Pregnancy-associated liver disease: a curriculum-based review

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ABSTRACT

Pregnancy is associated with changes in normal physiology, including changes to the normal parameters for blood tests. Abnormal liver function tests are a common reason for referral to gastroenterology. However, in the pregnant patient, there are unique potential causes. It is of prime importance to be aware of pregnancy-specific liver diseases as they can be serious and progress rapidly affecting outcomes for both the mother and fetus. Here, we provide an overview of the manifestations of pregnancy-related liver diseases and discuss their potential consequences.

INTRODUCTION

Pregnancy-associated liver disorders—though uncommon—will require the expert review of a gastroenterologist/hepatologist. Liver disorders may present inconspicuously during gestation. What is probably the most challenging factor is establishing the diagnosis in the context of the expected physiological changes of pregnancy. Prognostic models utilising existing hepatological scores (model end-stage liver disease) have been suggested to promote early recognition of those who are potentially at higher risk.¹ In this curriculum-mapped review (see [figure 1](#)), we discuss the most common pregnancy-related liver diseases encountered during gastroenterology training. An overview is provided in [table 1](#).

Hyperemesis gravidarum

Hyperemesis gravidarum is a condition of early pregnancy occurring in 1 in 200 pregnancies,² with symptoms mainly resolving by mid-pregnancy. It is the extreme form of nausea and vomiting of pregnancy leading to dehydration, ketosis and weight loss of >5% of body weight. Women often need hospitalisation, and in this situation, biochemical abnormalities include renal and electrolyte disturbance due to dehydration. In the cohort who are

hospitalised, a mild elevated aminotransferases occurs in 50%.² Abnormal liver function tests (LFTs) resolve on cessation of vomiting symptoms. The aetiology remains unclear, but we know that hyperemesis often recurs in future pregnancies.

Acute fatty liver disease of pregnancy (AFLP)

AFLP is a rare but life-threatening illness for both the mother and fetus. It is characterised by microvesicular fatty infiltration of the liver and usually occurs in the third trimester (median presentation 36 weeks), although can occur postnatally.³ Risk factors for its development include nulliparity, twin pregnancy and low maternal body mass index (BMI).³

Early recognition, prompt delivery and supportive care are essential to optimise maternal and fetal prognosis, as the postpartum clinical course is dependent on the interval between symptoms and termination of the pregnancy.⁴

Presenting symptoms are often non-specific including nausea, vomiting and abdominal pain. The hallmarks of liver failure (encephalopathy, coagulopathy and hypoglycaemia) may be present.

The diagnosis of AFLP is usually clinical. The Swansea criteria, validated in a large UK cohort ([box 1](#)), combine symptoms and laboratory results⁵ and offers an 85% positive predictive value and 100% negative predictive value for biopsy proven hepatic microvesicular steatosis. Practically, liver biopsy is rarely performed due to the need to stabilise and deliver affected women.

There is a link between fetal deficiency of long-chain 3-hydroxyacyl CoA dehydrogenase (LCHAD) and AFLP.⁶ Homozygous-deficient offspring spill unmetabolised long-chain fatty acids into the maternal circulation, accumulation can lead to hepatotoxicity.

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Knowledge
Knows the range of potentially serious liver diseases that can complicate pregnancy
Knows the various manifestations of pregnancy-associated liver disease including obstetric cholestasis and is aware of the urgency of such situations.
Knows how to manage the more severe pregnancy-associated liver diseases including eclampsia and acute fatty liver of pregnancy
Aware of importance of close liaison with obstetric colleagues over the timing of delivery
Skills
Is aware that, more than with any other aspect of liver disease, the optimum management of these diseases requires acute clinical acumen
Shows the ability to liaise and respond urgently to what is often rapidly escalating severity
Behaviours
Liaises closely and effectively with obstetric colleagues
Communicates effectively with concerned patients and relatives about the needs of the foetus and the overriding need to preserve the health of the mother

Figure 1 Curriculum item 3a: pregnancy-associated liver disease.

Mortality has improved recently due to early recognition and rapid fetal delivery followed by maternal supportive care. A recent meta-analysis by Wang *et al* showed that caesarean section is the safest method of delivery and is associated with better pregnancy outcomes.⁷ Although treatment, in the main, is supportive, there have been reports of liver transplantation and plasma exchange postdelivery.⁴

Intrahepatic cholestasis of pregnancy (ICP)

ICP is the most common liver disease in pregnancy, often presenting in the second and third trimesters. It has a variable incidence, ranging from 3% to 5% of pregnant women in Chile to 0.7% in the UK; it is rarely reported in African countries.⁸ It is likely that elevated

oestrogen and progesterone metabolites in pregnancy unmask the disease in genetically susceptible women.⁹ It is a reversible cholestasis characterised by pruritus and elevated serum bile acids with spontaneous relief of signs and symptoms within 6 weeks of delivery. ICP has a high recurrence rate. Jaundice occurs in <25% of patients with ICP and always after the onset of pruritus. If jaundice is the presenting symptom, further evaluation is necessary.

Risk factors include advanced maternal age, a history of cholestasis secondary to oral contraceptives, a personal or family history of ICP, multiple pregnancy and fertility treatment. Some studies suggest a higher prevalence in patients with hepatitis C, cholelithiasis and non-alcohol fatty liver disease.¹⁰

Table 1 Summary of pregnancy-related liver conditions

	Trimester	Features	Alanine aminotransferase	Bilirubin	Platelets	Recur	Comments
Hyperemesis gravidarum	First	Vomiting, dehydration, weight loss, ketosis	1–2× in 50% of patients	Normal	Normal	+++	Twin pregnancies
Intrahepatic cholestasis of pregnancy	Second and third	Bile acids↑ pruritus	1–4×	Normal in 75%	Normal	+++	Treat with ursodeoxycholic acid Deliver at 37 weeks (risk of late intrauterine death)
Acute fatty liver disease of pregnancy	Third	Creatinine↑ Uric Acid↑	1–10×	Can be elevated	Can be low but usually normal	Rarely	Maternal body mass index<20 Biopsy: microvesicular steatosis, foamy hepatocytes, hepatic necrosis 50% will have evidence of pre-eclampsia
Haemolysis, elevated liver enzyme levels and low platelet levels (HELLP)	Third May occur postpartum	Lactate dehydrogenase↑ Prothrombin and fibrinogen normal Uric acid↑	1–100×	Normal	Low	++	25% of cases will happen in postpartum period Associated with pre-eclampsia
Pre-eclampsia	>20 weeks	Hypertension Proteinuria±end organ damage	20%–30% will have abnormal liver function tests		Can be low in severe disease	++	Usually due to uteroplacental ischaemia Urgent delivery to avoid eclampsia, liver rupture and necrosis Up to 10%–20% will show features of HELLP ¹⁷

Box 1 Swansea criteria for diagnosis of acute fatty liver of pregnancy

Six or more criteria required in the absence of another cause

- ▶ Vomiting.
- ▶ Abdominal pain.
- ▶ Polydipsia/polyuria.
- ▶ Encephalopathy.
- ▶ Elevated bilirubin $>14 \mu\text{mol/L}$
- ▶ Hypoglycaemia $<4 \text{ mmol/L}$.
- ▶ Elevated uric acid $>340 \mu\text{mol/L}$.
- ▶ Leucocytosis $>11 \times 10^6 \text{ cells/L}$.
- ▶ Ascites or bright liver on ultrasound scan.
- ▶ Elevated transaminases (aspartate transaminase or alanine transaminase) $>42 \text{ IU/L}$.
- ▶ Elevated ammonia $>47 \mu\text{mol/L}$.
- ▶ Renal impairment; creatinine $>150 \mu\text{mol/L}$.
- ▶ Coagulopathy; prothrombin time $>14 \text{ s}$ or activated partial thromboplastin time $>34 \text{ s}$.
- ▶ Microvesicular steatosis on liver biopsy.

In ICP, bile acid concentrations are typically $>10 \mu\text{mol/L}$, with most complications occurring with levels $>40 \mu\text{mol/L}$.^{11 12} Aminotransferase levels may also be elevated. Ultrasonography should be performed to exclude cholelithiasis. Maternal outcomes are excellent; however, there is a risk of fetal distress, preterm labour, prematurity and intrauterine death.¹²

Delivery at 37 weeks should be considered because intrauterine death is more common in the last month of pregnancy, with few deaths before 37 weeks.¹³ Decisions should be tailored to the individual pregnancy.¹⁴ First-line therapy is ursodeoxycholic acid (UDCA) at 10–15 mg/kg maternal body weight which results in improved maternal symptoms and biochemistry in approximately 75% of cases.¹⁵ UDCA increases expression of bile salt export pumps and increases placental bile transporters. UDCA is more effective than cholestyramine or dexamethasone in controlling pruritus. Fat malabsorption can result in fat-soluble vitamin deficiencies. Some women do not respond to UDCA, and combining with rifampicin can improve the symptoms and biochemical results.¹⁶

Affected women also have an increased risk of hepatobiliary disease later in life, most commonly gallstones, hepatobiliary malignancies and immune mediated and cardiovascular diseases. If women have ongoing symptoms or biochemical hepatic impairment for more than 3 months postpartum an alternative/additional diagnosis should be sought.

Pre-eclampsia

Pre-eclampsia is defined as new onset gestational hypertension (in a previously normotensive woman) with significant proteinuria and can be complicated by

Table 2 Risk factors associated with gestational hypertension and pre-eclampsia

Moderate risk	High risk
Primigravida	Hypertension in previous pregnancy
Maternal age >40 years or <18 years	Systemic lupus erythematosus
Pregnancy interval >10 years	Antiphospholipid syndrome
Body mass index $\geq 35 \text{ kg/m}^2$	Autoimmunity
Family history of pre-eclampsia	Diabetes mellitus
Chronic kidney disease	Hypertension
Multifetal gestations	
Black race	
Hydrops fetalis	
In vitro fertilisation	
Partner related (new partner, limited sperm exposure)	

end-organ dysfunction, eclampsia and death. Proteinuria is defined as:

1. $\geq +1$ (30 mg/dL) on urine dipstick;
2. random Protein: Creatinine ratio $\geq 0.3 \text{ mg protein/mg creatinine}$;
3. $\geq 0.3 \text{ mg protein/24 hours}$.

Hypertension in pregnancy (gestational hypertension) is defined as systolic blood pressure $\geq 140 \text{ mm Hg}$ and diastolic blood pressure $\geq 90 \text{ mm Hg}$ without proteinuria $\pm$ end organ damage. Pre-eclampsia could occur in women with pre-existing chronic hypertension and diagnosis should be dictated by the new-onset proteinuria $\pm$ end organ damage. It typically occurs after 20 weeks of gestation. Several risk factors have been identified and these are listed in [table 2](#).

The pathophysiology of pre-eclampsia involves placental and maternal vascular dysfunction characterised by abnormal trophoblast invasion of spiral arteries. The symptoms of pre-eclampsia include severe headache, visual disturbances, emesis, oedema (peripheral and/or pulmonary), abdominal and epigastric pain, dyspnoea, chest pain, oliguria (in severe disease) and reduced mental status. Serum and urine investigations may reveal acute kidney injury, hyperuricaemia, hyperlipidaemia, neutrophilia, urinary sediment and raised haematocrit. Serious forms of the disease may be characterised by thrombocytopenia, haemolysis and elevated aminotransferases. It is believed that abnormalities to LFTs are secondary to reduced hepatic flow leading to hepatic ischaemia or periportal haemorrhage. Typically, clotting studies are normal unless there is progression to liver failure or placental abruption.

Patients with gestational hypertension including pre-eclampsia may have long-term health complications, and these need to be emphasised to patients. These are shown in [box 2](#).

It should be noted that pre-eclampsia can develop postpartum. Generally, a conservative approach should

Box 2 Long-term health risks for people with pre-eclampsia

- ▶ Non-gestational hypertensive disease.
- ▶ Gestational hypertension in future pregnancies (1 in 2–8 pregnancies).
- ▶ Increased pre-eclampsia risk in future pregnancies.
- ▶ End-stage renal disease.
- ▶ Cardiovascular disease including ischaemic heart disease and stroke.

be considered until week 34. Oral labetalol should be offered as first line for patients with blood pressure $\geq 150/100$ mm Hg. LFTs, renal function tests and full blood count should be performed at least twice weekly. The timing of birth for patients with pre-eclampsia should be reviewed carefully by an obstetric consultant. Successful conservative management could delay elective delivery until after 34 weeks, even for patients with severe hypertension (blood pressure $\geq 160/110$ mm Hg) if their blood pressure has been adequately controlled. Delivery before 34 weeks should be considered in patients who are refractory to antihypertensive therapy or if there are any other identified risk factors for the mother and/or fetus.

HELLP

The acronym HELLP was first described in 1982 and stands for haemolysis (with a microangiopathic blood smear), elevated liver enzymes (LFTs) and low platelet count. There is debate as to whether HELLP is a severe form of pre-eclampsia. The incidence of HELLP is 0.1%–0.8% of all pregnancies and risk factors include family history and HELLP in previous pregnancies as well as pre-eclampsia (10%–20% of patients).¹⁷ The pathogenesis of HELLP involves abnormal or aberrant placentation and more rarely fetal LCHAD deficiency.⁶

Patients with HELLP may present with a plethora of symptoms both in variety and severity, most usually between 28 and 36 weeks of gestation. The condition can also present postpartum. Commonly patients will demonstrate gastrointestinal symptoms including abdominal pain (especially right-upper-quadrant), nausea, vomiting and malaise. About 85% of patients are hypertensive (blood pressure $\geq 140/90$ mm Hg) and proteinuric. Apart from the deranged LFTs, other

severe hepatic manifestations have been described with HELLP including hepatic infarction, haemorrhage and rupture. Other serious complications include acute kidney injury, retinal detachment, pulmonary oedema, abruption placentae and disseminated intravascular coagulation.

All three elements of the HELLP acronym need to be satisfied in a pregnant patient before the diagnosis is made. When the diagnosis is considered, LFTs, blood film, full blood count, renal function tests and urine protein:creatinine ratio should be obtained especially in women presenting between 28 and 36 weeks of gestation and within 1–2 weeks postpartum. The Tennessee classification is the most widely used system, the parameters of which are outlined in [table 3](#).¹⁸

SCE STYLE QUESTIONS

1. Which of the following is the most accurate regarding the frequency of HELPP cases that occur in the postpartum period?
 - A. Less than 10%
 - B. 10%–20%
 - C. 25%–35%
 - D. 40%–50%
 - E. More than 50%

Answer: A

2. Which one of the following conditions has the highest risk of recurrence in subsequent pregnancies?
 - A. Acute fatty liver disease of pregnancy
 - B. Intrahepatic cholestasis of pregnancy
 - C. Pre-eclampsia
 - D. HELLP syndrome

Answer: B

3. Acute fatty liver of pregnancy is associated with which of the following?
 - A. Low maternal BMI
 - B. High maternal BMI
 - C. Singleton pregnancy
 - D. Underlying liver disease
 - E. Advanced maternal age

Answer: A

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Table 3 The Tennessee classification of HELLP syndrome (adapted from Sibai *et al*.¹⁸)

1	Platelet count $\leq 100 \times 10^9/L$
2	AST ≥ 70 IU/L and LDH ≥ 600 IU/L
3	Haemolysis on peripheral smear

Two out of three criteria=partial HELLP.

All criteria=full HELLP.

AST, aspartate aminotransferase; LDH, lactate dehydrogenase; HELLP, haemolysis, elevated liver enzyme levels and low platelet levels.

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