Liver diseases in pregnancy

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ABSTRACT

Liver disease in pregnancy can be related to a pre-existing condition (such as autoimmune liver disease) or arise as a consequence of pregnancy. In women with pre-existing disease, pre-pregnancy counselling is important to discuss the potential complications that may occur during pregnancy and how best to manage these. Acute fatty liver of pregnancy and HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome are pregnancy-related liver diseases and are considered obstetric emergencies. Women with liver dysfunction need appropriate investigations, including blood tests and imaging. They should be managed as part of a multidisciplinary team with obstetricians, obstetric anaesthetists, specialist midwives, gastroenterologists and obstetric physicians.

Introduction

Pregnancy directly affects the physiology of the liver and hepatic disorders can adversely affect pregnancy outcomes. In developed countries, approximately 3% of pregnant women are affected by some form of liver disease during their pregnancy.[1] Some of these conditions can be fatal for both the mother and fetus. It is, therefore, important to determine the underlying cause of abnormal liver function, enabling prompt management to reduce morbidity and mortality. Liver disease can be classified into those related to pregnancy and those unrelated to pregnancy (Table 1).

Pregnancy itself causes changes in physiology and laboratory findings. Alkaline phosphatase (ALP) increases as one isoenzyme is placental in origin and does not reflect liver disease. Albumin decreases and transaminases may remain normal or decrease slightly.[2] In pregnancy, diagnostic imaging (such as abdominal ultrasound and magnetic resonance imaging) can be undertaken as in the non-pregnant individual. There may be rare occasions where the use of computed tomography (CT) of the abdomen is required, which involves ionising radiation exposure to the fetus, of greater magnitude than CT of the areas of the body (eg chest and head). The merits of this imaging should be considered carefully by the healthcare professionals and discussed with the woman.[3]

Pregnancy-related causes of liver impairment are discussed in detail (summarised in Table 2).

Table 1. Classification of liver diseases in pregnancy

Pregnancy-related	Pregnancy-unrelated
Hyperemesis gravidarum	**Pre-existing liver disease**
Pre-eclampsia and eclampsia	Cirrhosis and portal hypertension
Intrahepatic cholestasis of pregnancy	Hepatitis B, C and E
HELLP syndrome	Non-alcoholic fatty liver disease
Acute fatty liver of pregnancy	Wilson's disease
	Autoimmune liver disease
	Co-incident with pregnancy
	Viral hepatitis
	Biliary disease (eg cholelithiasis and primary sclerosing cholangitis)
	Vascular alterations (Budd–Chiari syndrome)
	Drug-induced hepatotoxicity
	Liver transplantation

HELLP = haemolysis, elevated liver enzymes and low platelets.

Key points

- Abdominal ultrasound and magnetic resonance imaging are safe in pregnancy and can be performed if needed.
- Acute fatty liver of pregnancy and HELLP (haemolysis, elevated liver enzymes and low platelets) are obstetric and medical emergencies.
- Liver disease in pregnancy may be pregnancy related, a *de novo* presentation in pregnancy or pre-existing.
- Non-alcoholic fatty liver disease is associated with a two-fold increased risk of developing hypertensive disorders in pregnancy, such as pre-eclampsia.
- Pre-pregnancy counselling should be considered in women with liver pathology.

KEYWORDS: liver disease, pregnancy, imaging, obstetric emergencies

DOI: 10.7861/clinmed.2021-0497

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Table 2. Differential diagnoses and characteristics of liver diseases in pregnancy

Disease	HG	ICP	PET with liver dysfunction	HELLP	AFLP
Prevalence	0.3%–3.6%	0.1%–5%	5%–10%	0.2%–0.6%	0.01%
Trimester	1st/2nd	2nd/3rd	>20 weeks	2nd/3rd/postnatal	2nd/3rd/postnatal
Proteinuria	–	–	Yes	Yes	Yes
Platelets	–	–	decrease	decrease	decrease
Haemolysis	–	–	+	+	–
LDH	–	–	increase	≥600 IU/L	increase
Clotting	–	May be prolonged	Risk of disseminated intravascular coagulation	Risk of disseminated intravascular coagulation	Prolonged (PT >14 seconds or a APTT >34 seconds)
Hypoglycaemia	–	–	–	–	+
Uric acid	–	–	increase	increase	increase
Creatinine	–	–	increase	increase	increase
Liver US/CT	Normal	Exclude cholelithiasis	Hepatic rupture / haematoma / infarcts	Hepatic rupture / haematoma / infarcts	Often normal, may look bright NB fatty infiltration on US is a sign of MACROvesicular steatosis (NAFLD) not MICROvesicular steatosis (AFLP)
Treatment	Supportive, rehydration, antiemetics and vitamin supplementation	Ursodeoxycholic acid, anti-histamines, aqueous cream and consider delivery at 37 weeks (or sometimes before this if bile acids are greater than 100 μmol/L)	Antihypertensives, consider IV magnesium sulphate and consider delivery if deterioration in maternal or fetal condition	As per PET and urgent discussion with obstetricians regarding delivery	Correct coagulopathy, treat hypoglycaemia and expedite delivery
Complications	Hyponatraemia and encephalopathy	Preterm labour and stillbirth	Eclampsia, maternal / fetal mortality	Liver rupture and maternal/fetal mortality	Fulminant liver failure and maternal/fetal mortality
Recurrence	15%–81%	45%–90%	16%–52%	2%–19%	Rare; 25% in defect of fatty acid beta-oxidation

+ = present or positive; − = absent or negative; APTT = activated partial thromboplastin time; CT = computed tomography; IV = intravenous; LDH = lactate dehydrogenase; ULN = upper limit of normal; US = ultrasound; PT = prothrombin time.

Hyperemesis gravidarum

Hyperemesis gravidarum (HG) is severe protracted nausea and vomiting with a triad of dehydration, electrolyte imbalance and weight loss of more than 5% body weight.[4,5] The cause of HG is unknown but is associated with rising beta human chorionic gonadotrophin hormone (HCG) secondary to pregnancy itself and women with multiple pregnancy or trophoblastic disease (therefore, with larger volumes of placental tissue) are more likely to be affected. It usually occurs in the first trimester (as early as the 4th week of pregnancy) and affects 0.3%–3.6% of pregnancies. Risk factors include increased body mass index, pre-existing diabetes, asthma, psychiatric disorders, hyperthyroid disorders in a previous pregnancy or previous HG.[1,6] Symptoms resolve by the 20th week in 90% of women.[5]

Initial investigations include urine dipstick (with quantification of ketones), mid-stream urine, urea and electrolytes, full blood count, blood glucose monitoring (exclude diabetic ketoacidosis if the woman has pre-existing diabetes) and a pelvic ultrasound. In refractory cases or in women with history of previous admission, check thyroid function tests, liver function tests (LFTs), calcium, phosphate and amylase.[5] LFTs are abnormal in up to 40% of women with HG, most commonly with raised transaminases but bilirubin and amylase could also be slightly elevated.[5]

The pathogenesis of liver dysfunction in HG is not completely understood. There is evidence that malnutrition from HG can lead to elevation of transaminases, however, it can also occur in the absence of malnutrition.[7] Another theory is that raised maternal cytokine levels of tumour necrosis factor alpha (TNF-α) due to HG contributes to liver dysfunction.[8]

Biochemical abnormalities resolve on resolution of vomiting. Consideration of alternative diagnoses (eg viral hepatitis) should be made if there are persistent abnormalities of the liver.[9] Treatment is usually supportive and includes rehydration with correction of electrolytes, antiemetics, thromboprophylaxis with low-molecular weight heparin for inpatient stay and thiamine supplementation in some cases. Corticosteroids can also be used for refractory hyperemesis.[5,6,9]

Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy (ICP; also known as obstetric cholestasis) is characterised by pruritus with raised bile acids in the absence of a skin rash. The pruritus typically affects the palmar aspect of the hands and plantar aspect of the feet, but can affect any location on the body. ICP most often affects women in the second half of their pregnancy. It affects about 0.7% of pregnancies in England and about 1.2%–1.5% of Indian and Pakistani Asians. Adverse outcomes associated with ICP include premature labour, fetal distress and stillbirth.[5,9,10] A thorough history (including drug history) and examination should be carried out. Investigation findings include elevated serum bile acids >10 µmol/L (most complications occur with levels >40 µmol/L), increased levels of transaminases and gamma-glutamyl transferase (GGT; Table 2). It is important to note that the upper limit of transaminases, GGT and bilirubin in pregnancy is 20% lower than the non-pregnant range. Normal liver function does not exclude the diagnosis. LFTs should be repeated every 1–2 weeks if pruritus is persistent. Additional tests can include a viral screen for hepatitis A, hepatitis B, hepatitis C, Epstein–Barr virus and cytomegalovirus; liver autoimmune screen (anti-smooth muscle and antimitochondrial antibodies); and a liver ultrasound.[10] Ursodeoxycholic acid (10–15 mg/kg of bodyweight) is recommended to provide relief from pruritus and improve LFTs. A large trial (PITCHES) looked at the benefit of ursodeoxycholic acid in pregnancy, and did not demonstrate overall benefit in reduction of stillbirth, pre-term birth or neonatal unit admission, but there is likely to be some benefit for certain groups of pregnant women and clinicians may trial the use of ursodeoxycholic acid.[11,12] ICP resolves after delivery. Obstetric management may include early delivery in severe cases to minimise the risk of late stillbirth.[10]

Pre-eclampsia and eclampsia

Pre-eclampsia (also known as pre-eclamptic toxaemia or PET) is a multiorgan disease characterised by hypertension and proteinuria after 20 weeks of gestation that can involve the renal, hepatic, haematological and central nervous systems. It affects 5%–10% of pregnancies.[9] Clinical features include headache, visual disturbance, peripheral oedema, epigastric pain and vomiting. Abnormal liver enzymes are present in up to 30% of cases with aminotransferase activity as high as 10 times the upper limit of normal, whereas bilirubin concentrations are rarely increased. A liver biopsy is not indicated.[4,9] Management of hypertension includes labetalol, hydralazine and modified-release nifedipine. Intravenous magnesium sulphate is used for seizure prophylaxis and treatment. Pre-eclampsia is the leading cause of iatrogenic preterm delivery.[13] Admission is indicated for treatment of blood pressure (BP) >160/110 mmHg and aim for BP ≤135/85 mmHg. Consider admission for BP of 140/90 – 159/109 mmHg if there are concerns with maternal or fetal wellbeing. An obstetric assessment (including monitoring of the fetus) should be carried out.[14] Obstetric management may include early delivery in severe cases due to deterioration in maternal or fetal condition. Liver dysfunction usually normalises within 2 weeks of delivery. Hypertension may persist for a few weeks after delivery, therefore, postnatal follow-up in the community is crucial. Measurement of platelet count, transaminases and serum creatinine 48–72 hours after delivery is recommended.[14]

Haemolysis, elevated liver enzymes and low platelets syndrome

Five to 10% of women with pre-eclampsia develop haemolysis, elevated liver enzymes and low platelets (HELLP).[15] HELLP usually arises in the second or third trimester but can also develop after delivery (up to 30% of cases). It can be classified into mild, moderate or severe depending on the alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and platelet count.[16] Risk factors include advanced maternal age, multiparity and White ethnic origin. Importantly, hypertension and proteinuria are only present in about 85% of cases. Investigations should include full blood count, LFTs and coagulation screen (including fibrinogen, prothrombin time and partial thromboplastin time).[4,15] The prothrombin time remains normal unless there is evidence of disseminated intravascular coagulation or severe liver injury.[9] Treatment for hypertension is the same as pre-eclampsia but prompt delivery is usually indicated. HELLP syndrome usually resolves after delivery, however, if there is evidence of hepatic or renal failure, intensive care admission may be warranted.

Acute fatty liver of pregnancy

Acute fatty liver of pregnancy (AFLP) is a rare disorder that is a medical and obstetric emergency, which can lead to liver failure due to micro-vesicular fatty infiltration of hepatocytes. It usually occurs in the third trimester and the incidence is reported to be 1/7,000 to 1/16,000 pregnancies.[1,17] There is a significant increase in maternal and fetal mortality rates ranging from 1%–20%.[18] Risk factors include nulliparity and twin pregnancies. Symptoms include malaise, nausea, vomiting, polyuria, polydipsia, abdominal pain, jaundice and encephalopathy. Hypoglycaemia is a poor prognostic sign.[9] Common biochemical changes include renal dysfunction, raised aminotransferases, prothrombin time, serum uric acid and bilirubin. Raised serum ammonia concentration and lactic acidosis are indications of severe disease.[19] The Swansea diagnostic criteria are used to aid diagnosis of AFLP (Box 1).[1] Management is supportive and expedited delivery, if diagnosed antenatally.[19,20] Liver transplantation is warranted in cases of failure of recovery of liver function and severe hepatic encephalopathy. After delivery, resolution may take up to 4 weeks.

Liver diseases concurrent with pregnancy

Drug-induced liver disease occurs in pregnancy in about 3% of women and is a leading cause of liver failure. It can be direct,

Box 1. Swansea diagnostic criteria for diagnosis of acute fatty liver of pregnancy[1]

Six or more of the following features in the absence of another explanation:
Vomiting
Abdominal pain
Polydipsia/polyuria
Encephalopathy
High bilirubin (>14 μmol/L)
Hypoglycaemia (<4 mmol/L)
High uric acid (>340 μmol/L)
Leucocytosis (>11 × 10^6/L)
Ascites or bright liver on ultrasound
High AST/ALT (>42 IU/L)
High ammonia (>47 μmol/L)
Renal impairment (creatinine >150 μmol/L)
Coagulopathy (PT >14 seconds or APTT >34 seconds)
Microvesicular steatosis on liver biopsy

ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; PT = prothrombin time.

due to an immunological reaction or indirect. Drug-induced liver disease in pregnancy is underreported and the most common agents include antibiotics and antihypertensives. The treatment is to stop the offending agent and monitor the synthetic function of the liver.[21]

For viral hepatidides (such as hepatitis B), it is advised to reduce mother to child transmission, anti-viral therapy is recommended for viral levels >200,000 IU/mL.[22] Tenofovir, entecavir and lamivudine may all be used both in pregnancy and during breastfeeding.

Cirrhosis and portal hypertension are associated with a risk of bleeding varices. Physiological changes in pregnancy lead to an increase in plasma volume and compression of the inferior vena cava. This leads to an increase in portal pressures and may lead to new or an increase in size of varices. As standard practice, women with known varices should have endoscopy in the second trimester for surveillance and consideration of variceal banding. Propranolol should be continued for variceal bleeding prophylaxis during pregnancy.

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) can be considered a high-risk complication as it is associated with hypertensive disorders in pregnancy, gestational diabetes and postpartum haemorrhage and preterm birth. The rate of NAFLD was found to be as high as 28.9/100,000 in 2015.[23] Pre-pregnancy counselling and postpartum follow-up is advised, especially as it is a manifestation of metabolic syndrome.

Autoimmune liver disease

Autoimmune hepatitis can flare in pregnancy in 20% of women and disease activity should ideally be controlled prior to conception.[24,25] Disease flares can increase the risk of adverse fetal outcomes, such as prematurity and preeclampsia. The condition can be treated with corticosteroids and azathioprine, which are both safe in pregnancy.[24,25] In cases of chronic autoimmune liver disease, the treatment considerations are the same as compensated liver cirrhosis.

Wilson's disease

Wilson's disease is a rare autosomal recessive condition that impairs copper metabolism in the liver, reflected by increased caeruloplasmin levels in both the brain and the liver. Untreated, this condition can lead to spontaneous miscarriage but, if treated, successful pregnancies are possible. Pre-pregnancy copper chelation and not withholding drug therapy in pregnancy are thought to help improve pregnancy outcomes.[26,27]

Conclusion

Liver diseases in pregnancy can be difficult to manage due to various presentations that range from subtle liver biochemical changes to hepatic failure. Early detection, adequate monitoring and involvement of experienced physicians within the multidisciplinary team can help improve outcomes for these women and their babies. ■

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