Liver disease in pregnancy

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Abstract

Liver disease in the pregnant patient often causes concern. This chapter covers both acute liver pathologies that occur in pregnancy, and pregnancy in mothers with chronic liver disease, focusing on practical diagnostic and management strategies.

Keywords Acute fatty liver of pregnancy; cholestasis of pregnancy; cirrhosis; liver disease; MRCP; pre-eclampsia; pregnancy; variceal haemorrhage; viral hepatitis

Key points

- Chronic liver disease does not prevent successful pregnancies, and early conversations are important to allow pre-pregnancy planning
- Acute viral hepatitis is an important differential diagnosis for abnormal liver function tests in pregnancy
- Fetal, not maternal mortality, is influenced by intrahepatic cholestasis of pregnancy

Introduction

Abnormal liver function tests (LFTs) occur in at least 3% of pregnancies[1] based on standard laboratory ranges. This nearly doubles if lower thresholds for 'abnormal' amino-transaminases are used, and increases further if patients with chronic liver disease but normal LFTs are included. Registry studies suggest that the number of pregnant women with cirrhosis has doubled over 10 years;[2] this group presents many challenges to clinicians but benefits from planned care.

Chronic liver disease

Prepregnancy planning

Talking about pregnancy to women with liver disease who are of childbearing age is an important component of their liver disease management as misunderstandings are common but can be quickly addressed. Inviting women to meet with the obstetric team when preparing for pregnancy helps to identify potential risks and provides reassurance, particularly around medication.

Minimizing immunosuppression before conception may be possible in post-transplant or quiescent autoimmune patients. Mycophenolate is teratogenic and requires changing to an alternative at least 6 weeks before conception. Otherwise it is reasonable to continue azathioprine, ciclosporin or tacrolimus, paying attention to ciclosporin and tacrolimus dosing, which may need to be increased by up to 25%. Data on sirolimus and everolimus are sparse; case reports suggest they can be continued where there are no reasonable substitutions and in unplanned pregnancies.

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Treatment indications for chronic hepatitis B are unchanged by pregnancy, although immune-tolerant hepatitis B-infected mothers with high levels of viraemia are recommended to take tenofovir from 24 weeks to reduce viral transmission.

In cirrhosis, outcomes are determined by residual liver function, with no increased events in women with low Model for End-stage Liver Disease (MELD) scores.[3] After liver transplant, maternal and fetal outcomes are better than in other solid organ recipients, albeit worse than in the general maternity population (post-transplant live birth rate 92%, prematurity rate 42%, low birthweight rate 47%).[4]

New chronic liver disease

Clinical signs of cirrhosis or ultrasound findings suggesting advanced fibrosis often occur without abnormal LFTs. A detailed medical history can reveal historical alcohol exposure or risk factors for viral or non-alcohol-related liver disease. Transient elastography is a useful and safe tool to estimate risk of liver fibrosis and portal hypertension in this group.

Variceal bleeding

Variceal bleeding can occur at any time, although it is more common in later pregnancy and the second stage of labour. If portal hypertension is suspected, endoscopy is indicated early in the second trimester, to allow primary eradication using a variceal band. Women with small oesophageal varices in the pre-pregnant state benefit from reassessment at this juncture. β-Adrenoceptor blockers can cause fetal complications so are not recommended routinely.

In active bleeding, early resuscitation, antibiotics and band ligation improve outcomes. Vasoconstriction with octreotide is preferred over terlipressin, which can reduce uterine blood flow and induce contractions. If band ligation is unsuccessful, control of variceal haemorrhage with transjugular intrahepatic porto-systemic shunt (TIPSS) placement is an option in the second trimester, and removable self-expanding metal stents can be considered as a bridge to delivery in the third trimester, providing removal can be facilitated within 2–3 weeks.

Acute liver diseases (Table 1)

Viral hepatitis (Table 2)

Acute viral hepatitis, which would ordinarily be innocuous in healthy adults, can be rapidly progressive in pregnancy; very high transaminase concentrations or fulminant liver failure can

Summary of acute hepatobiliary diseases in pregnancy

Disease	Onset	Estimated frequency	Risk factors	Potential adverse outcomes	Key features	Key management
Hyperemesis gravidarum	First trimester	1:50	Multiple gestation	None	Hyperemesis, early onset	Supportive fluids and antiemetics
Intrahepatic cholestasis	Second trimester	1:160	Chronic hepatitis B	Higher risk of adverse fetal outcomes	Raised bile acids, raised transaminases	Ursodeoxycholic acid
Pre-eclampsia	Usually third trimester, can be postpartum	1:70	Primagravida, diabetes mellitus, hypertension, obesity, advanced maternal age	Maternal and fetal mortality	Hypertension, headache, oedema, proteinuria	Delivery
HELLP	Usually third trimester, can be postpartum	1:500	As above	Maternal and fetal mortality	MAHA, thrombocytopenia, raised ALT	Delivery
Acute fatty liver of pregnancy	Usually third trimester, can be postpartum	1:10,000	Multiple gestation Male fetus	Liver failure and maternal/infant death	Jaundice, RUQ pain, malaise, coagulopathy, encephalopathy	Delivery
Acute viral hepatitis	Any time but worse course in third trimester	Unknown	Viral exposure	Liver failure and maternal/infant death	Jaundice, significant ALT elevation	Consider antiviral agents
Thrombotic liver disease	Any time	1:6,000,000	Known thromboembolic tendency, family history	Liver failure	RUQ pain, jaundice	Early anticoagulation
Ruptured adenoma	More commonly in late pregnancy	<1:10,000,000	Known adenoma, family history of adenoma, long-term oral contraceptive use	Shock and placental failure	RUQ pain, shock	Embolization if shock present

ALT, alanine aminotransferase; HELLP, haemolysis elevated liver enzymes; and low platelets; MAHA, microangiopathic haemolytic anaemia; RUQ, right upper quadrant.

Table 1

be caused by hepatitis E, herpes simplex virus (HSV), cytomegalovirus and varicella zoster virus (VZV) hepatitis, although each can also be self-limiting. HSV hepatitis characteristically causes abdominal pain and high fever, often with neutropenia and thrombocytopenia but normal bilirubin concentrations. A widespread rash and malaise occurs with VZV. If HSV or VZV is suspected, treatment should be with empirical aciclovir while awaiting polymerase chain reaction (PCR) and serology results.

Thromboses affecting the liver

Both portal and hepatic vein thrombosis in pregnancy present with abdominal pain and can be catastrophic. In unwell patients, early cross-sectional imaging, ideally with contrast computed tomography (CT), is advantageous to confirm and identify the extent of thrombosis and sequelae including the presence of gut ischaemia. Early anticoagulation is warranted for all. Where life-limiting thrombosis is present, systemic or catheter-directed thrombolysis can be considered in pregnancy, based on case reports of use in massive pulmonary embolism (PE) and stroke. The authors recommend discussion on a case-by-case basis with obstetric colleagues and tertiary centres.

Gallstones

Symptomatic gallstone disease is the most common cause of right upper quadrant (RUQ) pain in pregnancy. Conservative management of uncomplicated disease is preferred until the postpartum period. Laparoscopic cholecystectomy for complications such as cholecystitis or gallstone pancreatitis appears to be safe in the second trimester. A recent systematic review of endoscopic retrograde cholangiopancreatography during

Viruses to consider in pregnant mothers with acutely deranged LFTs

- Hepatitis A[a]
- Hepatitis B[b]
- Hepatitis C[b]
- Hepatitis E[a]
- Herpes simplex 1 and 2[a]
- Cytomegalovirus[a]
- Epstein—Barr virus[b]
- Cytomegalovirus[a]
- Varicella zoster virus[c]

[a] Serology and viral PCR recommended.
[b] Screen with serology.
[c] PCR from a pustule swab.

Table 2

pregnancy reported high rates of successful duct clearance for choledocholithiasis with low complication rates, although procedures should only be performed in specialist tertiary centres.[5]

Hepatic adenoma

This is a rare, benign liver tumour that occurs predominantly in young women of childbearing age. Pregnancy stimulates growth of the lesion and increases the risk of rupture and haemorrhage. The presence of a small adenoma (<5 cm) should not deter conception, but surveillance every 3 months is required during pregnancy. Larger adenomas should be resected before pregnancy.

RUQ pain and shock indicate rupture and warrant cross-sectional imaging (CT, magnetic resonance imaging (MRI)) and urgent embolization, with a subsequent decision to proceed to liver resection either before or after delivery involving obstetric and surgical teams.

Pregnancy-specific liver conditions

Pre-eclampsia, haemolysis elevated liver enzymes and low platelets (HELLP) and acute fatty liver of pregnancy

These three conditions occur in late pregnancy, usually in the late second or third trimester, and carry high maternal and fetal mortality rates. Elevated transaminases are common to all conditions, and the Swansea diagnostic criteria (Table 3) can aid differentiation. Delivery is warranted with worsening abdominal pain, vomiting, falling platelet count, and rising bilirubin, lactate or prothrombin time, indicating onset of liver failure. Hepatic infarct or rupture should be suspected with sudden-onset severe pain; both can complicate pre-eclampsia and HELLP.

Hyperemesis gravidarum

LFTs are abnormal in 50% of patients with hyperemesis gravidarum (defined as vomiting, dehydration, ketosis and weight loss); complete resolution occurs with supportive measures alone.

Intrahepatic cholestasis of pregnancy (ICP)

ICP usually begins with pruritus affecting the hands and feet towards the end of the second trimester, often predating increases in serum transaminases and bile acids. Two-thirds of women have recurrent ICP in subsequent pregnancies, often with an earlier presentation. With prolonged cholestasis, malabsorption of fat-soluble vitamins results in vitamin K-reversible coagulopathy; however, fulminant liver failure does not occur despite aminotransaminases potentially exceeding 1000 IU/litre. Treatment with ursodeoxycholic acid is recommended for first-line management at doses of 10–15 mg/kg pre-pregnancy weight. Ursodeoxycholic acid can elevate serum bile acids values and exacerbate itch. ◆

Swansea criteria for acute fatty liver of pregnancy

In a patient in late pregnancy, the presence of 6 of the 14 criteria in the absence of an alternate explanation is diagnostic of acute fatty liver of pregnancy

Symptoms
- Abdominal pain
- Vomiting
- Polydipsia/polyuria
- Encephalopathy

Radiology and histology
- Ascites/bright liver on ultrasonography
- Diffuse/perivenular microvesicular steatosis on liver biopsy

Laboratory parameters
- Hyperbilirubinaemia
- Raised aminotransferases
- Hypoglycaemia
- Coagulopathy
- Deranged renal function
- Hyperuricaemia
- Hyperammonaemia
- Leucocytosis

Table 3

KEY REFERENCES

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 24-year-old woman presented with a 2-day history of abdominal pain and indigestion. She was 22 weeks pregnant with her first child, was taking no medication, drank no alcohol and had no other medical problems.

Clinical examination was unremarkable.

Investigations

- Haemoglobin 117 g/litre (115–165)
- White cell count 7.3 × 10^9/litre (4.0–11.0)
- Creatinine 70 micromol/litre (60–110)
- International normalized ratio 1.2 (<1.4)
- Bilirubin 38 micromol/litre (1–22)
- Alanine aminotransferase 862 U/litre (5–35)
- Alkaline phosphatase 209 U/litre (45–105)
- Albumin 34 g/litre (37–49)
- Ultrasonography confirmed no problems with the pregnancy but a 13 mm gallstone in the gallbladder

Her pain symptoms eased and she was keen to go home.

What is the most appropriate next step in her management?

A Admit for observation and repeat the blood tests the next day
B Discharge with early review by a hepatology specialist
C Discharge and arrange MR cholangiopancreatography before specialist review
D Draw blood for a viral serology screen and discharge with an early specialist review
E Contact the obstetric team for review before discharge

Question 2

A 30-year-old women presented with a 1-week history of non-specific symptoms of malaise and nausea. She was mildly itchy. She had developed vague abdominal pain in the previous 24 hours. She was carrying twins at 26 weeks in her second pregnancy.
On clinical examination, her temperature was 37.0°C, and blood pressure 110/65 mmHg. She was alert but pale, with excoriations and generalized tenderness in the right upper quadrant.

Investigations

- Haemoglobin 92 g/litre (115–165)
- White cell count 14 × 10^9/litre (4.0–11.0)
- Platelets 76 × 10^9/litre (150–400)
- Ferritin 8 micrograms/litre (15–300)
- Urea 13 mmol/litre (2.5–7.0)
- Creatine 88 micromol/litre (60–110)
- International normalized ratio 1.2 (<1.4)
- Bilirubin 38 micromol/litre (1–22)
- Alanine aminotransferase 982 U/litre (5–35)
- Alkaline phosphatase 222 U/litre (45–105)
- Bile acids 18 micromol/litre (0.0–10.0)
- Albumin 30 g/litre (37–49)
- Ultrasonography with Doppler demonstrated a bright liver with a rim of ascites

What is the most appropriate management of the likely diagnosis?

A Send serology and PCR and start aciclovir
B Start ursodeoxycholic acid
C Discuss delivery of the babies with obstetricians
D Start anticoagulation
E Arrange a blood work-up to diagnose microangiopathic haemolytic anaemia

Question 3

26-year-old woman presented for review. She had been found to have autoimmune hepatitis. She was currently trying to conceive. There was no other medical history and no use of herbal or recreational medication. She was taking prednisolone 5 mg daily, azathioprine 125 mg daily and a calcium supplement but had a history of poor concordance with treatment. At her last liver biopsy, 2 years previously, there had been severe inflammatory changes in keeping with autoimmune hepatitis.

Investigations

- Haemoglobin 121 g/litre (115–165)
- White cell count 6 × 10^9/litre (4.0–11.0)
- Platelets 135 × 10^9/litre (150–400)
- International normalized ratio 1.2 (<1.4)
- Bilirubin 16 micromol/litre (1–22)
- Alkaline aminotransferase 142 U/litre (5–35)
- Alkaline phosphatase 145 U/litre (45–105)
- Albumin 36 g/litre (37–49)
- Recently ultrasonography indicated that the liver was small and there was borderline splenomegaly

What should be prioritized as the next step in her management in relation to her intended pregnancy?

A. Counsel her against pregnancy as it is very high risk with uncontrolled autoimmune hepatitis
B. Continue taking medication and meet with the medical obstetric team
C. Arrange an endoscopy to assess for varices before pregnancy
D. Stop the prednisolone
E. Stop the azathioprine