



Spectrum of Liver: GI Disorders in Pregnancy

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Received: 28 January 2023 / Accepted: 10 March 2023 / Published online: 6 April 2023
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Abstract

Pregnant women are affected by gastrointestinal and liver disorders. These may or may not be related to pregnancy. Unrelated conditions are pre-existent or coincidental during pregnancy. Pregnancy may promote symptoms/alter course of new or pre-existing disease resulting in complications only during pregnancy. This in turn can have adverse effect on clinical course affecting mother and fetus. The management remains same but its effect on mother and fetus needs to be kept in mind with pro-active treatment. Severe liver diseases though rare during pregnancy can occasionally be life threatening. Pregnancy after bariatric surgery/liver transplant is possible but with thorough counseling and needs multidisciplinary approach. Endoscopy for GI problems, if required can be carried out by gastroenterologist with special attention. Hence, this article, for quick reference to tackle GI and liver disorders in pregnancy.

Keywords Gastro-intestinal · Liver · Pregnancy

Introduction

Gastrointestinal and liver disorders occurring in woman of reproductive age group are mostly benign and remain unaffected during pregnancy. Some disorders may occur during pregnancy, but it does not change the management and outcome [1]. Disorders like Hepatitis E could be life threatening in pregnancy which would have benign course otherwise [2]. Gastroesophageal reflux, constipation could be bothersome, hyperemesis worrisome and obstetric cholestasis, acute fatty liver, HELLP syndrome could be fatal. Pregnancy after bariatric surgery or liver transplant need multidisciplinary approach.

Gastro-intestinal System

Gastro-intestinal discomfort is common during pregnancy, most will experience at least one of them. Some may develop GI issues after pregnancy. Those with chronic GI issues can feel worsening of symptoms during pregnancy and need special attention. The commonest being nausea, vomiting, hyperemesis, gastrointestinal reflux (GERD), diarrhea—constipation, gall stones, colitis and irritable bowel syndrome (IBS). Certain disease like acute fatty liver of pregnancy develops only during pregnancy requiring urgent attention and delivery of fetus. Management of IBD with possibility of endoscopy needs special intervention by gastroenterologists. Hence this mini review article that can be referred quickly for proper management of GI and liver disorders in pregnancy.

Diseases During Pregnancy

GI complaints during pregnancy—nausea, vomiting, GI reflux, constipation. GI disorders unique to pregnancy—hyperemesis, intra-hepatic cholestasis, PIH with HELLP syndrome, acute fatty liver of pregnancy. Disorder exacerbated during pregnancy—Inflammatory Bowel Disease (IBD), Hepatitis E, physiological changes during pregnancy—hemodilution leads to decrease in hemoglobin/

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albumin. Alkaline phosphatase increases due to placental production, however aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), bilirubin and prothrombin time (PT) remain normal. Clotting factor changes make pregnancy a pro coagulation entity. Elevated levels of Progesterone lead to delayed gastric emptying time and high production of gastrin to acidity.

Careful history/physical examination is important to identify underlying drug induced hepatic impairment before presuming liver dysfunction to be secondary to pregnancy.

Gastro-intestinal Diseases

Common GI Problems

Nausea-vomiting is most frequent symptom affecting 50–70% of pregnant women. It usually occurs in first trimester and ceases by second trimester. Progesterone is believed to be the cause, with inhibitory effect on GI smooth muscle. Multiple/molar pregnancy leads to exaggerated symptoms due to increased HCG levels. Psychological factors like anxiety, depression, unwanted pregnancy, disturbed relationship can lead to these symptoms. Exclusion of other causes is necessary in case of persistence of symptoms in second/third trimester.

Most can be managed on dietary modification with non-pharmacological options. Small frequent meals with avoidance of fatty meal is recommended. Consumption of liquids containing electrolytes and sugar is advisable. Vit B1/B6 can be given as routine supplements. Cochrane review has found ginger to be useful. Histamine Receptor blockers (Anti H1) like promethazine, doxylamine are first line of therapy without any effect on fetus. Phenothiazines like prochlorperazine, chlorpromazine are equally safe. Ondansetron can be taken as second line of therapy due to possibility of fetal cardiac effect.

GastroEsophageal Reflux (GERD) is found in most pregnant women. It can affect quality of life but resolves after delivery. Lifestyle/dietary modifications like avoiding late night meals, elevating head end of bed while lying, left lateral position are recommended for patients with mild symptoms. For persistent symptoms—antacids based with calcium/magnesium are safe and first line of therapy. Aluminum based is better avoided as it has potential for developmental retardation. Histamine type 2 antagonists—Ranitidine are safe. Proton pump inhibitors (PPI) are considered safe and are reserved for non-responders or with GERD complications. All agents reduce iron absorption.

Constipation usually occurs in 40% of patients during pregnancy. Progesterone relaxes GI smooth muscles, leading to bowel hypomotility. Oral iron can exaggerate the same. Adequate water intake, high fiber diet and frequent

small meals are helpful. Osmotic laxatives like lactulose, polyethylene glycol (PEG), glycerin, sorbitol is helpful.

Specific GI Diseases of Pregnancy

Hyperemesis Gravidarum is unique to pregnancy with severe nausea/vomiting and weight loss of 5% pre-pregnancy values. Usually occurs before 20 weeks of pregnancy, at times requiring hospital admission. It is associated with hyperthyroid disorders, psychiatric illness, molar pregnancy, diabetes and asthma. Causative factors being increased levels of HCG, estrogen and transient thyrotoxicosis due to estrogen stimulation. There will be electrolyte imbalance with elevated liver enzymes, raised hematocrit and dehydration. USG should be done to rule out molar/multifetal pregnancy. Pregnancy unique quantification of nausea/emesis (PUQE score) can be used in tailoring therapy [3]. Correction of electrolyte imbalance with IV fluids, Vit B1/B6 with anti-emetic is therapy of choice. Total parenteral nutrition is given in life threatening cases.

Inflammatory Bowel Disease (IBD) affects younger women below age of 32 years. It may be associated with preterm/growth retarded fetal outcome even during quiescent phase hence Obstetricians need to monitor these patients in consultation with GI specialist. Active phase can lead to spontaneous abortion, preterm labor, premature rupture of membranes, still birth and PIH. It is advisable for IBD woman to have remission of 3–6 months before planning pregnancy. Possibility of exacerbation in Ulcerative colitis is more than Crohn's disease according to PIANO Multicentric study (Pregnancy in Inflammatory Bowel Disease and Neonatal Outcome).

Hemoglobin, ESR, CRP, and Albumin are diagnostic markers but are of less significance during pregnancy due to physiological changes. Research on Fetal Calprotectin (FC) as biomarker of active disease is on, as it remains unchanged during healthy pregnancy. Sigmoidoscopy is advisable in severe cases. Treatment should always be considered as active phase can cause fetal and maternal complications. Methotrexate/Thalidomide are contra indicated. Five amino-salicylates are safe but high doses of folic acid supplementation is needed as it interferes with absorption. Thiopurine monotherapy is used to stop remission while cyclosporine is used in women with relapse. Anti-tumor necrotic factor agents (anti-TNF), infliximab and adalimumab are low risk. Steroids are advisable during flare up but with limited duration/dosage. Amoxicillin-clavulanic acid is a preferred antibiotic. Medication can be stopped on individual basis depending on possibility of relapse/phenotype of patient. Surgery, if needed is relatively safe.

Bariatric Surgery

Pregnancy is possible after bariatric surgery. Proper pre-conception counseling is mandatory. It is advisable to use contraception for 1–2 years after BS. Non-oral routes of contraception are recommended like LARC. Malabsorption/weight loss causes nutritional deficiency, preconception and during pregnancy. Regular blood investigations are needed so that deficiencies can be treated. Dumping syndrome poses problem with oral GTT to diagnose Gestational Diabetes. D/D of abdominal pain should keep surgical causes in mind and immediate investigations/treatment is advisable. There is increase in incidence of SGA babies. These patients need multidisciplinary approach including qualified nutritionist, bariatric surgeon, endocrinologist and neonatologist.

Liver Diseases During Pregnancy

Liver disorders are divided into 2 groups: Coincidental with pregnancy and pre-existing diseases exacerbated during pregnancy [4].

Liver Diseases Incidental to Pregnancy

Jaundice

Can occur due to hemolysis/cholestasis.

Jaundice	Hemolysis	Cholestasis—intra/extra hepatic
Causes	Hereditary spherocytosis, sickle cell anemia, thalassemia, blood group incompatibility, HELLP syndrome	Intra-hepatic—Viral hepatitis, drug reaction, alcohol, hyperemesis, cirrhosis Extrahepatic—Gall stones, bile duct stricture, pancreatitis, malignancy
Lab Inv	Elevated unconjugated bilirubin AST, ALT, GGT—Normal	Elevated conjugated bilirubin/alkaline phosphatase
Clinical features		Pale Stools/Dark Urine

AST alanine transaminase, *ALT* aspartate transaminase, *GGT* gamma-glutamyl transferase.

Disease	Management	
Hepatitis A	Course unchanged	supportive management
Hepatitis B	Course unchanged, First ANC visit—status checked	Vaccination/IG to newborn and anti-viral to mother in PNC precaution mandatory

Disease	Management	
Hepatitis C	Course unchanged, First ANC visit—status checked	Precaution mandatory. No alteration of vertical transmission with mode of delivery
Herpes Simplex	Increased maternal/perinatal mortality—morbidity	Anti-viral—Acyclovir
CMV	Fetal malformations/neurological morbidity	Supportive

ANC antenatal care, *IG* immunoglobulin, *PNC* post-natal care, *CMV* cytomegalovirus.

Pregnancy and labor should be managed in tertiary care center with multidisciplinary consultations. Epidural anesthesia should be avoided in case of coagulopathy/thrombocytopenia.

Budd Chiari Syndrome

It is obstruction of large hepatic veins/supra—infrahepatic portion of IVC due to thrombosis causing congestion and necrosis of centrilobular portion of liver. It may be associated with APLA and Factor V Leiden mutation. Patients present with abdominal pain, hepatomegaly and ascites. Imaging helps in diagnosis and anticoagulants, thrombolytics and diuretics are part of treatment. Prognosis for pregnancy is poor. Surgical treatment is advisable post-delivery.

Liver Transplant Recipient

Pregnancy in Liver transplant recipient is possible, but clinician needs to counsel patients with regards to miscarriage, risk of deterioration of mother/risk of defects in offspring. Liver sustains metabolic/hormonal function and produces fetulin—B protein for zona pellucida permeability. During pregnancy immune response decreases but has no effect on graft (Recipient).

Contraception counseling is strictly advisable 1–2 years following transplant for post-operative healing, recovery of menstrual cycles, liver functions and stable immune modulations.

Pregnancy is advisable in those who are on low dose immune suppressants with proper allograft function (stable levels of bilirubin—ALT/AST) with no failure of other organs. Pre-operative investigations should include X-ray chest/CT abdomen. Those on oral hypoglycemic agents have to change to Insulin. ART can be advised in case of failure of spontaneous conception. Multidisciplinary approach with good nutritional advice and regular antenatal visit is advisable. Immunosuppressants like prednisolone (< 15 mg/day), AZA (< 2 mg/kg/day), CsA (Cyclosporine A) and Tac (Tacrolimus) can be used. Post-liver

transplant, thrombocytopenia is of concern. If present, during pregnancy, patient needs to be hospitalized and treated after thorough investigations.

It is advisable to give antenatal steroids for fetal lung maturity. Increased incidence of PIH, FGR and preterm labor is noted. C section is indicated for obstetric reasons only. Breast feeding is recommended by American Academy of Pediatrics.

Only after proper counseling, woman of reproductive age group should not be discouraged from pregnancy following Liver Transplant.

Pregnancy Specific Liver Conditions

Obstetrics Cholestasis or Intra-Hepatic Cholestasis of Pregnancy (ICP)

Occurs in late pregnancy with pruritus, elevated bile acids and serum aminotransferase. Symptoms disappear 2–3 weeks after delivery, however liver functions may take 6 weeks to become normal. High levels of estrogen/progesterone cause lower secretion of bile acids causing pruritus in palms/soles. Alkaline Phosphatase may be raised. GGT will be raised in patients with genetic component. ICP is associated with increased fetal risk. Ursodeoxycholic acid-UDCA (10–15 mg/kg body weight) is treatment of choice. Antihistamines can be given for symptomatic relief with local application of moisturizer. Cholestyramine (Category C) can be used as an alternative to UDCA but can cause infant coagulopathy. Supplementation with fat soluble vitamin A, D, E and K should be considered as bile acid binding decreases absorption [5]. Patient should be delivered by 37 completed weeks of gestation.

HELLP Syndrome

Hemolysis/elevated liver enzymes/low platelets. It occurs in 1% of all pregnancies, usually in third trimester of which 90% patients had PE in pregnancy. 5–10% of women with severe PE develop HELLP syndrome. Endothelial and micro-vascular injury leading to micro-angiopathic anemia with hepatic necrosis and thrombocytopenia. Most complaint of headache, nausea-vomiting, visual disturbance, epigastric pain with generalized edema/weight gain. The Mississippi Classification helps to identify severity of disease. Platelets less than $50,000/\text{mm}^3$ can be associated with DIC.

Non-recovery can lead to multi organ failure including acute liver failure. They should be managed in ICU with prompt delivery of fetus as treatment of choice for recovery.

Acute Fatty Liver of Pregnancy

It is rare but very serious disorder occurring in late third trimester/early postpartum. Maternal and perinatal mortality is up to 20%. AFLP results from mitochondrial dysfunction of fetal liver leading to accumulation of long chain fatty acids in fetal and maternal circulation causing maternal toxicity. Patients presents with symptoms of nausea, vomiting, anorexia, headache, abdominal pain. 70% of patients will have fever/jaundice and 50% will have PE. Elevated white cell count/aminotransferase with deranged PT/aPTT with hyperbilirubinemia and hypoglycemia is usually found. D/D is HELLP syndrome, ICP, hepatitis. AFLP is medical emergency and prompt delivery with ICU care facility is management of choice.

Hepatitis E Infection

HEV-enterically transmitted viral infection causing hepatitis. It has very virulent course during pregnancy with progression to fulminant hepatic failure. Usually found in second/third trimester with maternal mortality up to 10–20%. High mortality is due to hormonal and immunological factors. There is shift from Th1 to Th2 cells with decreased cytokines and high levels of hormones (E/P/HCG) leading to decreased cell mediated immunity. No studies so far have documented this causal relationship. Complications like encephalopathy, GI bleeding, renal failure, convulsions, preterm delivery, and fetal death can occur. Vertical transmission has been reported but is self-limiting in neonate. Fulminant hepatitis is rare in newborn. Supportive treatment with strict vigilance is recommended. Prevention is the best mode of therapy.

Endoscopy in Pregnancy

GI endoscopy though safe, is associated with increased risk of preterm births and growth retarded babies [5]. Upper GI endoscopy is done for GI hemorrhage, dysphagia, refractory nausea/vomiting to rule out peptic ulcer or gastric outlet obstruction. Sclerotherapy and endoscopic band ligation are safe during pregnancy. Epinephrine, thermo/electrocoagulation (bipolar) procedures are successful during pregnancy. Epinephrine can decrease blood flow to fetus and electrocoagulation can transmit electric current to fetus.

Sigmoidoscopy and colonoscopy are done for lower GI bleed, suspicious mass in colon, stricture or persistent diarrhea with unknown etiology. Sigmoidoscopy is considered safe, while colonoscopy is advised only when absolutely necessary.

Sedative drugs like propofol, midazolam and meperidine are safe but are best avoided in first trimester unless absolutely indicated.

Clinical approach to pregnant women is challenging. Clinician needs to evaluate disease and give therapy that will not cause any harm to fetus and mother. Proper consideration is necessary while treating patients with IBP and during endoscopy. Multidisciplinary approach is mandatory in fulminant and complicated cases.

Conclusion

Gastrointestinal and liver diseases have broad spectrum in pregnancy. Occasionally they present for the first-time during pregnancy. Management remains same but one has to be more vigilant to reduce maternal and fetal morbidity. Multidisciplinary approach is mandatory for better outcome without complications.

Funding Not applicable.

Declarations

Conflict of interest There is no conflict of interest with publication of manuscript or an Institution or product that is mentioned in the manuscript and/or is important to outcome of study presented.

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