achieved and diabetic complications are controlled or treated.

Acute complications of diabetes in pregnancy

1. **Diabetic ketoacidosis**

   Diabetic ketoacidosis (DKA) occurs in approximately 0.5 to 3.0 percent of diabetic pregnant women.[1] Most cases occur in women with type 1 DM, but it may also occur in poorly controlled Type 2 diabetes mellitus, rarely it may be the first presentation of diabetes in pregnancy or poorly controlled Gestational diabetes mellitus.

   It can be regarded as a true obstetric emergency as fetal mortality rates of 10 to 30 percent have been reported, with increased risks of preterm birth and maternal mortality is less than 1 percent. [1]

   DKA is the result of an exaggerated counter-regulatory response to a perceived lack of glucose supply at the cellular level. Pregnancy is a ketogenic state, a state of increased insulin resistance, accelerated starvation, and respiratory alkalosis, especially in the late second and throughout the third trimester. Several pregnancy hormones such as human placental lactogen and prolactin antagonize the effects of insulin at the cellular level.

   Precipitating factors can be infection, intractable vomiting (secondary to Hcg), inadequate insulin doses, non-compliance or inappropriate insulin cessation, tocolytics (beta agonists), steroids (administred for fetal lung maturation) or even unrecognised new onset diabetes.

The presentation of DKA is similar to any non-pregnant patient- nausea, vomiting, thirst, polyuria, polydipsia, abdominal pain, a change in mental status. Laboratory findings include hyperglycemia (>250mg/dl), acidemia (arterial pH <7.30), an elevated anion gap (>12 mEq/L), ketonemia, low serum bicarbonate (<15 mEq/L), elevated base deficit (>4 mEq/L), and renal dysfunction.

But in pregnancy, the index of suspicion must be high as ketoacidosis tends to develop at lower level of glucose i.e euglycemic DKA. This could be due high rate of maternal glucose transfer to fetus and placenta, as its their major source of energy.

The exact mechanism by which maternal diabetic ketoacidosis affects the fetus is unknown. Ketoacids as well as glucose readily cross the placenta. Whether it is the maternal acidosis, hyperglycaemia, severe volume depletion, or electrolyte imbalance that has the most detrimental effect on the fetus is unclear. The long term effect of diabetic ketoacidosis episodes during pregnancy on surviving fetus is lacking. Some studies have shown a direct relationship between plasma ketone levels in pregnant diabetic women and a lower IQ in the child.[2]

Management includes an aggressive volume replacement, initiation of intravenous insulin therapy, correction of acidosis, correction of electrolyte abnormalities and management of precipitating factors, as well as monitoring of maternal-fetal response to treatment.

When diabetic ketoacidosis occurs after 24 weeks of gestation, fetal status should be continuously monitored for fetal hypoxemia and acidosis. During acute DKA, Cardiotocography can show absence of baseline heart rate variability, persistent late deceleration, and non-reassuring biophysical profile all suggesting fetal distress. After correction of the metabolic derangements, fetal abnormalities usually improve; however, it may take 4–8 hours for the fetal heart rate tracing to become normal.

The decision for delivery can be challenging and must be based on gestational age, maternal condition (whether the mother is responding to aggressive therapy or deteriorating), and fetal condition (whether the fetal heart rate pattern is improving or deteriorating).The maternal metabolic abnormalities must be corrected first to avoid the delivery of a hypoxic, acidotic preterm infant for whom in utero resuscitation may have resulted in a better outcome.

Morbidity and mortality can be reduced with early detection of and targeted therapy with intensive monitoring. The most important is to recognise DKA, as onset in pregnancy can be insidious, usually at lower glucose levels, and often progresses more rapidly as compared with non-pregnancy.

To prevent complications, there should be increased diabetic screening, education of diabetic pregnant women about the risks of diabetic ketoacidosis, precipitating factors, and the importance of reporting signs and symptoms and frequent check-ups.

2. Hypoglycemia

Hypoglycemia is usually defined as plasma glucose concentration below 70 mg/dL. It is an inevitable consequence of tight glycemic control.

Symptoms can include anxiety, palpitations, sweating, shakiness , diaphoresis, hunger, and paresthesia, abnormal mentation, irritability, ataxia, paresthesia, headache, stupor, and eventually (if untreated) seizure, coma, and even death.

Those at greatest risk, are those with hypoglycemic awareness or asymptomatic nocturnal hypoglycaemia.

The CEMACH study [3] showed 61% of women with T1DM and 21% of T2DM had recurrent hypoglycaemia during pregnancy and 25% had severe hypoglycaemia. In this study, recurrent hypoglycemia was not associated with poor pregnancy outcomes but may increase maternal mortality.

Though theoretically and in animal studies, it has been shown that hypoglycaemia during pregnancy may cause fetal growth retardation, small for gestational age infants and impaired fetal beta cell function, but few human studies available haven't confirmed this. Studies in children of mothers with recurrent hypoglycemia, showed no relation between intellectual performance, psychomotor development, and hypoglycemia.[3]

Management of mild to moderate hypoglycaemia includes administering 15–20 g of glucose in the form of glucose tablets (3–5 g/10 kg body weight) or pure glucose drinks. In case of severe hypoglycaemia and unconsciousness, Glucagon 1 mg can be given subcutaneously at home as it does not cross the placenta or iv dextrose infusion in hospital.

Hypoglycemia can be minimised by patient education, dietary and exercise modifications, medication adjustment, meticulous glucose monitoring by the patient, and conscientious surveillance by the clinician.

Appropriate self-management training include correctly identifying the alarm symptoms of hypoglycaemia and proper way to treat it, carrying snacks, hypoglycemia awareness, and carbohydrate counting & clear insulin dose adjustment instruction (especially in type 1 diabetes)

Pregnancy and Chronic Complications of diabetes

1. **Nephropathy** is a progressive disease and the pregnancy risk increases with more advanced disease. It has been seen that pregnancy outcome is favorable in women with small elevations in serum creatinine <1.4 mg/dl, proteinuria <1 g/24 h, and normal BP. In contrast, serum creatinine >3 mg/dL or creatinine clearance <50 mL/minute and severe hypertension or proteinuria in the nephrotic range (>3 g/24 h) and/or pre-existing cardiovascular disease is associated with a high risk for poor maternal and fetal outcome. The long-term survival of a mother with diabetic nephropathy has improved considerably in recent years, but the long-term likelihood of renal dysfunction is still increased. [5]

   Effects of Diabetic Nephropathy on Pregnancy Outcome

   Diabetic nephropathy can affect pregnancy outcome by development of severe hypertension with deterioration of kidney function in the mother, preterm delivery due to high maternal BP and pre-eclampsia, and fetal intrauterine growth restriction and fetal distress caused by placental dysfunction. Severe congenital malformations have been described with a slightly higher prevalence in women with diabetic nephropathy compared with diabetic women with normal kidney function. However, this may be due to the poorer metabolic control in early pregnancy often found in these women

   Management includes Intensive glycemic control, low-dose aspirin from 12 gestational weeks onward, and intensive antihypertensive treatment.

   ADA guidelines [5] suggest treatment with ACE inhibitors or ARBs may be stopped before conception, due to possibility of teratogenicity and switched to antihypertensive treatment that are regarded safe in pregnancy, such as methyldopa, labetalol and nifedipine.

   NICE guidelines [6] recommend to stop ACE inhibitors or ARBs either pre-conception or as soon as pregnancy is diagnosed. This is supported from small studies (involving 8-24 persons) suggesting intensive RAAS use (capable of decreasing proteinuria to levels < 300 mg/day)

together with optimization of glycemic control, reduces the incidenceof heavy proteinuria during pregnancy.

However, general consensus is even if these drugs are given during organogenesis, the risk of malformations is so low that interruption of the pregnancy in not necessary.

In late pregnancy, close obstetrical surveillance is important to diagnose complications, prevent stillbirths, and plan the time of delivery. Vaginal delivery is the preferred mode of delivery if there are no obstetric contraindications. Cesarean delivery is performed for standard obstetric indications.

In addition to clinical control, including BP and protein excretion, ultrasound evaluations are performed in order to detect possible growth restriction.

In late pregnancy cardiotocography is often performed once or twice weekly in order to detect cardiac morbidity and prevent stillbirth, measurements of the flow profile in the umbilical artery or the uterine artery may be added.

When pre-eclampsia has developed, it is often wise not to postpone the delivery of the fetus. Maturation of fetal lung function with glucocorticoid treatment before preterm delivery before 34 gestational weeks is also recommended in diabetic women.

In most women, elective delivery is indicated if labour has not occurred by the estimated date of confinement. Even for low-risk women, there is little benefit in allowing the pregnancy to extend beyond this date, and maternal and/or perinatal risk may increase.

2. Diabetic retinopathy

Diabetic retinopathy (DR) is a major microvascular complication of diabetes mellitus and is often the first complication to appear. Pregnancy is a major risk factor for the progression of retinopathy and may be associated with increased prevalence and severity of retinopathy compared to non-pregnant diabetic women.

Earlier, proliferative retinopathy was a contraindication to pregnancy because of the substantial risk of severe visual loss, but with the use of laser photocoagulation and the establishment and recognition of high-risk characteristics, the likelihood of visual loss has been reduced.

Pre-conception counselling & Screening

All diabetic women planning for pregnancy should receive screening by Dilated fundus examination exam prior to conception. Patients with severe non-proliferative and proliferative changes have a greater tendency for progression during pregnancy. Appropriate treatment of pre-existing PDR with photocoagulation before attempting pregnancy may protect against rapidly progressive PDR during pregnancy.

The patient should be counselled about the risk of progression of DR and the importance of good metabolic control before and throughout pregnancy to prevent it.

Effects of Pregnancy on Diabetic retinopathy

Pregnancy does not have any long term effect on DR, but progression can occur in 50%-70% of cases. The greatest risk of worsening occurs during the second trimester and cam persist as long as 12 months postpartum. [7]

The risk factors for the progression of retinopathy in pregnancy are severity of retinopathy at conception, diabetes duration, metabolic control before pregnancy, and the presence of additional vascular damage (i.e. pre-existing or concomitant hypertensive disorder).

The retinopathy which progresses during pregnancy has a high tendency for regression in the post-partum period. However, the length of time required is not exactly known.

Theres no robust data regarding GDM. As the glucose intolerance in GDM transient in most cases, these women are not generally at risk of developing DR during pregnancy. However, as a proportion of women with GDM do in fact have undiagnosed T2DM, this subgroup may develop DR during or following pregnancy.

Patient is often asymptomatic, there may be abrupt worsening of visual acuity or increase in floaters.

If Fundus examination is not done preconception, then she should be screened at the first first trimester. Mydriasis is usually achieved using tropicamide, which is category C drugs (the potential benefit may justify use, despite the potential risk).

After first trimester eye exam, follow-up care depends on the degree of retinopathy observed. If no retinopathy to moderate non-proliferative retinopathy is present, the patient should be re-examined in 3-12 months. Severe non-proliferative retinopathy or any degree of proliferative retinopathy requires follow-up every one to three months until delivery. If there was disease present prior to pregnancy, regardless of the severity, a six-month post-partum follow-up appointment is recommended.

The standard of care for treatment of proliferative diabetic retinopathy is Pan-retinal laser photocoagulation therapy and may be given during pregnancy. If a pregnant woman develops severe non-proliferative changes, immediate laser photocoagulation is indicated to prevent proliferative changes.

Data regarding intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections during pregnancy is not clear. Few case reports of early miscarriages have been reported in patients who received anti-VEGF injections during early pregnancy. More studies are needed, so if an anti-VEGF injection is recommended, the patient must be well-educated about the potential risks and the pregnancy must be closely monitored.

Surgical intervention may be indicated in some complicated cases, including tractional retinal detachment, non-clearing vitreous hemorrhage, and neovascular glaucoma. In these cases, collaboration between the ophthalmologist and the obstetrician is necessary.

Effect of diabetic retinopathy on pregnancy

Many studies have addressed a possible relationship between the DR and the perinatal outcome. It has been found that women with severe form of disease are more likely to develop obstetric complications compared to women with no retinal or minimal retinal changes. Incidence of severe congenital malformations and/or foetal death is higher in patients with proliferative changes. This may be as severity of retinopathy can be correlated with the presence of angiopathy elsewhere, especially the kidneys.

3. Diabetic neuropathy

Diabetic neuropathy is one of the most common complications of diabetes mellitus, most common is symmetric polyneuropathy, which may be accompanied by autonomic neuropathy. Symptoms of Autonomic neuropathy include gastroparesis, vomiting, constipation, diarrhea, urinary frequency or retention, and postural hypotension. Many of these symptoms are common during pregnancy in non diabetics and thus may go unrecognized.

Effect of pregnancy diabetic on neuropathy

Pregnancy has not been found to have any long term impact on progression of neuropathy.

Effect of diabetic neuropathy on pregnancy

Autonomic neuropathy can increase risk of hyperemesis gravidarum (due to gastroparesis), hypoglycemia unawareness, and orthostatic hypotension.

Severe diabetic gastroparesis can lead to extreme hypo- and hyperglycemia, increased risk of diabetic ketoacidosis, weight loss, and malnutrition in the absence of appropriate management. The effects of gastroparesis can be mitigated by utilizing dietary modification, adjusting the insulin regimen, and other medical therapies (eg, antiemetic and prokinetic agents). Some may require hospitalisation and parenteral nutrition.

A recent Croatian study of 94 type-1 diabetic pregnant women females with 8.5% incidence of moderate and severe autonomic neuropathy, did not show any increase in the perinatal morbidity and mortality associated with moderate and severe autonomic neuropathy.[8]

4. **Cardiovascular diseases**

Pregnant women with pre-gestational diabetes are also at increased risk of macrovascular cardiac disease- coronary artery disease, heart failure, stroke. In addition, pregnancy-related volume expansion may unmask previously subclinical disease, such as asymptomatic diastolic dysfunction.

Acute myocardial infarction can also occur in pregnancy. Symptomatic coronary artery disease in women with pregestational diabetes mellitus is most commonly seen in those with long-standing disease, nephropathy, and hypertension. Preexisting coronary artery disease may be a contraindication to pregnancy because of the pregnancy-associated hemodynamic changes that may result in myocardial infarction and death.

Preconceptional screening and counselling

Cardiac evaluation should be based on the patient's history and physical examination. The ADA recommends an ECG for women starting at age 35 years who have cardiac signs/symptoms or risk factors and, if abnormal, further evaluation

Women with abnormal cardiac findings on examination, electrocardiogram (ECG), or by history should be referred to a cardiologist for further evaluation (such as exercise tolerance testing), management, and counseling.

Conclusion

Preconception counseling should be a part of routine diabetes care for all women with diabetes and reproductive potential.

A medical risk assessment including both preprandial and postprandial capillary glucose levels, assessment of cardiovascular, renal, and ophthalmologic status should be offered for all women with overt diabetes and those with a history of gestational diabetes mellitus during a previous pregnancy.

Effective contraception (with consideration of long-acting, reversible contraception) should be prescribed and used until a woman's treatment regimen and A1C are optimized for pregnancy.

Lifestyle intervention must be encouraged and initiated well before pregnancy begins, because birth defects occur during the critical 3-6 weeks after conception.

Finally all involved specialities must work in unison with the patient as several studies have shown

improved diabetes and pregnancy outcomes when care has been delivered from preconception through pregnancy by a multidisciplinary group focused on improved glycemic control and risk mitigation.

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HYPERTHYROIDISM IN PREGNANCY

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[1]This article will let you through the journey of the problems in relation to the prevalence of hyperthyroidism in pregnancy, therapeutic issues, pregnancy planning, and clinical management. No controlled trials of management have been conducted, but consensus guidelines have recently been published.2

To Begin with we will start with a Case Scenario

A 32 year old woman develops Graves' hyperthyroidism (the commonest cause of hyperthyroidism) four months after the birth of her first child. She receives treatment with antithyroid drugs for six months. In her second pregnancy she complains of palpitations, excessive sweating, and heat intolerance at 16 weeks' gestation. Although she experienced these symptoms in previous pregnancies, the current symptoms are much worse.

On investigation ,She is found to be severely hyperthyroid, with raised concentrations of serum free thyroxine (51.7 pmol/l (normal range 9.8-23.1 pmol/l) and free triiodothyronine (19.9 pmol/l (3.5-6.5 pmol/l)) and with suppressed concentrations of thyrotrophin (thyroid stimulating hormone) (<0.02 mU/l (0.35-5.5 mU/l)). She is treated with propylthiouracil, initially 150 mg three times daily, which is reduced eventually to 50 mg twice daily as she becomes euthyroid. Thyrotrophin receptor antibodies are measured at 30 weeks' gestation and are negative. Propylthiouracil is continued throughout pregnancy and she breast feeds while taking the drug. The drug is stopped two months postpartum; thyroid function is normal three weeks later.

How common is hyperthyroidism in pregnancy?

Hyperthyroidism occurs in 2/1000 pregnancies in the United Kingdom.3 Graves' hyperthyroidism (defined as hyperthyroidism that is the result of stimulation of the thyroid by thyrotrophin receptor stimulating antibodies (TRAb)) is the commonest cause of hyperthyroidism in young women (about 85% of cases) in the United Kingdom.1 The prevalence of undiagnosed hyperthyroidism in women is about 4.7/1000 4 and 0.2% of UK women have been previously diagnosed and treated. In areas of mild iodine deficiency the prevalence is higher.5 6 Box 1 outlines the causes of hyperthyroidism in pregnancy.

In addition to true hyperthyroidism, the more common clinical entity of transient gestational hyperthyroidism may be seen particularly in the first trimester, with a prevalence in Europeans of 2-3% but a much higher prevalence in South Asian populations.

Indian Data, The prevalence of hyperthyroidism has been studied in several studies. In an epidemiological study from Cochin, subclinical and overt hyperthyroidism were present in 1.6% and 1.3% of subjects participating in a community survey.[7] In a hospital-based study of women from Pondicherry, subclinical and overt hyperthyroidism were present in 0.6% and 1.2% of subjects. More than a third of community-detected hyperthyroid cases have positive anti-TPO antibodies, and about 39% of these subjects have a goiter

Hyperthyroidism does not often arise for the first time in early pregnancy, but clinicians need to be aware of the symptoms and signs (box 2).

Box 1 Causes of hyperthyroidism in pregnancy

- Graves' disease
- Transient gestational hyperthyroidism
- Toxic multinodular goitre
- Single toxic adenoma
- Subacute thyroiditis
- Trophoblastic tumour
- Iodide induced hyperthyroidism
- Struma ovarii
- Thyrotrophin receptor activation

Box 2 Does hyperthyroidism commonly arise de novo in pregnancy?

Most pregnant women with hyperthyroidism are known to have had thyroid disease before the onset of gestation and will already be receiving treatment. A new diagnosis of hyperthyroidism is uncommon in early pregnancy, as untreated disease is associated with reduced fertility. However, in a series of 14 970 first trimester blood samples, undiagnosed Graves' hyperthyroidism was present in about 0.15%.[8] Features such as tachycardia, palpitations, systolic murmur, bowel disturbance, emotional upset, and heat intolerance may be seen in normal pregnancy but should alert the clinician to the possibility of hyperthyroidism, particularly if a goitre or more specific feature of thyroid disease (weight loss, eye signs, tremor or pre-tibial myxoedema) is observed. Newly diagnosed hyperthyroidism should be aggressively treated.

How does hyperthyroidism affect pregnancy?

Pregnancy outcome

Pre-eclampsia, heart failure, fetal loss, premature labour, and having a low birthweight baby are more likely to occur in untreated or poorly controlled thyrotoxic women than in those receiving adequate treatment.8 A retrospective review of 11 reports documented a 5.6% incidence of fetal death or stillbirth in 249 pregnancies and a further 5% incidence of fetal and neonatal abnormalities.9 A study of 60 cases of hyperthyroidism in pregnancy over a 12 year period found that metabolic status at delivery correlated with pregnancy outcome. Preterm delivery, perinatal mortality, and maternal heart failure were more common in women who remained thyrotoxic despite treatment or whose hyperthyroidism was first diagnosed during pregnancy.

Women with thyroid hormone resistance (where thyroid hormone and thyrotrophin concentrations are inappropriately high—that is, not due to autoimmunity) also have a high miscarriage rate, indicating a direct toxic effect of thyroid hormones on the fetus.

Fetal and neonatal thyroid dysfunction

Improvement of Graves' hyperthyroidismduring a woman's pregnancy is often associated with a reduction in the titre of maternal serum TRAb concentrations and a change from stimulatory to blocking antibodies. If antibodies do not decline they will cross the placenta and stimulate the fetal thyroid, evidenced by signs of fetal hyperthyroidism such as tachycardia, intrauterine growth retardation, cardiac failure, and the development of fetal goitre.

One to five per cent of neonates of mothers with Graves' disease have hyperthyroidism as a result of the transplacental passage of maternal TRAb concentrations. Presentation of neonatal hyperthyroidismmay be delayed as antithyroid drugs administered to the mother are cleared more rapidly from the fetal circulation than maternal stimulating antibodies.

Maternal euthyroidism is particularly important in the later stages of pregnancy, as poorly controlled hyperthyroidism can lead to suppression of the fetal pituitary thyroid axis resulting from placental transfer of thyroxine. A case-control study noted a low thyrotrophin concentration, a blunted result (that is, suppressed compared with the normal response) with a thyrotrophin releasing hormone test, and low serum thyroxine concentration in a group of neonates whose mothers had had poorly controlled hyperthyroidism in the third trimester of pregnancy. The condition may last up to six months, as described in two case series. Subclinical hyperthyroidism has no known associated adverse pregnancy outcomes.5

How does pregnancy affect hyperthyroidism?

A deterioration in previously diagnosed thyroid disease is not uncommon during the first trimester of pregnancy and may be due to an increase in the titre of TRAb concentrations or high levels of human chorionic gonadotrophin acting as a thyroid stimulator. Relapse may also be caused by impaired absorption of antithyroid medication secondary to vomiting that is associated with pregnancy or by reluctance to continue medication in the first trimester.

Human immune regulation involves homoeostasis between T helper 1 (Th1) and T helper 2 (Th2) activity, with Th1 cells driving cellular immunity and Th2 cells humoral immunity. The immune status of pregnancy is a Th2 state, which allows tolerance of the fetus during pregnancy, and this is thought to be the reason why the severity of Graves' hyperthyroidism (and other autoimmune diseases) usually lessens after the first trimester.1

Hyperthyroidism before pregnancy may remit during pregnancy but will recur in the postpartum period as the immune status reverts to a Th1 state.

On rare occasions, labour, caesarean section, and infections may aggravate hyperthyroidism to the extent that cases of thyroid storm (a life threatening form of hyperthyroidism) have been observed.

How is hyperthyroidism treated in pregnancy?

Prepregnancy planning and counselling

Ideally, a woman who knows she has hyperthyroidism should seek prepregnancy advice, although no evidence exists yet for the benefit of this.

Patients already treated for hyperthyroidism caused by Graves' disease

Although patients who have already been treated for hyperthyroidism may have received antithyroid drugs, had surgery, or had radioiodine therapy and be euthyroid (whether receiving thyroxine or not), neonatal hyperthyroidism may still occur. TRAb concentration should be measured early in pregnancy in a euthyroid pregnant women who has previously had surgery or radioiodine therapy. If the concentration is high at this time, the fetus should be evaluated carefully during gestation (with serial ultrasonography) and the antibodies measured again in the third trimester. If the TRAb concentration is high at 36 weeks, the neonate needs to be checked for hyperthyroidism after delivery.

Treatment of hyperthyroidism in pregnancy

Box 3 outlines the main elements in managing hyperthyroidism in a pregnant woman. At all stages of pregnancy antithyroid drugs are the preferred treatment Radioiodine is contraindicated (box 4) and surgery requires pretreatment with antithyroid drugs to render the patient euthyroid.

Drugs used in hyperthyroidism

Drug	Mode of action	Dose	Adverse effects
Propylthiouracil	Inhibits thyroxine synthesis; inhibits peripheral conversion of thyroxine to triiodothyronine	Starting: 300-450 mg/day; maintenance: 50-100 mg/day	Rash, fever, agranulocytosis
Carbimazole	Inhibits thyroxine synthesis	Starting: 15-40 mg/day; maintenance: 5-15 mg/day	As above, plus aplasia cutis and methimazole embryopathy
Propranolol	Reduces adrenergic symptoms	10-40 mg, 3 -4 times/day (short term use only)	Bronchospasm, intrauterine growth restriction, neonatal hypoglycaemia

Box 3 Management of hyperthyroidism in pregnancy

- Confirm diagnosis
- Discuss treatment with patient (effect on patient, effect on fetus, breast feeding)
- Start propylthiouracil
- Render patient euthyroid—continue with low dose of an antithyroid drug up to and during labour
- Monitor thyroid function regularly during gestation (every four to six weeks) and adjust the dose of antithyroid drug if necessary
- Do serial ultrasonography of the fetus
- Check TRAb at 30-36 weeks' gestation if hyperthyroidism is caused by Graves'disease
- Inform the paediatrician that the woman has hyperthyroidism and that the neonate may therefore be at risk of hyperthyroidism
- Review management postpartum—check for exacerbation
- Check infant for thyroid dysfunction if indicated

Box 4 Hyperthyroidism inadvertently treated with radioiodine in early gestation

Administration of radioactive iodine (iodine-131), either for diagnostic tests or treatment, is contraindicated during pregnancy, and all women who could potentially become pregnant should have a pregnancy test before being given ^{131}I.

In many clinics, however, routine pregnancy testing is not done before administration of ^{131}I. Despite denial of pregnancy, several reports of inappropriate administration of radioiodine have highlighted the concern about the fetal radiation risk.

Because fetal thyroid uptake of ^{131}I starts after 12 weeks' gestation, exposure before 12 weeks is not associated with fetal thyroid dysfunction. Administration of up to 555 MBq ^{131}I for hyperthyroidism during the first trimester therefore does not compromise fetal thyroid function, and the low fetal whole body irradiation is not considered sufficient to justify termination of pregnancy.

However, the fetal thyroid concentrates iodine after 13-15 weeks' gestation and is relatively more avid for iodine than the maternal thyroid; in addition, the fetal tissues are more radiosensitive. ^{131}I given after this gestational age therefore potentially leads to substantial radiation to the fetal thyroid, resulting in biochemical hypothyroidism and even cretinism in the neonate. However, the likelihood of these effects is not certain, and in these circumstances dosimetry studies should be done to enable more accurate patient counselling with regard to, for example, termination of pregnancy.

If the pregnancy continues to term, intrauterine hypothyroidism may be diagnosed by umbilical cord sampling. Management should maintain high normal maternal circulating thyroxine levels. The neonate should be evaluated at birth specifically for hypothyroidism and for malformations that are more common with higher doses of radiation. The neonate should be treated promptly with thyroxine as appropriate; treatment may need to be lifelong.2

The thionamides carbimazole, methimazole (the metabolite of carbimazole), and propylthiouracil are all effective in inhibiting thyroidal biosynthesis of thyroxine during pregnancy. Propylthiouracil is the preferred drug in pregnancy as carbimazole and methimazole are (albeit rarely) associated with teratogenic effects.

An early study also reported less placental transfer of propylthiouracil than of methimazole, but results of a more recent study measuring propylthiouracil and methimazole concentrations and examining placental perfusion in vitro have not shown any advantage for propylthiouracil in relation to placental transport. Furthermore, the two drugs seem to have no difference in effect on fetal and neonatal thyroid function.

This use of propylthiouracil as the initial preferred drug for maternal hyperthyroidism is an expert consensus recommendation of the Endocrine Society.2 In countries where propylthiouracil is not available, carbimazole and methimazole are acceptable as the potential fetal and maternal dangers of not treating active hyperthyroidism far outweigh the small risk of rare congenital abnormalities.

Aside from potential induction of hypothyroidism—and the noted possible teratogenic effects—several studies have shown that no long term adverse effects result from exposure to antithyroid drugs in utero, in particular on IQ scores or psychomotor development in individuals exposed to methimazole and propylthiouracil who were evaluated up to the age of 23 years.

The starting dose of propylthiouracil is relatively high, 300-450 mg a day, up to 600 mg daily if necessary, given in two to three divided doses. Some improvement is usually seen after one week of treatment with antithyroid drugs, but four to six weeks may be needed for a full effect. Once the hyperthyroidism has been controlled, the dose needs to be gradually reduced by a quarter to a third every three to four weeks, typically to 50-100 mg twice daily. The main principle of treatment is to administer the lowest dose of antithyroid drugs needed for controlling clinical symptoms, with the aim of restoring normal maternal thyroid function but ensuring that fetal thyroid function is minimally affected.

Of seven published studies examining whether a relation exists between dose of antithyroid drug and neonatal thyroid function, the dose of the drug correlated with neonatal thyroid function in three studies but did not correlate in a further four. Furthermore, even doses as low as propylthiouracil 100 mg a day have been reported to cause mild transient fetal hypothyroidism. Current maternal thyroid status rather than dose of antithyroid drug has therefore been suggested as the most reliable marker for titration of antithyroid drug treatment to avoid fetal hypothyroidism. In practice, to avoid fetal hypothyroidism, maternal free thyroxine concentrations should be kept in the upper third of the normal reference range for non-pregnant women, as with this management serum free thyroxine concentrations are normal in more than 90% of neonates.

The administration of levothyroxine together with propylthiouracil as a “block and replace” regimen is not advisable in pregnancy as the amount of antithyroid drug may be excessive in proportion to the

amount of thyroxine that crosses the placenta, resulting in fetal goitre and hypothyroidism.

No consensus has been reached on the duration of antithyroid drug treatment during pregnancy as no good level of evidence exists. Some authorities suggest stopping the drug in the third trimester or after four to 12 weeks of treatment with subsequent close monitoring, but relapse of disease may occur, which is most undesirable during labour. Therefore we believe that the drug should be continued in a low dose up to and during labour.

β-adrenergic blocking agents such as propranolol may be used for a few weeks to ameliorate the peripheral sympathomimetic actions of excess thyroid hormone, but prolonged use can result in restricted fetal growth, impaired response to hypoxic stress, postnatal bradycardia, and hypoglycaemia.

Fetal surveillance

Because of the risk of fetal thyroid dysfunction in women with raised TRAb concentration or those taking antithyroid drugs, serial ultrasound scans of the fetus should be performed. Ultrasound evidence of fetal thyroid disease includes intrauterine growth restriction, tachycardia, cardiac failure, hydrops, advanced bone age, and goitre.

If fetal hyperthyroidism is diagnosed, treatment involves modulation of maternal antithyroid drugs. If fetal hypothyroidism has resulted from administration of antithyroid drugs to the mother, this treatment should be decreased or stopped and administration of intra-amniotic thyroxine considered. Early delivery may need to be considered in the case of fetal thyroid dysfunction, depending on the gestation at diagnosis and the severity of fetal symptoms.2

Postpartum period

Breast feeding

Because propylthiouracil and methimazole are secreted in human milk (the former less so because of its more extensive binding to albumin), concerns have been expressed in the past about the safety of breast feeding in women taking antithyroid drugs. However, only limited quantities of propylthiouracil and carbimazole are now known to be concentrated into milk. As long as the doses of methimazole or propylthiouracil can be kept moderate (propylthiouracil <250-300 mg a day, methimazole <20 mg a day), the risk for the infant is negligible, and no evidence based argument exists to advise mothers against breast feeding when they take an antithyroid drug. It is prudent to monitor periodically the infant's thyroid function while the mother is taking antithyroid drugs, although a recent reassuring study showed that thyroid function in breastfed infants was not affected, even when antithyroid drugs induced maternal hypothyroidism. The mother should also be advised to take her medication after a feed.2

Maternal and neonatal follow-up

The mother has a significant risk of exacerbation of hyperthyroidism postpartum, and thyroid function should be checked at 6 weeks and 3 months post delivery.

If a high TRAb concentration has been noted at 30 weeks, the neonate should be tested for hyperthyroidism after six hours and, if the test is positive, carbimazole should be started. If the mother has been taking an antithyroid drug up until delivery, the baby should be screened again several days later as he or she may well be euthyroid at birth but develop hyperthyroidism as the antithyroid drug is metabolised. The mother can be reassured that the disease in her baby will be self limiting to about three months because of the disappearance of the thyrotrophin receptor stimulating antibodies in the baby during this time.

Conclusions

- Close teamwork between obstetricians and endocrinologists minimize fetal and maternal risks of

Graves' disease, leading to good prognosis of both of them.

- First line therapy for Grave's disease during pregnancy includes antithyroid drugs (preferably propylthiouracil).
- To asses fetal thyroid function, fetal ultrasound at 28–32 weeks should be performed if there is evidence of active maternal Grave's disease.
- The improvement in the management of hyperthyroidism in pregnancy, particularly due to Graves' disease will depend on:
    - The capacity of the evaluation of thyroid function during gestation
    - - Further elucidation of the immunology of Graves' disease focusing on the TSH receptor and its interaction with stimulating antibodies and artificial designer compounds, which will provide a rational immunologic therapy.

Although untreated hyperthyroidism has potentially serious adverse effects on the mother and fetus, when treated promptly and monitored appropriately, the outcome for mother and fetus can be excellent.

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"Systemic Lupus Erythematosus and Pregnancy"

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Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease, involving complex pathogenic mechanisms. It mainly affects females [Female: Male= 9:1], of childbearing age group. Pregnancies in all SLE patients should be considered "high risk" due to potential maternal and fetal complications. For the best pregnancy outcomes, a planned pregnancy during a time of good control of SLE (on pregnancy compatible medications) and follow up by a multidisciplinary team with individually tailored plan is essential. SLE is the commonest autoimmune rheumatic disease encountered in pregnancy, so it is important to know pregnancy management in such patients (1)

Placental pathology in SLE pregnancy

Autoantibody production and immune complex formation leading to tissue deposition and injury is characteristicof SLE and its manifestations. The hormonal changes during pregnancy induces a shift from Th1 to Th2 lymphocytes making Th2-response autoimmune disorders, such as SLE,more likely to flare. Immune responses such as complement activation and T-cell signalling have been implicated in the development of placental insufficiency(2).

There are various antibodies that are involved. Anti-phospholipid (APL) antibodies can directly damage the placental phospholipid membrane resulting in compromised feto-maternal circulation. Placental villus dysplasia caused by placental vasculopathyis also autoimmune in nature. Other changes seen are excessive intervillous fibrin deposition and infarction (3).

Clinical features and Diagnosis

The clinical course is variable and characterized by periods of disease flare, interspersed with periods of remission. Common clinical signs and symptoms of SLE include fatigue, fever, arthritis, photosensitive rash, serositis, glomerulonephritis, vasculitis, hematologic abnormalities.

The revised classification criteria for the diagnosis of SLE was given by the European League Against Rheumatism (EULAR) and American college of Rheumatology (ACR) in 2019 [Table 1]. In this revision, an elevated antinuclear antibody is a mandatory entry criterion. Once this is present, the other additive criteria weighted, hierarchically, can be added to a numerical score. A score of 10 or more is required for diagnosis of SLE. (4)

Table 1: Revised Classification for SLE – EULAR, 2019(4).

Entry criterion
Antinuclear antibodies(ANA) at a titer of >1:80 on HEp-2cells or an equivalent positive test (ever).

If absent, do not classify as SLE
If present, apply additive criteria

Additive criteria
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score.
(Additional criteria within the same domain will not be counted)

Clinical domains and criteria	Weight	Immunology domains and criter	Weight
Constitutional		**Antiphospholipid antibodies**	
Fever	2	Anti-cardiolipin antibodies OR Anti-β2GPq antibodies OR Lupus anticoagulant	2
Hematologic		**Complement proteins**	
Leukopenia	3	Low C3 OR Low C4	3
Thrombocytopenia	4	Low C3 And Low C4	4
Autoimmune hemolysis	4	**SEL-Specific antibodies**	
Neuropsychiatric		Anti-dsDNA antibody* OR Anti-Smith antibody	6
Delirium	2		
Psychosis	3		
Seizure	5		
Mucocutaneous			
Non-Scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Effect of pregnancy on SLE

The long-term disease progression of SLE is usually not affected by pregnancy. Best predictor of the course of SLE during pregnancy is the state of disease activity at the onset of pregnancy, especiallypre-existing lupus nephritis. Flare is less likely if disease is in remission for six or more months prior to conception. It is always important to check for possibility of medication noncompliance, due to safety concerns of pregnancy. Risk of disease flare is 60% in women with severe disease prior to pregnancy compared to 10% in patient with a quiescent disease state (5). Pregnancy induced hormonal and immunological changes may lead to lupus flare. Skin, kidneys, blood, and joints are the most common organs affected during disease flare in pregnancy (2)

A lupus flare is difficult to diagnose during pregnancy as the signs and symptoms may mimic those of normal pregnancy. The Lupus Activity Index in Pregnancy is a validated, pregnancy-specific lupus activity scale (2).

Hydroxychloroquine (HCQ) promotes quiescence of lupus in pregnancy. During pregnancy HCQ, low dose oral prednisone,azathioprine and calcineurin inhibitors (ciclosporin A, tacrolimus) are commonly used for management of lupus flare. High dose glucocorticoids including pulse intravenous therapy and intravenous immunoglobulin can be considered for moderate to severe flare(1).Counselling of couple is needed for emphasis to continue pregnancy safe medication.

Effect of SLE on pregnancy

In women with SLE, overall maternal mortality is 20-fold higher than the general population but, not higher than non-pregnant women with SLE (1). There is increased risk of both maternal and fetal complications and therefore pregnancy with SLE is considered high risk. Maternal risks include lupus flare (lupus nephritis in particular), gestational diabetes, preeclampsia, venous thromboembolism [VTE]. Fetal risks include miscarriage, intrauterine fetal demise, preterm rupture of membranes, preterm birth, fetal growth restriction, and neonatal lupus (including congenital heart block).

Maternal complications

Fertility Issues

Fertility in women with SLE does not appear to be affected by disease itself. But it may be negatively affected by the associated chronic renal disease, periods of anovulation during a disease flare or immunosuppressant medications including high doses of corticosteroids and Cyclophosphamide (CYC). In addition, autoimmune oophoritis may contribute to premature ovarian failure, although data are limited (2). CYC treatment associated ovarian insufficiency risk depends on patient age and cumulative monthly CYC dose, it can be reduced by monthly gonadotropin-releasing hormone agonist co-therapy (10). CYC treatment associated ovarian insufficiency was more common in past when it was preferred therapy for lupus nephritis. Now mycophenolate mofetil is preferred in such cases, which does not cause infertility (6).

Hypertensive disease

Women with SLE have an increased risk of developing hypertensive disease in pregnancy specially women with lupus nephritis, antiphospholipid antibodies and those on corticosteroids. Preeclampsia can complicate 12% to 26% of pregnancies in women with SLE (2). Proposed mechanisms for preeclampsia, includes imbalances in angiogenic factors and uteroplacental ischemia (2). Differentiation of preeclampsia from lupus flare is difficult but important for management concerns. Both conditions can manifest with increasing proteinuria, deteriorating renal function, hypertension, and thrombocytopenia, and can even co-exist.

Gestational diabetes mellitus (GDM)

In women with SLE, especially on oral prednisone at 10 gm or higher, there is increased risk of GDM (6).

Venous thromboembolism (VTE)

40% women with SLE have APL antibodies, which may significantly affectpregnancy outcomes. In this group of women depending on history of obstetric or thrombotic complications (antiphospholipid syndrome) treatment with aspirin alone with or without prophylactic or therapeutic heparin should be given (6).

Fetal complications

In a lupus pregnancy, adverse fetal outcomes are attributed to multiple factors such as active disease within 6 months prior to conceptionor during pregnancy, secondary antiphospholipid antibody syndrome, hypocomplementemia, double-stranded DNA antibodies, thrombocytopenia, chronic hypertension, pre-existing renal disease, and first-trimester proteinuria. (2)

Pregnancy loss

A study of 202 pregnancies in women with SLE done in 2015 found a11% pregnancy loss rate, with 55% occurring within the first trimester, 40% in the second trimester, and 5% in the third trimester. Women with a combination of high clinical disease activity and the presence of serological markers are at highest risk for pregnancy loss. Same study concluded that a positive lupus anticoagulant test in the first trimester is the strongest predictor of pregnancy loss whereas a previous positive result was not associated with increased risk for first trimester loss (6)

Preterm Birth

A 2017 meta-analysis found a pooled relative risk of 2.98 (95% CI [2.32–3.83]) for preterm birth in SLE patients versus controls, which was strongly associated with active disease. (7).

Fetal growth restriction

In women with SLE, fgr is commonly due to placental insufficiency particularly among pregnancies complicated by active disease, LN, on chronic glucocorticoid treatment hypertension, and/or APS(1).

Neonatal lupus Erythematosus (NLE)

Neonatal lupus occurs in 1–2% of all pregnancies affected by SLE and is caused by the transplacental passage of maternal IgG antibodies (anti-Ro/SSA and anti-La/SSB) (2). Maternal disease activity is not related to development of neonatal lupus (5). Prospective studies show that among infants who are exposed to maternal anti-Ro/SSA and/or anti-La/SSB antibodies,around 10% develop an NLE rash, 20% transient cytopenias, and 30% mild transient transaminitis. These complications spontaneously resolve after 14-16 weeks as the child's maternal antibodies disappear(5). However, injury to conduction pathway of fetal heart by these antibodies can lead to permanent damage. Congenital Heart Block (CHB), occurring mostly between 16 and 24 weeks, affects 2% of pregnancies with positive antibodies and no history of previously affected pregnancies. The risk increases to 10–15% in those who have a prior history of another neonate affected with cutaneous lupus and up to 15–20% in those with a prior neonate affected with CHB. CHB is a long-term, essentially irreversible complication with increased fetal and neonatal mortality and the need for a pacemaker in up 70% of affected neonates (5)

In anti SSA/Ro positive pregnancies, HCQ reduces the recurrence rate of CHB by >50%, so this drug should be prescribed in such cases (2)

Oral Dexamethasone 4 mg daily is recommended for pregnant women with anti-Ro/SSA and/or anti-La/SSB antibodies and fetus with first- or second-degree heart block, but not for third degree (complete) heart block (10).

Management

Like many medical conditions in pregnancy, a multidisciplinary approach involving the rheumatologist, obstetrician experienced with high-risk care, fetal medicine specialist, paediatric cardiologist in cases of

fetal heart block and a nephrologist (if renal disease is present or if it develops later), is necessary for successful pregnancy outcome in woman with SLE.

Pre-conceptional counselling and workup

Effective pre-conceptional risk assessment and stratification with tailored counselling is the first step towards the management of such high-risk cases.

The objective of the pre-conception consult is to gather detailed information regarding disease activity, as well as a thorough review of medical, surgical, and obstetric history. All medications and baseline investigations should be noted. [Table 2]. Women with SLE, who are planning pregnancy and need medical therapy should be started on pregnancy compatible medications and to be followed for compliance and efficacy.

Table 2:Preconception visit checklist (1)

Age
Past Obstetric history (including any maternal and fetal complication)
Past and current lupus activity, especially lupus nephritis
Preexisting organ damage
Recent Serological profile (anti-ds DNA, anti-Ro/La antibodies, complement levels)
Presence of Antiphospholipid antibodies (aPL)/syndrome (APS)
Presence of autoimmune thyroid antibodies
Additional medical disorder (e.g. hypertension, diabetes, renal disease, thyroid disorder)
Medication history
Baseline blood pressure
Baseline investigations: complete blood picture, urinalysis, creatinine, electrolytes, Liver Function Test +/- organ specific investigations

Based on this information, women with SLE can be divided into the 3 following groups which simplifies the overall approach to managementwith adjustment for individual situations (1):

1. SLE in remission, or stable low disease activity and on stable medication: It is safe to plan a pregnancy for women of this group.Medications should be reviewed and adjusted, as necessary.
2. SLE at an early stage following recent diagnosis, or active disease: these women should use effective contraception and postpone pregnancy until SLE condition improves (or ideally, enters remission). Pregnancy compatible medication should be prescribed, and further review should be done to monitor efficacy and tolerability.
3. Severe impairment of organ function and/or pre-existing severe organ damage: pregnancy should be discouraged. Important to know severe lupus flare (including renal flare) within the past 6 months, chronic kidney disease stage 4–5 (creatinine >2.5–2.8 mg/dL), stroke, severe restrictive lung disease (forced vital capacity <50% of predicted), pulmonary hypertension (estimated systolic pulmonary artery pressure >50 mmHg, or symptomatic), heart failure (left ventricular ejection fraction <40%),severe valvopathy, uncontrolled hypertension, previous severe early-onset (< 28 weeks) preeclampsia or HELLP despite therapy with aspirin plus heparin are some clinical conditions in which pregnancy is absolute or relatively contraindicated(1).

Once the women are stable with inactive disease, for at least 6 months, discussion of potential medical (effect of pregnancy on SLE) and obstetric risks(effect of SLE on pregnancy), and appropriate planning for pregnancy, can be undertaken. Risks associated with antiphospholipid syndrome (APS) and anti-Ro and/or anti-La antibodies should be discussed if applicable.

Antenatal management

Management includes strict maternal and fetal surveillance.

[A] Maternal:

At the first visit, women should be seen by both obstetrician and rheumatologist to ascertain disease status and pregnancy risk. Further visits should be individualized according to obstetric and medical complications. The assessment and tests needed during the antenatal period are summarized in table 3.

As a guide, women should be reviewed every 4 weeks from 16 to 28 weeks, every 2 weeks from 28 to 34 weeks, and every week from 34 weeks (9). Each visit should document the presence or absence of flare or preeclampsia symptoms, plus blood pressure, dipstick urinalysis, symphysial-fundal height, and fetal heart rate (8).

Elevated anti-dsDNA and low (fall of ≥25%) C3 indicate active SLE or impending flare in over 80% of patients. Proteinuria and/or an active urine sediment (red blood cells, white blood cells, and cellular casts), is often associated with Lupus nephritis whereas only proteinuria is seen in patients with preeclampsia.

Presence of anaemia should be investigated. Iron-deficiency anemia, anemia of chronic inflammation or hemolytic anemia are the usual differential diagnosis. In SLE, iron replacement should not be given without proof as it may worsen the autoimmune disease.

A low platelet count can be a clue to the presence of antiphospholipid antibodies.

Increased risk of pregnancy loss and preterm births are associated with autoimmune thyroid antibodies (6).

All women with SLE should take low-dose aspirin (75 mg) from 12 weeks till 36 weeks of pregnancy to reduce the risk of preeclampsia. In addition, ACR recommends if possible, all women with SLE should take hydroxychloroquine (HCQ (10). Thromboprophylaxis should be given to those are at high risk for VTE. Document an anesthetic plan for labor and delivery.

Table 3: Antenatal visit assessments and tests (1,6)

First Visit/ when pregnancy is confirmed	Physical examination, including blood pressure Complete blood count (CBC) Renal function tests (creatinine, urinalysis, spot urine protein/creatinine ratio) Test for anti-Ro/SSA and anti-La/SSB antibodies (if not done in pre-pregnancy) Lupus anticoagulant and anticardiolipin antibody studies (If not done prior) TSH and autoimmune thyroid antibodies. Anti–double-stranded DNA (anti-dsDNA) test Complement (CH50 or C3 and C4) tests Liver Function test Serum uric acid
Lab tests at regular intervals	CBC Creatinine Urinalysis with examination of urinary sediment Spot urine protein/creatinine ratio or 24-hour urine collection
Labs at the time of flare/ active disease	Anti-dsDNA antibodies Complement (CH50, or C3 and C4)

[B] Fetal:

EULAR recommends, after accurate pregnancy dating, women should be offered routine pregnancy screening and scans (9). Supplementary fetal surveillance in the third trimester at monthly intervals – frequency may be individualized if there are signs of fetal compromise.

Considering the increased risk of CHB, in patients with positive anti-Ro/ SSA and/or anti-La/SSB antibodies, serial fetal echocardiography and determination of fetal PR interval every 1-2 weeks from 16-18 weeks till 26–28 is recommended (7). This screening of CHB should done weekly if, in addition to antibodies if there as a history of an infant with complete heart block (CHB) or neonatal lupus erythematosus(5,10)The fetal heart rate auscultation and documentation should be done at every 1-2 weeks.

Delivery

Women with SLE have an increased risk of preterm birth both spontaneous and iatrogenic. Many may require delivery prior to 39 weeks due to maternal and/or fetal concerns (severe lupus flare, preeclampsia, FGR). Steroids, preferably betamethasone, for fetal lung maturity are essential if the gestational age is between 24 to 34 weeks. Magnesium sulphate is recommended for neuroprotection if the fetus is less than 32 weeks of gestation(1). Available data are suggestive of high caesarean section rates in women with SLE: this may be for many reasons(1). Mode of delivery is as per obstetric indication.

Maternal medications adjustment willbe required for delivery. Women on heparin, whether therapeutic or prophylaxis, require adjustment of dose prior to planned delivery. LMWH should discontinue it at the onset of spontaneous labor or 24 hours before induced labor or elective cesarean sectionIntravenous hydrocortisone is required to cover the physiological stress of labor and delivery, if women on long term steroids (1).

Postnatal

It is important for continued vigilance postpartum due to the increased risk of lupus during this period. Thromboprophylaxis should be given to all women according to their VTE risk. The threshold for postpartum thromboprophylaxis is lower than antenatal as this is a time of greater risk.The safety of medications and their use during breast feeding should be individualized. HCQ, prednisone, cyclosporine, azathioprine, and tacrolimus are considered compatible with breast feeding.Cyclophosphamide, Methotrexate, MMF, and leflunomide are contraindicated in lactation.If using prednisone >20 mg/day, discard the breast milk obtained within 4 hours of medication(10).

Contraception

Based on their disease activity (including medications) and thrombotic risk (particularly aPL status), all women with SLE should be counselled about the use of effective contraceptive measures. Long-acting reversible contraceptives [LARC] methods are suitable. Non- hormonal intrauterine device is the optimal choice in women with SLE considering their highefficacy and safety. Combined hormonal contraceptives can be consideredin patients with stable/inactive SLE and negative aPL. Avoid transdermal estrogen progestin patch in these women (10).

SLEMedications in pregnancy

Use of medications should be balanced against effect of uncontrolled SLE and compatibility of medication with pregnancy. Table 4 summarises the various medications that are indicated for the treatment of SLE.

Table 4: SLE medication in pregnancy(1):

	Pre- conceptional	Pregnancy	Lactation
Anti-inflammatories and analgesics			
NSAIDs (eg, ibuprofen)	Ideally stop before pregnancy	Can be used with caution intermittently in first and second trimesters. Avoid after 32 weeks	Safe
Aspirin 75 mg	Safe	Safe	Safe
Paracetamol	Safe	Safe	Safe
Corticosteroids (non-fluorinated)			
Prednisolone/ methylprednisolone/ hydrocortisone	Safe	Safe Aim to use steroid sparing immunosuppressant (eg, azathioprine) with either lowest effective maintenance	Safe – only small amounts in breast milk (5%–25%)
Immunosuppressants (including anti-malarial)			
HCQ	Safe	Safe	Safe
Azathioprine		Safe. daily dose should not exceed 2 mg/kg per day.	Safe
Tacrolimus	Safe	Safe	Safe
Cyclosporine	Safe	Safe	Safe
Mycophenolate mofetil	Stop, ideally 3 months before planned pregnancy and switch to pregnancy safe medication	Stop before pregnancy	Avoid
Methotrexate	Stop >3 months before planned pregnancy	Contraindicated in pregnancy	Avoid
Cyclophosphamide	Stop >3 months before planned pregnancy	Stop before pregnancy.	Avoid

Conclusion

Most lupus pregnancies can be managed successfully with strict maternal and fetal surveillance and timely interventions. Coordinated care by obstetricians and multidisciplinary team is important. Women in sustained lupus remission prior to conception have a low rate of maternal and fetal complications. Hence, pre-conceptional counselling is of paramount importance. All women with SLE should be started on HCQ prior to pregnancy if possible for better outcomes.

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Liver Diseases in pregnancy

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Liver tests abnormalities are observed in 3-5% of pregnant women; pregnancy induced liver dysfunction being most common. Physiological changes of pregnancy do not affect liver transaminases, serum bilirubin, and prothrombin time; any abnormalities in these point towards liver dysfunction. Non-specific symptoms of liver diseases like vomiting, nausea and abdominal pain are commonly neglected and increase the likelihood of delay in diagnosis.

Liver diseases during pregnancy can be broadly classified into disorders unique to pregnancy, those coincidental with pregnancy, and preexisting liver diseases exacerbated by pregnancy (Table 1). Besides, pregnancy-related physiologic changes may predispose to certain hepato-biliary diseases like cholelithiasis and Budd-Chiari syndrome (BCS).

An urgent diagnosis is required so that prompt referral and timely management can prevent adverse maternal and fetal outcome. Therapeutic decisions in liver disorders have implications for the fetus too, which make the scenario complex and challenging.

Normal physiological changes in pregnancy

Pregnancy results in a hyper-dynamic circulation which can worsen pre-existing liver diseases. It is also a pro-coagulant state predisposing to increased thrombosis and related disorders. In normal pregnancy, most liver biochemical tests are normal; any elevation of serum aminotransferases, bilirubin, or bile acid concentrations are pathological and should prompt further evaluation. A rise in serum alkaline phosphatase (ALP) in the third trimester is considered normal, as it is of placental origin rather than from the liver. Its elevation in the non-pregnant population usually indicates cholestasis. Elevated serum gamma-glutamyl transpeptidase (GGT) is also a marker of cholestasis, but is unaffected in pregnancy. So, if both ALP and serum GGT levels are elevated in pregnancy, it suggests a cholestatic liver injury pattern, on the contrary, isolated elevation of ALP is of no significance.

Approach towards the diagnosis

Symptoms of liver disease include jaundice, high-colored urine, pruritus, clay-colored stools, abdominal pain, nausea, vomiting, etc., or the patient may present with liver tests abnormalities.

The first step in assessing a woman presenting at any stage of pregnancy should be the same as with any non-pregnant patient (Figure 1). Some pregnancy induced liver diseases typically present in a particular trimester, thus the timing may suggest their prompt identification. Some pregnancy induced liver diseases may also present in the postpartum period. Imaging plays an important role in differential diagnosis; ultrasound (US) is safe and the preferred imaging modality for rapid assessment of hepato-biliary diseases. Magnetic resonance imaging (MRI) without gadolinium can be used in the second and third trimesters as an adjunct to US.

Syndromic approach to differential diagnosis

In pregnancy, or even otherwise in patients presenting with jaundice, a syndromic approach based on pathophysiology is useful in pinpointing the diagnosis. Based on the pattern of symptoms, abnormal hematological/biochemical parameters, the disease can be classified into disorders of hemolysis, hepatocellular injury, or cholestatic liver injury; mixed patterns are often seen. In disorders of hemolysis,

patients have anemia, indirect hyperbilirubinemia and evidence of hemolysis on workup, notably urine colored is unaltered. Patients with hepatocellular injury present with a prodrome (fever, nausea, myalgia, etc.) preceding jaundice; or with liver failure (ascites, encephalopathy, etc.). On the other hand, patients with cholestatic features usually present with generalized pruritus and clay-colored stools.

Liver diseases unique to pregnancy

Hyperemesis Gravidarum (HG)

HG occurs in 0.3-2% of pregnancies, and presents in the first trimester with intractable vomiting, dehydration, weight loss, electrolyte imbalance, and nutritional deficiency. in most cases, it resolves by the twentieth week of gestation. Liver involvement is seen in 50% to 60% of cases, manifesting as mild to moderate elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels; jaundice is rarely seen. Liver enzymes return to normal levels after resolution of HG without any long-term sequelae.

Intrahepatic cholestasis of pregnancy (ICP)

ICP has a prevalence of 0.3-5.6%, and presents in the second and third trimesters as generalized pruritus, predominantly affecting palms and soles. Jaundice occurs in less than 25%, some patients have pale stools. The disease is self-limiting and resolves by 2-3 weeks after delivery. Laboratory abnormalities include mild elevations of AST and ALT and a significant increase in GGT level. Vitamin K deficiency leads to prolonged prothrombin time (PT), if uncorrected can result in postpartum hemorrhage. Bile acid concentrations are elevated, and a concentration >40 µmol/l is associated with a higher risk of prematurity, fetal distress, and death. First-line therapy is ursodeoxycholic acid (UDCA), early delivery at 37 weeks is recommended as intrauterine death is more common in the last month of pregnancy.

Hypertensive disorders of pregnancy: **Pre-eclampsia/eclampsia/HELLP syndrome**

Pre-eclampsia can occur in 3-5% of pregnancies; patients usually present at 20 weeks of gestation to as late as 4 weeks post-partum. Patients with liver involvement commonly present with epigastric or right upper quadrant pain, likely due to hepatomegaly stretching Glisson's capsule, rarely sub-capsular hematoma, and hepatic rupture can occur. Bilirubin is usually less than 5 mg/dL; however, striking elevations of transaminases are observed in around 30% of pre-eclampsia cases.

Multiple organ dysfunction defines defines severe eclampsia and can complicate about 25% of cases. Complications include severe liver involvement, renal insufficiency, neurological dysfunction, hematologic derangements (like thrombocytopenia, disseminated intravascular coagulation), and placental abruption.

No specific therapy is recommended for liver dysfunction, the only curative therapy is delivery of the fetus. Treatment aims at management of blood pressure, seizures, and multiorgan failure by a multidisciplinary team. Patients with severe preeclampsia should be delivered after 34 weeks of gestation and expectant management should be done between 25 and 34 weeks provided the patient is stable. Vaginal delivery is the preferred route but is not always possible.*HELLP syndrome* (syndrome of Hemolysis, Elevated Liver enzymes, and Low Platelets)

HELLP syndrome represents a form of pre-eclampsia/eclampsia; It complicates 10% to 20% of cases. It predominantly occurs in the third trimester, however 30% cases, present in early postpartum period. Notably, HELLP syndrome can occur in patients without hypertension. To identify HELLP syndrome, two diagnostic criteria have been laid, the Tennessee classification, and the Mississippi Triple Class System (Table 2). Management is on the lines of severe pre-eclampsia; additionally intravenous dexamethasone can be given to improve platelet counts.

Imaging should be done urgently if the patient is complaining of right upper quadrant abdominal pain, shoulder tip pain, or having hypotension; these features indicate enlarging subcapsular hematomas or

hepatic rupture and an emergent need of surgical or radiological intervention. Liver transplantation (LT) has also been successfully performed in selected cases.

Acute Fatty Liver of Pregnancy (AFLP)

AFLP usually presents in the third trimester, although up to 20% patients can present postnatally. About 50% of patients with AFLP can have pre-eclampsia, and there is some overlap with the HELLP syndrome, causing diagnostic difficulties. Typically, the disease is characterized by microvesicular fat deposition in the liver and is caused by inherited deficiencies of mitochondrial enzymes. Maternal mortality is reported to be 10-15%, and fetal mortality is up to 20%.

Patients usually present with anorexia, nausea, vomiting, and abdominal pain, or with acute liver failure features (jaundice, encephalopathy, hypoglycemia, and coagulopathy). Biochemical abnormalities include moderate to severe aminotransferase elevations, hyperbilirubinemia (usually < 5mg/dl), and coagulopathy. Proteinuria can also occur in AFLP as in cases of pre-eclampsia. US can demonstrate abnormality consistent with fatty infiltration. A liver biopsy can confirm the diagnosis but is usually not performed owing to coagulopathy. Clinical diagnosis can be made by the Swansea criteria with certainty if at least six of the features are present (Table 3). It is also important to quickly rule out other causes of acute liver failure (ALF) in pregnancy (see below).

AFLP management involves prompt termination of pregnancy. The decision on the mode of delivery is based on obstetric assessment (likelihood of controlled vaginal delivery in less than 24 hours) in consultation with a multidisciplinary team. Patients should be managed in the Intensive care unit (ICU) and standard medical treatment of ALF is followed. Despite delivery, laboratory and clinical abnormalities may persist for a week postpartum; or rarely progress to liver failure requiring LT.

Liver disease coincidental with pregnancy

Acute viral hepatitis

Acute viral hepatitis is the commonest cause of jaundice occurring in pregnancy. Hepatitis A virus infection in pregnancy usually has a benign course similar to the non-pregnant population. Hepatitis E virus infection is more common in adults, and the incidence of acute liver failure and related maternal mortality in pregnancy is higher (15-25% of cases) as compared to HAV infection. Herpes simplex related hepatitis is rare, mucocutaneous lesions are seen only in less than 50% of cases, requiring a high index of suspicion. Mortality is high in untreated patients, empirical treatment with acyclovir is warranted pending confirmatory serologies or viral genome detection. Bloodborne pathogens like hepatitis B or C viruses causing acute hepatitis are rare in pregnancy, when detected need to be evaluated further regarding the need for antivirals; spontaneous clearance of the virus can occur.

Patients have a prodrome of fever, nausea, vomiting, myalgia, etc which is followed by jaundice. Biochemical abnormalities include elevated AST, ALT levels (more than 10-20 times normal) with relatively normal/mildly elevated GGT. Prolongation of PT (INR >1.5) uncorrected with vitamin K is a sinistral finding and may herald ALF. Etiological diagnosis can be easily achieved with commonly available serologies of related viruses.

The management is largely supportive as in the non-pregnant population. Patients with coagulopathy or ALF should be managed by a multidisciplinary team in ICU, LT can be offered in those fulfilling poor prognostic criteria (King's college hospital criteria, etc.).

Budd-Chiari syndrome

BCS or hepatic venous outflow tract obstruction (HVOTO) is a rare disorder causing thrombosis of the hepatic veins or the terminal portion of the inferior vena cava (IVC). It results in liver sinusoidal congestion, ischemic injury leading to liver dysfunction and portal hypertension. Twenty percent of cases of BCS syndrome occur in pregnancy or in the early postpartum period.

Patients usually present with varied acute or subacute symptoms like jaundice, right upper quadrant

abdominal pain, ascites, and rarely ALF. A history of recurrent systemic arterial or venous thrombotic syndromes like cerebral ischemic stroke, deep vein thrombosis may be elicited in some cases. Doppler of IVC and hepatoportal circulation rapidly establishes the diagnosis. A preexisting cause of hypercoagulability should be sought in all patients.

Management of BCS presenting in pregnancy is similar to the nonpregnant population. Vitamin K antagonists are contraindicated in pregnancy; anticoagulants of choice are low-molecular-weight heparins. Historically, BCS in pregnancy was associated with poor maternal and fetal outcomes, but with improvement in treatment standards, survival rates have improved from 50% to 90%. BCS currently is not considered a contraindication to pregnancy in patients with well-controlled disease. LT has been used as a rescue measure in some patients. Lifelong anticoagulant is recommended in patients with the preexisting procoagulant state.

Sepsis and other tropical infections

Sepsis in pregnancy can lead to cholestastatic jaundice.Several tropical diseases can also cause the syndrome of jaundice, encephalopathy, coagulopathy (ALF mimics) as a part of multi-organ involvement. List of such infections includes septicemia from any systemic bacterial infection, malaria, dengue, typhoid, scrub typhus, leptospirosis, etc. Urgent sepsis workup including cultures and specific diagnostic tests for identification of specific organisms should be done. Management is the same as in non-pregnant patients barring a few exceptions like few antibiotics or drugs in pregnancy are avoided.

Underlying liver diseases in pregnancy

Cirrhosis and portal hypertension

In women with cirrhosis, fertility is reduced due to metabolic and endocrine dysfunction. In pregnancy, there is a risk of hepatic decompensations with the development of jaundice, ascites, variceal hemorrhage, and encephalopathy. With improvement in standard care, maternal mortality has reduced to around 1.6%, although decompensation can occur in 10% of cases. Outcomes of pregnancy are unrelated to the etiology but depend on the severity of the maternal liver disease as assessed by prognostic scoring systems like Child's score or the model for end stage liver disease (MELD).

Portal hypertension worsens in pregnancy, and patients with pre-existent varices have an increased risk of hemorrhage especially in the second trimester and peripartum. If the patient is cirrhotic before pregnancy, endoscopic screening of varices in the second trimester is recommended. Depending on the risk of bleeding as assessed by variceal morphology, either repeated endoscopic ligation or prophylactic beta-blocker are advised.

In cases of decompensated cirrhosis, the decision to terminate a pregnancy must be individualized depending on the severity of liver disease and stage of pregnancy. Assisted vaginal delivery may be preferred to shorten the second stage of labor. Cesarean section is performed according to obstetric indications; there is an increased risk of bleeding, poor wound healing, and infection.

Chronic viral hepatitis:

Every pregnant woman should be screened for chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) in the initial visit, recommended tests are hepatitis B surface antigen (HBsAg) and anti-hepatitis C (Anti HCV) antibody.

Chronic hepatitis B infection:

The prevalence of HBsAg positivity in pregnant women varies from 1-9% in India, most infections are incidentally detected during screening. The patients are usually inactive carriers, only a few have chronic active hepatitis warranting antiviral treatment. Although AST/ALT levels are increased during pregnancy and postpartum, these return to normal. Jaundice and hepatic decompensations are rare but can occur in a patient having advanced hepatic fibrosis or cirrhosis.

To prevent maternal and child transmission (MTCT), all infants born to HBsAg positive mothers should

receive hepatitis B immunoglobulin preferably within 24 hrs in addition to the complete dosage schedule of hepatitis B vaccine. Despite receiving passive and active vaccination, transmission occurs in up to 25% of infants born to mothers with HBV DNA levels greater than 200,000 IU/mL, therefore, initiation of antivirals at 24-28 weeks is recommended in such cases. Tenofovir and lamivudine are currently the recommended drugs, and are continued for up to 12 weeks after delivery. Subsequent discontinuation at 1–3 months postpartum is recommended in whom the antivirals were started for the sole purpose of prevention of MTCT, who otherwise do not need continued therapy as per their hepatitis B infection status. Notably, mode of delivery is not associated with an increased risk of transmission and breastfeeding should be encouraged.

Chronic hepatitis C infection:

In a recent meta-analysis, the pooled seroprevalence of hepatitis C in pregnant women in India was 0.88%. In one such study, 50% of pregnant women harboring anti HCV antibodies had detectable HCV RNA suggesting the presence of active infection.

Presence of detectable HCV RNA is an indication of treatment with highly effective direct-acting antivirals (DAA). DAA before pregnancy cures the patient thus eliminating the risk of MTCT if they become pregnant. Women who become pregnant while on DAA therapy should discuss the risks versus benefits of continuing treatment with their physicians on a case-to-case basis; the safety of DAA has not been established in pregnancy.

HCV-infected pregnant women have a higher incidence of ICP and adverse fetal outcomes. However, HCV infection confers a little increased risk to pregnant women except in the context of advanced fibrosis or cirrhosis. Neonatal transmission occurs in 5 to 15% of HCV RNA positive mothers, coinfection with HIV has been associated with an increased risk. Currently, there is no role of available antivirals in preventing MTCT.The mode of delivery does not influence the risk of vertical transmission. Breastfeeding is not contraindicated unless the mother has cracked or bleeding nipples or in the presence of HIV coinfection.

Autoimmune hepatitis (AIH)

AIH is characterized by chronic lymphoplasmacytic interface hepatitis with varying degrees of hepatic fibrosis; acute flare can present as acute hepatitis or ALF. Circulating autoantibodies and elevated serum globulin levels are hallmarks of the disease. Association with other autoimmune disorders like autoimmune thyroiditis, type 1 diabetes, ulcerative colitis, etc. is seen in a few. It's more common in young females, hence obstetricians should have a high index of suspicion in pregnant females having unexplained elevations of liver enzymes or chronic liver disease.

Pregnancy in autoimmune hepatitis has unfavorable maternal and fetal outcomes, but with improvements in the standard of care, pregnancy and liver disease can be successfully managed. The most common maternal complication is disease flare either during the gestational period (7–21%) or in the postpartum period (up to 50%). In the majority, a flare can be controlled by increasing immunosuppression, but in some cases with underlying cirrhosis, hepatic decompensations can occur needing LT for survival.

Conclusion

Liver disease in pregnancy is a distinct group of patients due to the increased morbidity and mortality for both the mother and baby. The spectrum of disease and presentation varies widely, causing delays in diagnosis and management. Women of childbearing age should have pre-pregnancy counselling. Once a pregnant woman presents with liver disease, early diagnosis, rapid referral to specialist physicians and management by a multidisciplinary team is of utmost importance. Maternal and fetal outcomes are improving due to ongoing research, improved guidelines and better therapeutic options.

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Table 1: Liver diseases in pregnancy

Diseases Unique to Pregnancy	Diseases coincidental to Pregnancy	Underlying Chronic Liver Disease
Hyperemesis gravidarum	Acute viral hepatitis	Cirrhosis
ICP	Budd-Chiari syndrome	Portal hypertension
Pre-eclampsia	Sepsis	Chronic hepatitis B or C
HELLP syndrome	Tropical infections	Autoimmune hepatitis
AFLP	Others: • Gallstones • Drugs	Others: • Primary sclerosing cholangitis • Primary biliary cirrhosis • Wilson's disease

ICP, Intrahepatic cholestasis of pregnancy; HELLP, hemolysis, elevated liver enzymes, low platelets; AFLP; acute fatty liver of pregnancy.

Table 2: Diagnosis of HELLP syndrome and its grading

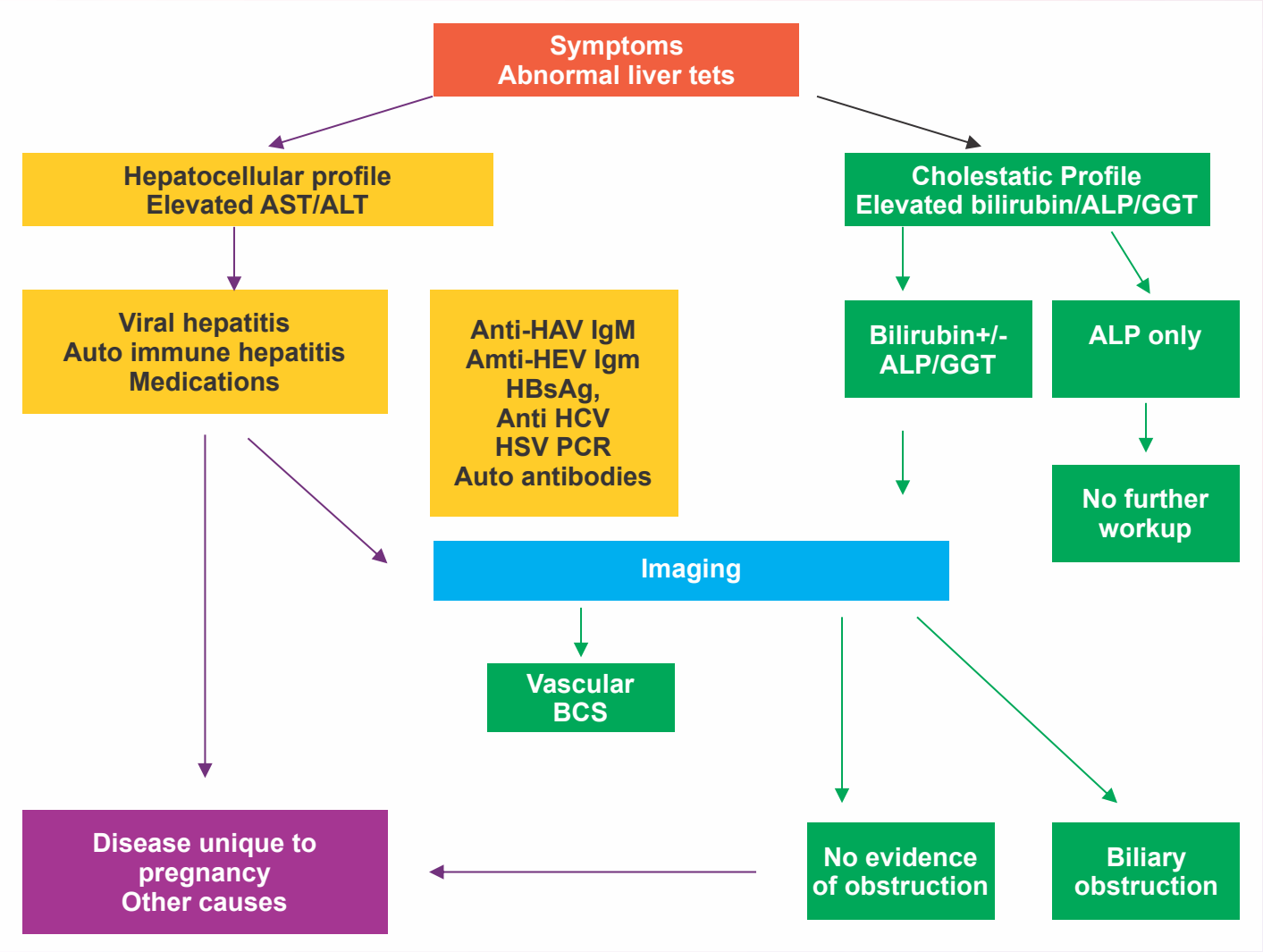
Tennessee Classification	Mississippi Classification
Complete syndrome • Platelets <100,000/L • AST >70 IU/L • LDH > 600U/L	Class 1 • Platelets <50,000/L • AST or ALT >70 IU/l • LDH > 600U/L
Incomplete syndrome • One or two elements of the triad	Class 2 • Platelets 50,000 to 100,000/L • AST or ALT >70 IU/L • LDH >600 IU/L
	Class 3 • Platelets 100,000 to 150,000/L • AST or ALT >40 IU/L • LDH >600 IU/L

HELLP, hemolysis, elevated liver enzymes, low platelet count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase.

Table 3: Swansea criteria for diagnosis of acute fatty liver of pregnancy

Atleast6 of the 15 criteria should be fulfilled the diagnosis of AFLP, in the absence of other causes

1. Vomiting
2. Abdominal Pain
3. Polydipsia/ polyuria
4. Encephalopathy
5. Bilirubin >0.8 mg/ dL
6. Hypoglycemia <72 mg/dL
7. Elevated urea >950 mg/ dL
8. White blood cell count >11 x 10^9/ L
9. Ascites
10. ALT >42 U/L
11. Ammonia >66 µmol/dL
12. AKI or creatinine >1.7 mg/dL
13. Coagulopathy or PT >14 s
14. “Bright liver” on ultrasound
15. Microvesicular steatosis on liver biopsy


Symptoms
Abnormal liver tets
Hepatocellular profile
Elevated AST/ALT
Cholestatic Profile
Elevated bilirubin/ALP/GGT
Viral hepatitis
Auto immune hepatitis
Medications
Anti-HAV IgM
Amti-HEV Igm
HBsAg,
Anti HCV
HSV PCR
Auto antibodies
Bilirubin+/-
ALP/GGT
ALP only
No further
workup
Imaging
Vascular
BCS
Disease unique to
pregnancy
Other causes
No evidence
of obstruction
Biliary
obstruction

Cancers and Pregnancy

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Introduction

Cancer during pregnancy is an uncommon occurrence, with an estimated incidence of 1 in 1,000 pregnancies corresponding to 0.07-0.1% of all malignant tumors.Most common cancers associated with pregnancy are breast, cervical, haematological, ovarian, thyroid, lymphoma colon and central nervous system cancers. Cancer itself rarely affects the growing fetus however when it does occur during pregnancy,it can be more complex to diagnose and treat. The pregnancies complicated by cancer are considered as high risk pregnancies.

Tests used for diagnosis and the treatment required can have medical, ethical and psychological issues and thus the cancer care should involve a multidisciplinary team approach involving obstetricians, oncologists(radiation, medical),paediatriciansand psychologists. Main priorityis to cure the mother andmanagement planned should adhere to standard protocol similar to that fornon-pregnant patients. It is possible to carry out cancer treatment during pregnancy with slight modifications without compromising fetal safety.

Diagnosis of cancer during pregnancy

Clinical presentation

The symptoms that are normal in pregnancy can mask the symptoms caused by a malignancy as nausea, vomiting, abdominal discomfort, vaginal discharge/bleeding and fatigue are common complaints in normal pregnancy also. Thus, normal physiological changes (breast and uterus) during pregnancy may make the physical examination difficult. Thus causing delay in seeking advice and treatment. Therefore, it is important to do a careful clinical examination in all pregnant women during routine antenatal check-ups.Special attention should be given, if women have any persisting/worsening complaints as delay in diagnosis can lead to late presentation, treatment complexity and poor prognosis.

Once cancer is diagnosed during pregnancy,a comprehensive evaluation for staging should be done as for non-pregnant women, but should only be performed if they change clinical practice. While evaluating the main concern is fetal exposure to ionizing radiation, contrasts used for imaging and surgical/ anaesthetic procedures conducted during pregnancy.

Investigations

Tumor markers

Tumor markers helps in diagnosis, prognostication and follow-up and to assess response of treatment in patients with cancer. However, should be used with cautionas due to physiological variations in serum levels during pregnancy, their sensitivity and specificity may be lower. Thus, physiological changes and the accompanying alteration in serum parameters during pregnancy may further complicate the diagnosis of malignancy. Normally in pregnancy, the values of hemoglobin and haematocrit are lower, whereas the value of alkaline phosphatase is increased. Commonly used tumor

markers CA 125 for epithelial ovarian cancer, alpha-fetoprotein used for germ cell tumors and CA 15-3 for breast cancer are also physiologically raised in pregnancy. While, levels of serum markers; CEA, CA19-9, LDH and HE-4 are not increased during pregnancy. However, there are some exceptions like LDH, which increases in hypertensive disorders and inhibin B levels increases during third trimester of pregnancy.

Imaging

Evaluation of malignancy and assessment of metastatic disease often require imaging. The major concern is of radiation exposure to the fetus and its consequences. The severity of radiation exposure depends on the gestational age at which imaging is performed. Exposure occurring in early first trimester during the stage of organogenesis, have a higher chance to cause fetal malformations. However, exposure to ionizing radiation anytime during pregnancy might result in cognitive impairment. The major determinant factor is the cumulative radiation dose that is received by the fetus. Higher the dose of radiation,more severe is the impairment, with an exponential risk in exposures if the threshold dose is exceeded, that is100 mGys.(Table1)

Table 1. Radiation doses for commonly performed radiologic examination

Examination	Doses (mGy)
X-Ray chest	0.0005–0.01
Contrast tomography(CT) Head and neck	0.001–0.01
Mammography	0.001-0.01
X-Ray Abdomen	0.1–3.0
Intravenous pyelography	5–10
X-Ray Lumbar spine	1.0 –10
CT chest/ pulmonary angiography	0.01–0.66
CT Abdomen	1.3–35
CT Pelvis	10 –50
18F PET/CT whole body	10 –50

The preferred modalities of imaging in pregnancy are ultrasound and magnetic resonance imaging (MRI), which are associated with minimal or no increased risk. Ultrasound can be used both for diagnosis and staging. It is a non-invasive imaging modality and can be used to perform guided biopsies especially in case of breast lump or from lymph nodes. MRI without contrast can be used safely in all trimesters and is the preferred imaging modality for diagnosing and staging the disease.Whenever required X-ray with adequate abdominal shielding can be used if necessary for proper staging and management of the patient.But CT abdomen and pelvis, fluoroscopic images used in procedures should be avoided, as they deliver higher doses of radiation to fetus.

Treatment during pregnancy

Surgery

The aim of surgical management is for diagnosis, treatment and staging. Risks associated with surgical procedure and use of anaesthetic agents includes slightly increased risk of miscarriage, and increased likelihood of preterm delivery and low birth weight (1.5-2 times RR). The complication rate and morbidity

are more with pelvic and abdominal surgeries. However, owing to the potential benefits of treatment and minimal fetal risk surgery can be performed in all trimesters, if indicated. It is preferable to carry out surgery in the early second trimester as gestation advances it is technically complicated due to uterine enlargement. In selected cases, if it is not emergency then it can be postponed till fetal lung maturity without compromising care.

Regional anaesthesia is preferred, if possibleand a left lateral tilt is recommended to prevent aortocaval compression. Excessive uterine manipulationshould be avoided, tocolytics should be given if surgery is carried out after 28 weeks to prevent premature labor with adequate steroid coverage.

Surgery can be carried out safely after first trimester and depending on gestational age and surgeon's skill it can laparoscopic/open surgery. At ≤ 22 weeks pelvic lymphadenectomy can be performed but at > 22 weeks, it is difficult to perform complete lymph node dissection due to uterine enlargement.

Systemic treatment

Chemotherapy

Physiological changes of pregnancy influence the exposure and efficacy of systemic treatment. Chemotherapy should not be initiated during first trimester due to risk of fetal malformations (10%–20%). The delay in treatment until second trimester for fetal benefit should be balanced against maternal risk due to cancer . The chemotherapy agents that can be administered a fter 14 weeks of gestationincludetaxanes, platinum, anthracyclines, etoposide and bleomycin. However, there is increased risk of fetal growth restriction, prematurity and preterm rupture of membrane with use of chemotherapeutic agents.Small for gestation neonates are commonly associated with platinum-based chemotherapy, whereas increased risk of NICU admission is seen with taxanes. Most of chemotherapeutic agents due to small molecular weight can cross placenta so, w hen chemotherapy is initiat ed deliver y should be planned carefully . Awindow period of 3-week is recommended between the last cycle and delivery for both maternal and fetal bone marrow recovery. Therefore, it should not be administered beyond 37 week s due to risk of onset of spontaneous labor.

Targeted therapy and immunotherapy

Targeted therapy is directed at specific tumor related receptors which also play a role in fetal development. Hence, their use might increase the risk of fetal complications. Rituximab used for treat B cell malignancies has teratogenic effect when used during first trimester , but canbe used with caution in second and third trimesters. Another monoclonal antibody Trastuzumab used in metastatic breast cancer is associated with severe oligo/anhydramnios and lung hypoplasia in second and third trimester , hence its useshould be delayed until after delivery. Based on the limited evidence, use of targeted therapies and immunotherapy is not supported during pregnancy.

Radiation therapy

Radiotherapy in pregnancy is not routinely recommended as the dose used is 10 4-105 times higher than that used for the diagnostic methods and main concern with its use is the possible harm to the fetus. Whenever possible the radiation therapy should be delayed until delivery. However, when given, the dose should not exceed 50 -100 mGy and should be done with p roper shielding. Depending on the gestational age, radiation dose/dose rate, distance of target lesion from fetus, leakage from equipment and scattered radiation from collimator, the effects of radiation on fetus may include fetal death, malformations, gro wth restriction and carcinogenesis. In pelvic cancers, there is no role for radiation therapy during pregnancy, unless fetal death is unavoidable. Possible treatment options should be discussed with patient and her family.

Specific cancers

Breast cancer

Although rare, it is one of the most prevalent cancer encountered during pregnancy and in postpartum period. Incidence of pregnancy -associated breast cancer is ~ 15 -35/100,000 deliveries, with most cases being diagnosed during first postpartum year. Similar to non-pregnant women, it often presents as palpable mass, skin changes or blood mixed discharge from nipple. However, diagnosis is often challengingdue to the normal physiologic changes in breast during pregnancy or lactation period .Majority of cancer diagnosed in pregnancy are infiltrative type, poorly differentiated, metastatic and are usually ER/PR/HER2/neu-negative.When breast cancer is suspected in pregnancy, avoid delay in diagnosi s. Any breast lump persisting for more than 2 weeks needs to be evaluated.

Ultrasound is the first line imaging modality to assess the extent of disease, lymph nodes and for guided biopsies during pregnancy. Mammography is considered safe with a low fetal exposure risk to detect contralateral or multifocal disease, despite limitations of increased parenchymal density found in pregnancy it has shown to have a sensitivity of more than 80%. MRI during pregnancy or lactation may be difficult to interpret due to pregnancy related changes in the breast. In a retrospective study sensitivity of breast MRI was foundto be 98% for diagnosis of pregnancy-associated breast cancer and in 28% patients breast MRI changed the surgical management.

Patients with breast cancer should be evaluated for distant metastasis and in order to protect fetus chest X-ray with abdominal shielding to evaluate lungs, ultrasound or MRI of liver and/or non contrast skeletal MRI for bone metastasis should be done.

Treatment during pregnancy is same as for the nonpregnant women with some modificati on to protect fetus . However, the treatment approach should be with curative intent to achieve local control and to prevent distant metastasis .Depending on the stage of cancer, women may undergoeither a local excision or mastectomy.Axillary staging and lymph node dissection are important components of breast cancer t reatment, provides prognostic information and is used in selecting adjuvant treatment. The use of sentinel lymph node biopsies during pregnancy is controversial. Adjuvant chemotherapy can be started in 2 nd and 3 rd trimester of pregnancy. Most commonly used regimen are the anthracycline and cyclophosphamide based regimens. However, data from case reports have shown that taxanesappears to be feasible and safe to use during 2nd and 3rd trimester with minimal maternal, fetal or neonatal toxicity. Radiation and/or hormonal therapy are contraindicated during pregnancy and should be deferred till postpartum period.

Cervical cancer

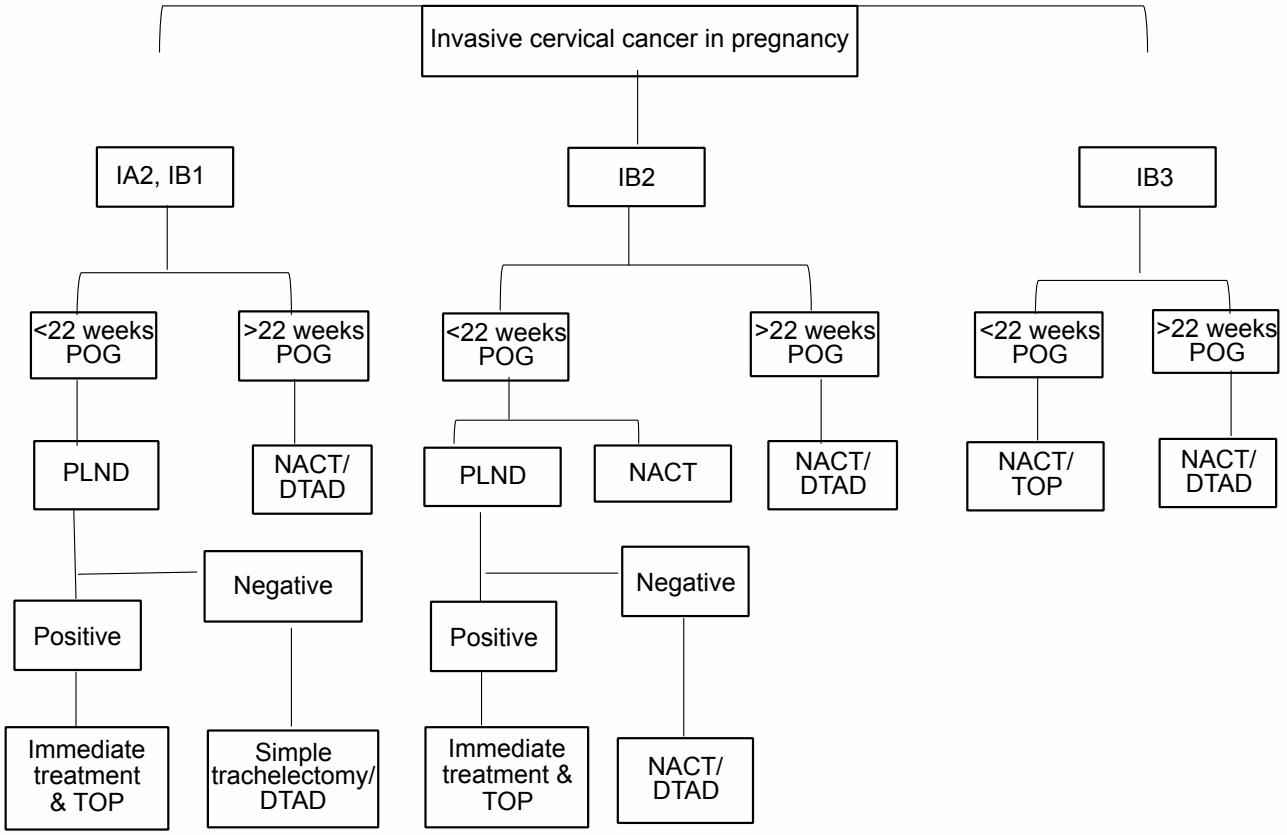
Cervical cancer is one of the most common gynaecological malignanc y diagnosed during pregnancy, with an estimated incidence of 0.8-1.5 cases/10,000 births. Abnormalities in cervical cytology are detected in about 5% of pregnancies and low grade lesion often regresses or remains unchanged during pr egnancy.Signs and symptoms during pregnancy depends upon the size of the lesion and stage. Most of patients are diagnosed at an early stage and is often suspected when an abnormality is detected on cervical cytology which are reported in about 5 - 8% women in pregnancy similar to non - pregnant women. Patients may also present with abnormal bleeding, discharge or abdominopelvic pain.

Treatment of low grade lesions should be deferred t illdelivery withre-evaluation and definitive therapy 6-8 weeks after delivery.Even for high-grade lesions, the risk of progression to invasive cancer is only 0.4%during pregnancy and may even regress postpartum, thus obviating the need for excision.

Major challenge is when invasive cancer is diagnosed during pregnancy.Amultidisciplinary team approach is required for management and it is important to take into account the desires of the woman regarding preservation of the pregnancy. Immediate, definitive treatment, regardless of gestational age, is generally appropriate if there is documented lymph node metastasis, disease progressing

during pregnancy or the women choose termination of pregnancy. Staging of the disease and assessment of regional lymph node involveme nt must be done appropriately. For assessment of locoregional spread MRI is the best imaging modality.

Figure 1: Flowchart of stage wise cervical cancer management in pregnancy

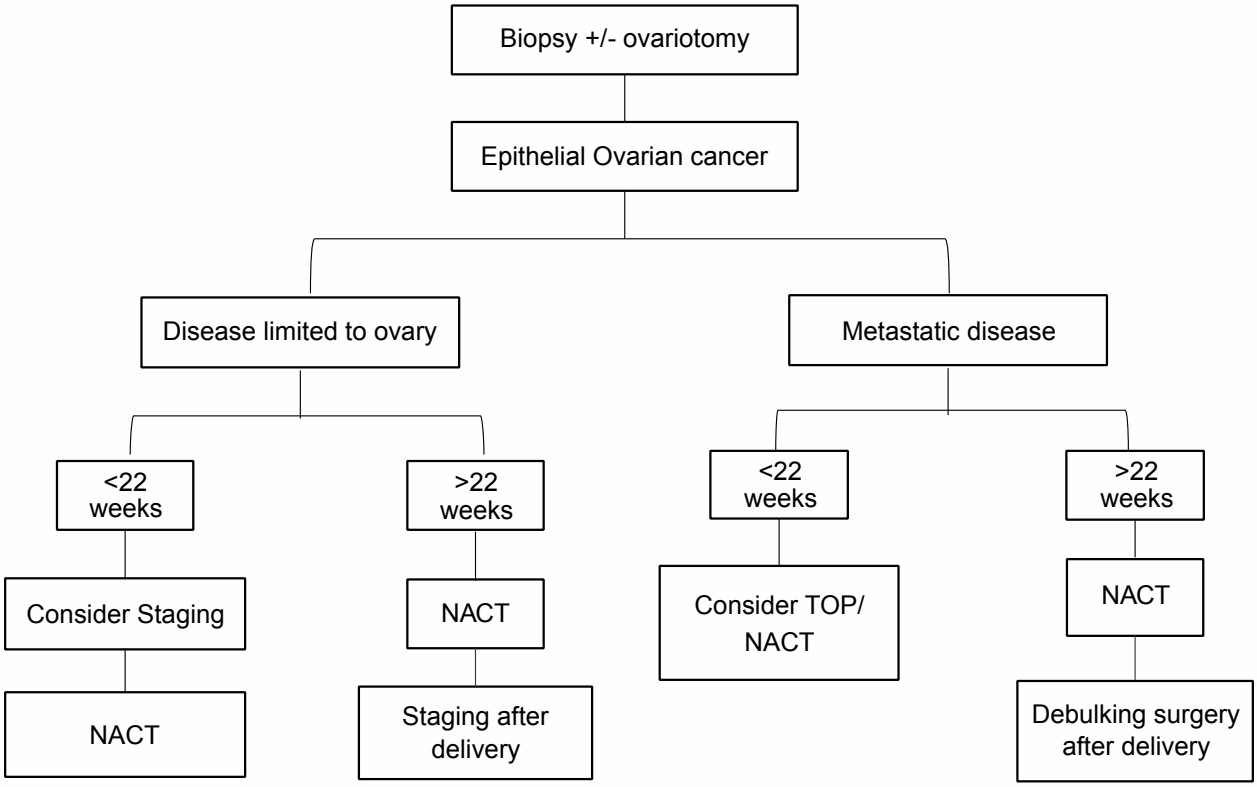


Ovarian Cancer

Adnexal masses are reported to complicate about 0.15-5.7% of pregnancies. Majority of masses are benign and ~1-3% of these masses may be malignant.[23]Malignant germ cell tumors are the most common ovarian malignancy encountered during pregnancy with dysgerminoma being the commonest followed by yolk sac tumors.[24] Other ovarian malignancy diagnosed during pregnancyare sex cord stromal tumors, borderline tumors and rarely epithelial ovarian cancer. Despite this fact, majority of suspiciousovarian masses during pregnancy are in fact borderline ovarian tumors which comprises of 10–20% of all ovarian malignancies and are often diagnosed at the time of surgery.

The ovarian malignancies are mostly diagnosed in early stage. The most common symptoms that precede the diagnosis include abdominal or pelvic pain, constipation, and/or urinary complaints. As most of these symptoms are also present in normal pregnancy, the diagnosis may be delayed and about 1/3rd of patients are diagnosed incidentally during antenatal ultrasound. Ultrasonography has high sensitivity and specificity in diagnosing ovarian masses both with transvaginal or transabdominal scan. However, MRI is best for diagnosing ovarian malignancy, nodal metastasis and peritoneal disease. Tumor markers are less helpful in diagnosis as CA125, beta hCG, AFP can be elevated due to the gestational changes. CA 19-9, LDH, inhibin B, anti-Mullerian hormone and HE4 are not affected with pregnancy status and can be used for diagnosis. However, the definitive diagnosis can only be made with histopathology of ovarian mass.

Figure 2. Flowchart of management of ovarian malignancy in pregnancy



*NACT- neoadjuvant chemotherapy, TOP- termination of pregnancy

Early-stage ovarian cancer can be treated surgicallybetween the 14-22week with surgical staging which includes infracolic omentectomy, peritoneal biopsies andevaluation of suspicious lymph nodes. Rupture of ovarian tumor or spillage during surgery should be avoided. In case of epithelial ovarian cancer, carboplatin/paclitaxel-based chemotherapy can be safely given during 2nd and 3rd trimester and should be stopped atleast 3 weeks prior to delivery to avoid myelosuppression. (Fig 2) In case of germ cell tumor(GCT), except for stage 1A dysgerminoma and stage 1 grade1 immature teratoma rest other malignant germ cell should be treated with NACT during pregnancy. BEP is standard regime for GCT, but as etoposide has been associated with growth restriction and neonatal bone marrow suppression,it is recommended that paclitaxel-carboplatin or cisplatin-vinblastine-bleomycin can be used as alternatives to BEP regime.

If an advanced epithelial ovarian cancer is diagnosed at <22 weeks, termination of pregnancy should be considered. However, in patients who are desirous to continue pregnancy, biopsy or oophorectomy should be performed, followed by neoadjuvant chemotherapy. Cytoreductive surgery should be planned after delivery. In patients at>22 weeks, NACT is given till fetal lung maturity, caesarean deliveryfollowed by complete cytoreductive surgery is a feasible option. The oncological outcomes are same as in nonpregnant patients.

Obstetrical and neonatal care

Once cancer is diagnosed during pregnancy, it is important to ascertain the accurate gestational age, evaluate fetal growth and development and exclude pre-existing malformations. In addition to iron, folic acid and nutritional supplementation, counselling of patient and her family is important to optimize the maternal and fetal status. A regular fetal monitoring for growth and well-being is required. If patients are started on chemotherapy, special attention should be given to monitor fetal growth, preterm

contractions and fetal anemia or cardiotoxicity. If surgical intervention is performed fetal monitoring should be done before and after the surgical procedure to confirm fetal status.Prophylactic use of tocolytics can be considered if surgery is performed after 28 weeks to prevent preterm delivery and corticosteroid for fetal lung maturity. If possible, term delivery should be aimed to avoid prematurity and long-term neonatal morbidity. The mode of delivery is mainly determined by obstetrical indications except in case of cervical and vulvar cancers. Vaginal delivery in case of cervical and vulvar cancermay result in excessive bleeding due to tumor laceration and dissemination of malignant cells at the episiotomy site. Thus, caesarean section is indicated in patients with these cancers and a classical uterine incision should be given to avoid trauma to lower uterine part. Caesarean delivery can be combined with simple or radical hysterectomy.

Post-delivery placenta should be examined for any metastatic disease. Metastasis to placenta and fetus are rare, but if detected child should be followed three monthly to look for any signs.Tumors most likely to metastasize to placenta are melanomas and haematological malignancies.

There is risk of venous thromboembolism due to malignancy as well as pregnancy per se in antepartum and postpartum period. Therefore, thromboprophylaxis should be considered, especially in postoperative period. Treatment can be started immediately after vaginal delivery or 1 week after uncomplicated Caesarean section. Breastfeeding is allowed if there is no ongoing chemotherapy or targeted therapy and if the time since last chemotherapy dose is at least 3 weeks. Treatment should be individualised and women should be educated regarding risks of recurrence with future pregnancies and the need for continued surveillance. It is also important to discuss postpartum contraception if fertility is maintained.

Psychological effect of cancer

Cancer diagnosis during pregnancy can lead to both psychological and emotional trauma to the mother. Most crucial point in cancer management is breaking the bad news to patient and her family. Even there is dilemma for the clinician given that treatment should be directed to save two lives: maternal and fetal. Thus cancer management requires a multidisciplinary team approach.Counselling is an important part of management and can reduce the distress of patient and her family, as stress and anxiety during pregnancy have been shown to be associated with adverse birth outcomes, developmental and cognitive impairments in the neonate. Thus, a careful continuous assessment and psychological support is required in all patients diagnosed with cancer, along with follow-up in the postpartum period.

Conclusion

Once cancer is diagnosed in pregnancy, it is important to promptly assess the ongoing pregnancy status, the gestational age, fetal growth and viability and weighing the maternal benefits and risks. A multidisciplinary team approach is needed to tackle this infrequent medical problem during pregnancy. MRI(non-contrast) and ultrasound are the preferred imaging modalities during pregnancy in terms of fetal radiation exposure. Surgical management can be safely performed during pregnancy and should not be delayed if indicated. Chemotherapy adds to the therapeutic armamentarium during pregnancy and helps in pregnancy continuation and prevention of prematurity.

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We thought of adding a spice to our content.....and why not when we have expert in the field Dr Gita Guin Madam as our President.....

In the modern era of medico legal implications every one of us are stuck one or other time while managing high risk cases..... And confused what all precautions to be taken to safeguard ourselves while managing our patients.....we have to keep ourselves updated not only in patient management aspect but also in keeping ourselves safe from all Medicolegal implications....

Let us discuss some important questions with Respected Dr Geeta Guin madam and update ourselves,

1) What investigations apart from routine investigations should be carried out and how often should they be repeated?

Theoretically speaking, every investigation relating to a particular high risk pregnancy is important. However, depending on the severity of symptoms, disease and availability of resources, both, of the hospital and patient, investigations should be individualized and well justified, for doing and not doing, either. Similarly, investigations should be repeated as per the disease nature, progression and resource availability and sometimes, guidelines, national, institutional or otherwise.

2) Which all consents are important?

Consents relating to

A) Information of condition of patient and prognostication. This can be repeated, as the case may be.
B) Procedure specific consent
C) Consent of refusal of treatment
D) Consent of referral
E) Any other as the case may be

3) Whom all should we include in the team to manage a high Risk pregnancy?

Management of a high risk pregnancy is undoubtedly multidisciplinary and must always include the pediatrician as well.

4) What all precautions to be taken while delivering a high Risk case to protect ourselves from Medicolegal allegations?

The key to managing a high risk pregnancy and avoiding litigation is,

A) Good counselling. Avoid promising too much or hiding the possibility of probable complications in the fear of losing patients.
B) Always anticipating the worst and being prepared.
C) Not being hesitant in calling for help. Similarly being generous in helping others when called upon
D) Step by step and logical documentation of events and treatments. Avoiding contradictory records when more than one physician is involved.
E) Keeping the option of referral open, whether on patients' demand or for limitations of facility.
F) Keeping all documents safely for minimum 5 years.
G) Always having a professional indemnity with adequate cover. Whenever there is reason to believe that there is a likelihood of a litigation under CPA, informing the insurance company regarding the same
H) In case of an adverse event, seeking help of local rush team and medico-legal consultants.
I) Sharing congenial relation with professional brethren.
J) Doing only as much work as one is capable of, by education, experience and training.

5) Are there any guidelines available which should be followed while managing such patients in India

Wherever available, it is prudent to follow national guidelines. The Institution can develop its own guidelines based on the national recommendations, keeping in view the local circumstances and resources in mind. Where there are no such guidelines, it is prudent to keep in line with the practices in the medical college of the area and/or general state of practice in the locality/region.

पलाश के फूल

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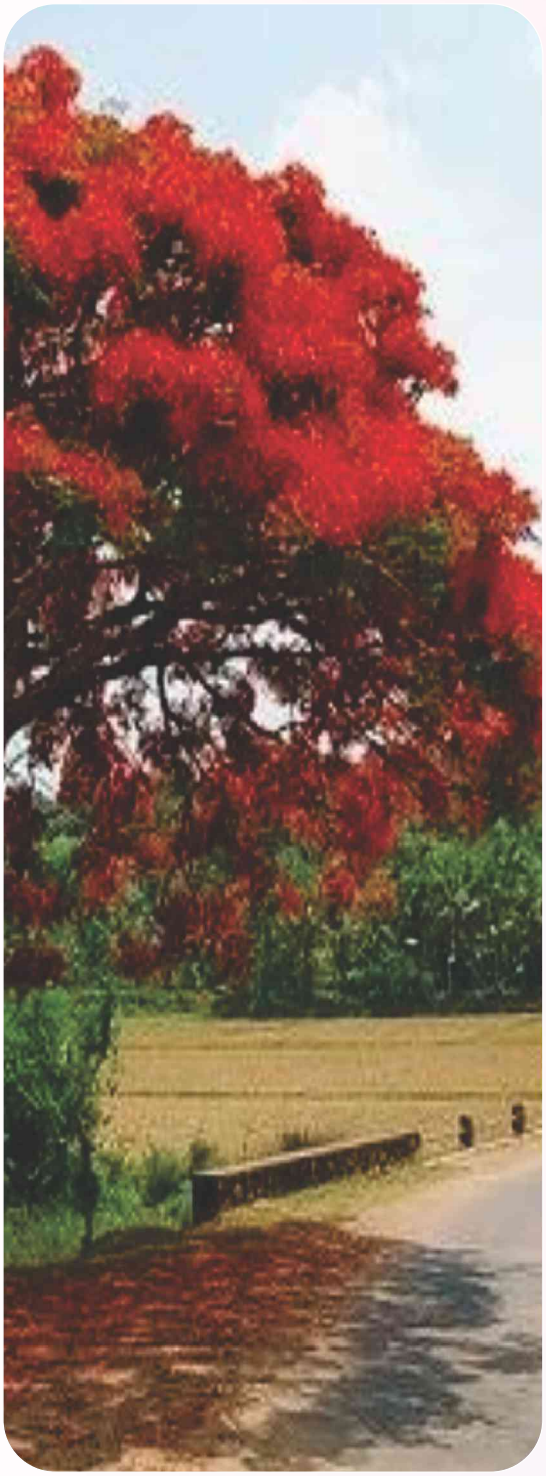
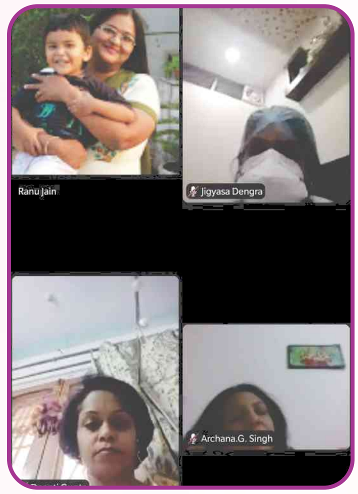


गुज़रती हूँ जब जब उस राह में अनजानी आस में,
पहचानी चाह में मिल जाते ही तुम रोज़ वहल तने से,
टँके से...कभी पसरे से सुर्ख धधकते ,
कुछ अधूरे से रंग निचोड़ अपना,धरती रंगीन किये जा रहे हो
पतझड़ की डाल पर वसंत की आग किये जार
ये क्या कर रहे हो...सुनो तुम पलाश
ये क्या कर रहे हो...सुनो तुम पलाश।
मैं सुलझी,उलझी ...कभी बिखरी सी
दहकती ,चमकती...कुछ अधूरी सी
रिश्तों के गाले बुने जा रही हूं अपनी डाल पर सीमित,
रंगों से सलचे जा रही हूं यूं ही जिये जा रही हूं...
सुनो तुम पलाश जाने क्यों जिये जा रही हूं .सुनो तुम पलाश।
पतझड़–वसंत का तो रहेगा आना–जाना।
आँचल समेटा है मैंने...तुम दायरों में सिमट जा
मैं तुम सी हूं या तुम मुझसे...छोड़ो भी ये कशमकश है

रख हौंसला..दुनियादारी की टोकरी से...सजान
अब अपना अपना आकाश है खिलते रहना है...
खिलते रहना है हमें ..सनो छ पलाश
सुनो तुम पलाश

Executive Committee Meeting



Safe Delivery Day

सेफ मदरहुड डे पर प्रदर्शित किया माइम एक्ट

जबलपुर। शिशु का जन्म एक सृजन है और इसमें परिवार एवं हेल्थ केयर वर्कर्स की टीम का अनूठा योगदान निरंतर 9 माह बना रहता है। नेशनल सेफ मदरहुड डे पर, इसी विचार को अपने माइम एक्ट द्वारा जबलपुर स्त्री विशेषज्ञ संघ से डॉ. अनुराधा डांग, डॉ. कावेरी शॉ, डॉ. गीता गुइन, डॉ. निधि जैन, डॉ. सोनल रिछारिया, डॉ. रानू जैन, डॉ. दीप्ति गुप्ता, डॉ. श्वेता सिरसीकर, डॉ. मनोज द्वारा डॉ. स्वाति वर्मा जैन दमोह द्वारा रचित कविता सृजन पर दर्शाया गया। जबलपुर स्त्री रोग विशेषज्ञ संघ द्वारा माइम एक्ट राष्ट्रीय सेफ मदरहुड कमेटी में चेयरपर्सन डॉ. प्रीति कुमार लखनऊ के आग्रह पर भेजा गया ताकि इसे राष्ट्रीय स्तर पर दिखाकर जनसाधारण में जागरूकता लाई जा सके।

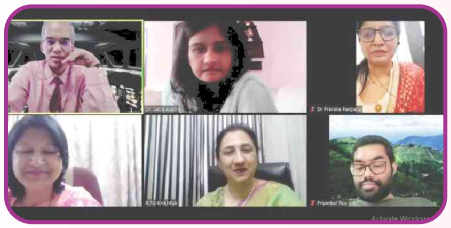
स्त्री विशेषज्ञ संघ ने मनाया मदरहुड डे

● संस्कारधानी टुडे, जबलपुर
sanskardhanitoday.com

राष्ट्रीय स्तर पर 11 अप्रैल को प्रतिवर्ष सेफ मदरहुड डे एवं सिर्फ डिलीवरी डे के रूप में मनाया जाता है जिसका उद्देश्य भारतवर्ष में मां के मृत्यु दर को कम करना एवं सेफ डिलीवरी प्रैक्टिस पर ध्यान केंद्रित करना है। शिशु का जन्म एक सृजन है और इसमें परिवार एवं हेल्थ केयर वर्कर्स की टीम का अनूठा है। इसी विचार को अपने माइम एक्ट द्वारा जबलपुर स्त्री विशेषज्ञ संघ से डॉअनुराधा डांग,डॉ कावेरी शा,डॉ गीता गुइन, डॉ निधि जैन, डॉ सोनल रिछारिया, डॉ रानू जैन, डॉ दीप्ति गुप्ता, डॉ श्वेता सिरसीकर, डॉ मनोज द्वारा डॉ स्वाति वर्मा जैन, दमोह द्वारा रचित कविता सृजन पर दर्शाया गया।

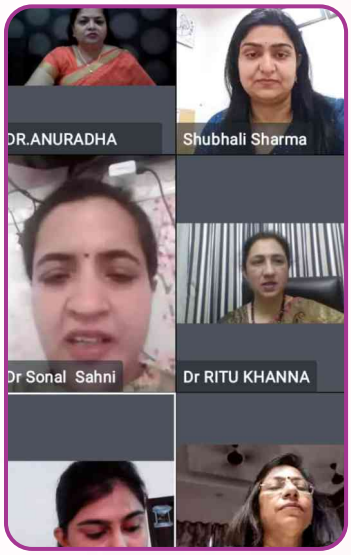
सुरक्षित मातृत्व एवं सेफ डिलीवरी डे के उपलक्ष में द्वारा श्रजन माइम एक्ट राष्ट्रीय सेफ मदरहुड कमिटी में चेयरपर्सन डॉ प्रीति कुमार लखनऊ के आग्रह पर भेजा गया इसे ताकि इसे राष्ट्रीय स्तर पर दिखाकर जनसाधारण में जागरूकता जागृत की जा सके और सुरक्षित मातृत्व के लिए परिवार और हेल्थ केयर वर्कर्स की अहम भूमिका को समझाया जा सके इस कार्यक्रम में फॉग्सी अध्यक्ष डॉक्टर अल्पेश गांधी अहमदाबाद,डॉ जयदीप टैंक मुंबई, डॉक्टर पराग विनी वाला पुणे, डॉक्टर अतुल गनात्रा, डॉ अलका अग्रवाल जबलपुर, सहित कई चिकित्सा एवं जनसाधारण से जागरूक लोग लिंक द्वारा जुड़े रहे। कर्म का आयोजन समिति के द्वारा ऑनलाइन किया गया जिस का सफल संचालन डॉ पारुल गुप्ता, डॉ रश्मि शर्मा, वर्तिका डॉक्टर संगीता मेहरोत्रा, सबसे संगीता आर्य, अनुपम सिंह द्वारा किया

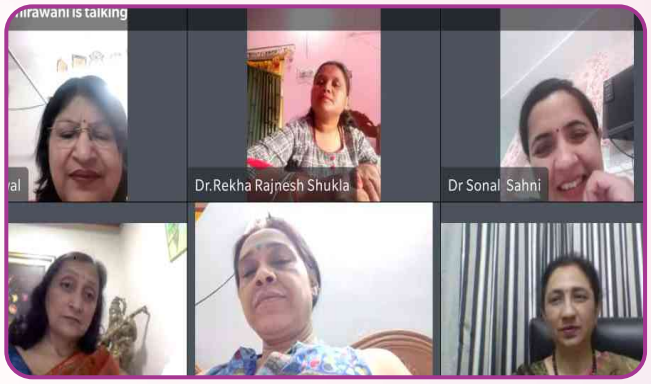
Evidence Based Management of Preterm Labor

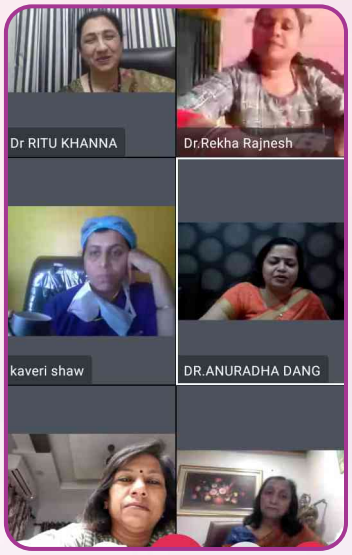


Safe Motherhood

Seeds of Fertility - The Ovarian Factors

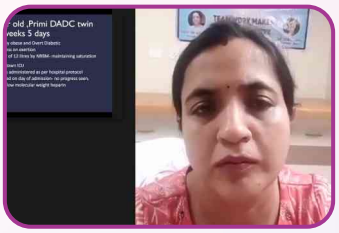




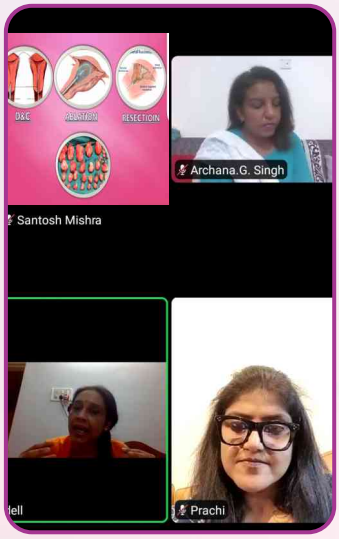


Nurses Day Celebration

Combating of Covid in Pregnancy



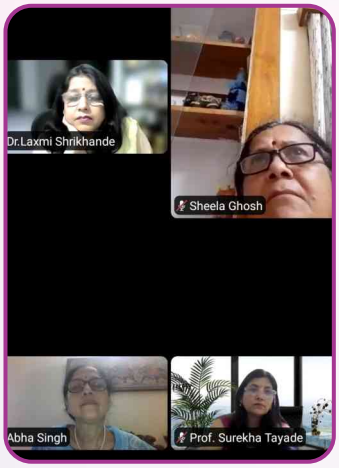
Save the Uterus



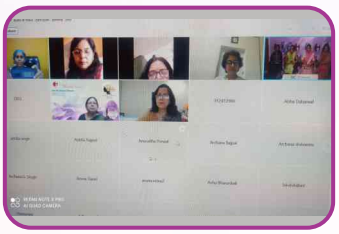
Adolescent Competition - For Corona Warriors

Anti Tobbaco Day Awareness

Garbh Sanskar



Womans Health-womans Day



YUVA FOGSI Preparation

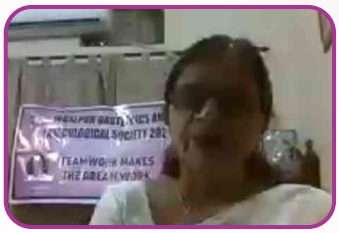

Awareness programme on PCOD


Executive Body Meeting


Covid During Pregnancy

Tree Plantation

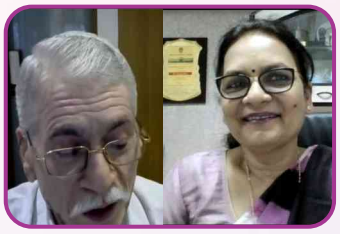
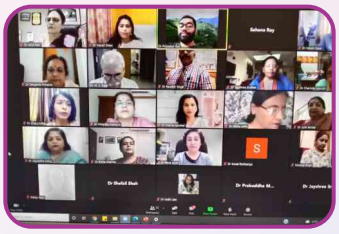

Breast feeding Awareness



Grabh Sanskar Awareness Programme

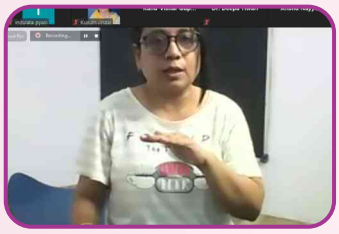

Awareness on Covid 3rd Wave durig pregnancy and Black fungus

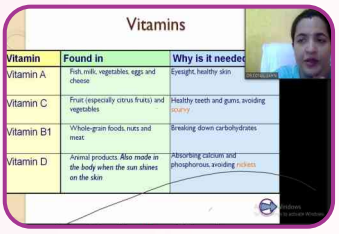
Happy Learning

Awareness Programme on Save Girl Child

Yoga Day Celebration





Urogynaecology