

# Managing hepatic complications of pregnancy: practical strategies for clinicians

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## ABSTRACT

Liver disorders specific to pregnancy are rare but can have potentially serious consequences for mother and fetus. Pregnancy-related liver disorders are the most common cause of liver disease in otherwise healthy pregnant women and pose a challenge to physicians because of the need to take into account both maternal and fetal health. A good knowledge of these disorders is necessary as prompt diagnosis and appropriate management results in improved maternal and fetal outcomes. This review will focus on pregnancy-specific disorders and will aim to serve as a guide for physicians in their diagnosis, management and subsequent monitoring.

## INTRODUCTION

Liver disease occurs in up to 3% of all pregnancies and can be directly related to pregnancy, coincidental or associated with a previous established diagnosis.<sup>1</sup> The majority of liver disease that occurs during pregnancy in otherwise healthy women is pregnancy related, and includes hyperemesis gravidarum (HG), intrahepatic cholestasis of pregnancy (IHCP), hypertension-related diseases such as pre-eclampsia and eclampsia, the syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP syndrome) and acute fatty liver of pregnancy (AFLP). This review will provide an update on the diagnosis, management and prognosis of these liver diseases that are unique to pregnancy. This review focuses on the hepatologist's role in caring for pregnant women with liver diseases. However, for all conditions discussed in this review, it is important that the hepatologist is working within a multidisciplinary team with obstetrics, midwifery and in some cases, intensive care.

## NORMAL PHYSIOLOGICAL CHANGES DURING PREGNANCY

Physiological changes occur in pregnancy, which impact the normal ranges for liver function tests (LFTs) (table 1).<sup>2</sup> Therefore,

## Key points

- ▶ Pregnancy-specific liver diseases can be differentiated based on their timing within pregnancy, clinical features and laboratory values.
- ▶ In hypertension-related disease, differentiating between haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome and acute fatty liver of pregnancy (AFLP) is challenging and criteria for both diseases have been developed to aid diagnosis.
- ▶ Prompt delivery of the fetus is the most important management for pre-eclampsia with liver involvement, HELLP syndrome and AFLP.
- ▶ Intrahepatic cholestasis of pregnancy is managed pharmacologically and with early delivery at 37 weeks gestation.
- ▶ Management of hyperemesis gravidarum is supportive.
- ▶ Prognosis of pregnancy-specific liver diseases has improved in recent years with earlier diagnosis and improvements in multidisciplinary management.
- ▶ In the majority of cases, pregnancy-specific liver diseases have no long-term impact on liver function.

interpretation of LFTs during pregnancy must take these changes into account. Maternal alkaline phosphatase concentration increases as it is produced by the placenta and fetal bone maturation. Maternal alpha fetoprotein concentrations increase as it is produced by the fetal liver. There is haemodilution of serum albumin, whereas the concentrations of aminotransferases (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)), bilirubin and gamma-glutamyl transpeptidase (GGT) remain within the normal prepregnancy range or are slightly decreased, and therefore, any elevation in these tests requires further investigation. Haemoglobin is often slightly reduced because of haemodilution. Clotting factors and fibrinogen are typically increased. Platelet counts tend to gradually decrease as the pregnancy progresses.

## HYPEREMESIS GRAVIDARUM

Nausea and vomiting are common symptoms during pregnancy. A total of 0.3%–3.6% of



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**Table 1** Reference ranges for biochemical tests by trimester of pregnancy

Biochemical test	Non-pregnant	First trimester	Second trimester	Third trimester
Haemoglobin (g/L)	120–158	116–139	97–148	95–150
White cell count ( $\times 10^9/L$ )	3.5–9.1	5.7–13.6	5.6–14.8	5.9–16.9
Platelets ( $\times 10^9/L$ )	165–415	174–391	155–409	146–429
Prothrombin time (s)	12.7–15.4	9.7–13.5	9.5–13.4	9.6–12.9
ALP (U/L)	33–96	17–88	25–126	38–229
Albumin (g/L)	41–53	31–51	26–45	23–42
ALT (IU/L)	7–41	3–30	2–33	2–25
AST (IU/L)	12–38	3–23	3–33	4–32
GGT (U/L)	9–58	2–23	4–22	3–26
Bilirubin, total ( $\mu\text{mol/L}$ )	5–22	1–7	1–14	1–19
Bile acids ( $\mu\text{mol/L}$ )	0.3–4.8	0–4.9	0–9.1	0–11.3

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase.

pregnant women develop severe or protracted nausea and vomiting, termed HG.<sup>3</sup> Risk factors include hyperthyroidism, psychiatric illness, molar pregnancy, pre-existing diabetes and multiple pregnancy.<sup>4</sup> The aetiology is poorly understood, but is thought to involve hormonal, immunological and psychological factors.<sup>5</sup>

### Diagnosis

The most commonly used definition of HG is severe or protracted nausea and vomiting leading to dehydration, electrolyte abnormalities and loss of at least 5% of prepregnancy body weight.<sup>6,7</sup> HG develops in the first trimester and is a clinical diagnosis after excluding other causes of nausea and vomiting.<sup>7</sup>

Abnormal LFTs develop in approximately 50% of patients from mild elevation in serum aminotransferases to 20 times the upper limit of normal (ULN) (table 2).<sup>18</sup> Jaundice and hepatic synthetic dysfunction are rare. Hypokalaemia, hypomagnesaemia, hypophosphataemia, raised serum urea and creatinine are common. Biochemical and liver function abnormalities should normalise on resolution of symptoms and persistently deranged LFTs warrant consideration of an alternative diagnosis, such as viral hepatitis.<sup>9</sup>

### Management

Treatment of HG is supportive with intravenous rehydration, electrolyte replacement and antiemetics.<sup>179</sup> There is varying guidance on antiemetic therapy and a Cochrane meta-analysis has found that no single antiemetic is superior to others.<sup>10</sup> Specific medications for first-line to fourth-line therapy recommended for use are demonstrated in table 3. The American College of Obstetricians and Gynecologists (ACOG) and the European Association for the Study of the Liver (EASL) recommend pyridoxine alone or in combination with doxylamine as first-line therapy.<sup>11</sup> The Royal College of Obstetricians and Gynaecologists (RCOG) does not recommend use of pyridoxine based on a lack of evidence on efficacy.<sup>7</sup> Corticosteroids should only be used after standard treatment

has failed and are recommended by ACOG, RCOG, EASL and the American Association for the Study of Liver Diseases (AASLD), although the evidence for their effectiveness is conflicting.<sup>179–182</sup> Thiamine supplementation is required to prevent Wernicke's encephalopathy, which is recommended by AASLD, RCOG, ACOG and EASL.<sup>179,11</sup>

Ongoing vomiting, despite medical therapies, should prompt consideration of enteral or parenteral nutrition.<sup>7,11</sup> There are no established criteria for enteral or parenteral feeding. Enteral feeding with nasogastric, nasoduodenal or nasojejunal tubes is safer, leaving total parenteral nutrition as a last resort.<sup>7,13</sup>

Serum urea and electrolytes should be checked daily and maternal body weight should be monitored.<sup>7</sup> The Pregnancy-Unique Quantification of Emesis score is a validated system based on three parameters including (1) duration of nausea, (2) number of vomiting episodes and (3) number of dry heaves (in the preceding 12 hours) which can be used to monitor progress.<sup>14</sup>

### Prognosis

Poor weight gain in HG is associated with fetal growth restriction, preterm birth, small for gestational age babies and low Apgar scores.<sup>15–17</sup> Maternal complications are uncommon and include Wernicke's encephalopathy, which presents with confusion and nystagmus. HG typically resolves by 20 weeks gestation but may in rare cases persist throughout the pregnancy.<sup>18</sup> There are no long-term consequences on liver function.<sup>1</sup> Recurrence of HG in subsequent pregnancies is common.<sup>15,19</sup>

### INTRAHEPATIC CHOLESTASIS OF PREGNANCY

IHCP, also termed obstetric cholestasis, is the most common pregnancy-specific liver disease and affects 0.3%–5% of pregnancies.<sup>20</sup> It is characterised by pruritus with elevated serum bile acids or abnormal LFTs in the second half of pregnancy.<sup>21</sup> Pathophysiology involves reduced bile flow, leading to bile salt deposition in the skin and placenta. A combination of hormonal, genetic

**Table 2** Typical features and differential diagnoses of pregnancy-specific liver diseases

	<b>Hyperemesis gravidarum</b>	<b>Intrahepatic cholestasis of pregnancy</b>	<b>Pre-eclampsia with hepatic impairment</b>	<b>HELLP syndrome</b>	<b>Acute fatty liver of pregnancy</b>
Timing of presentation in pregnancy	First trimester	Second/third trimester	After 20 weeks	Third trimester	Third trimester
Main clinical findings	Severe nausea and vomiting, dehydration, weight loss	Pruritus, jaundice	Abdominal pain, hypertension, proteinuria, headache	Abdominal pain, vomiting, hypertension, proteinuria, headache	Abdominal pain, vomiting, jaundice, encephalopathy
AST/ALT	1–5 × ULN	1–8 × ULN	2–10 × ULN	2–30 × ULN	5–15 × ULN
Bilirubin	Normal	1–6 × ULN	Normal	1.5–6 × ULN	6–8 × ULN
Bile acids	Normal	>10 μmol/L	Normal	Normal	Normal
Platelets	Normal	Normal	Normal - ↓	↓ - ↓↓	↓
Haemolysis	No	No	No	+	+
LDH	Normal	Normal	Normal - ↑	↑	↑
Fibrinogen	Normal	Normal	Normal	Normal	↓↓
Hypoglycaemia	No	No	No	No	+
Uric acid	Normal	Normal	↑	↑	↑
Creatinine	↑	Normal	Normal - ↑	Normal - ↑	↑ - ↑↑
Key steps in management	Supportive, rehydration, antiemetics	UDCA, delivery at 37 weeks	Blood pressure control, delivery after 34 weeks	Delivery, platelet transfusion, blood pressure control	Delivery, intensive care
Differential diagnosis	Hepatitis, cholecystitis, peptic ulcers, gastroenteritis, pancreatitis	Cholelithiasis, viral hepatitis, autoimmune liver disease	HUS, TTP, SLE exacerbation, septic shock	HUS, TTP, SLE exacerbation, septic shock	HUS, TTP, paracetamol toxicity, hepatitis, SLE exacerbation
Complications	Preterm birth, fetal growth restriction, Wernicke's encephalopathy	Preterm birth, fetal distress, stillbirth	Liver haematoma, rupture, infarction, Pulmonary oedema, cerebral haemorrhage, preterm birth, fetal growth restriction	Liver haematoma, rupture, infarction, Pulmonary oedema, cerebral haemorrhage, DIC, preterm birth, fetal growth restriction	Acute liver failure, DIC, postpartum haemorrhage, acute renal failure, gastrointestinal bleeding

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DIC, disseminated intravascular coagulation; HELLP, haemolysis, elevated liver enzymes, low platelets; HUS, haemolytic uraemic syndrome; LDH, lactate dehydrogenase; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

and environmental factors are thought to contribute to this reduction in bile flow.<sup>22</sup> Risk factors include previous cholestasis secondary to the contraceptive pill (OCP), pre-existing hepatitis C viral infection, advanced maternal age, multiple pregnancy and a family history of the disorder.<sup>23</sup>

### Diagnosis

There is no international consensus on diagnostic criteria for IHCP, but generally the diagnosis is based on unexplained pruritus in pregnancy with raised bile acids or abnormal LFTs.<sup>24</sup> The predominant symptom is pruritus, especially of the palms and soles and is usually worst at night.<sup>20</sup> It typically develops in the third trimester, however, presentations as early as week 7 of gestation have been documented.<sup>1</sup> There may be excoriation

marks, but any other rash should lead to consideration of alternative skin conditions, such as eczema and pruritic eruption of pregnancy.<sup>25</sup> The pruritus is followed by generalised symptoms, such as fatigue, nausea and jaundice in <25% of IHCP.<sup>26</sup> Alternative diagnoses should be sought if jaundice is the presenting symptom.<sup>26</sup> There may be other features of cholestasis such as steatorrhoea and dark urine.<sup>27</sup>

The onset of pruritus typically precedes biochemical abnormalities.<sup>28</sup> LFTs should be checked in pregnant woman with pruritus and repeated if normal.<sup>21 29</sup> Elevated fasting serum bile acids are the most sensitive indicator of IHCP.<sup>21</sup> Abnormalities in LFTs are common, with aminotransferases elevated up to 10 times the ULN, and can be as high as 1000 IU/L. When jaundice does occur, it

**Table 3** Medications recommended for treatment of hyperemesis gravidarum by major authoritative bodies

	RCOG	ACOG	EASL
First line	Antihistamines: <ul style="list-style-type: none"> <li>▶ Promethazine</li> <li>▶ Cyclizine</li> </ul> Phenothiazines: <ul style="list-style-type: none"> <li>▶ Prochlorperazine</li> <li>▶ Chlorpromazine</li> </ul>	Pyridoxine (vitamin B <sub>6</sub> ) alone or in combination with doxylamine	Pyridoxine (vitamin B <sub>6</sub> ) alone or in combination with doxylamine
Second line	<ul style="list-style-type: none"> <li>▶ Metoclopramide</li> <li>▶ Domperidone</li> <li>▶ Ondansetron</li> </ul>	<ul style="list-style-type: none"> <li>▶ Dimenhydrinate</li> <li>▶ Diphenhydramine</li> <li>▶ Prochlorperazine</li> <li>▶ Promethazine</li> </ul>	Dopamine antagonists <ul style="list-style-type: none"> <li>▶ Metoclopramide</li> </ul> Phenothiazines <ul style="list-style-type: none"> <li>▶ Chlorpromazine</li> <li>▶ Prochlorperazine</li> </ul> Anticholinergics <ul style="list-style-type: none"> <li>▶ Dicycloverine</li> </ul> Antihistamine <ul style="list-style-type: none"> <li>▶ Cyclizine</li> </ul>
Third line	Corticosteroids: <ul style="list-style-type: none"> <li>▶ Initially hydrocortisone intravenously</li> <li>▶ Prednisolone orally with clinical improvement</li> <li>▶ Taper dose gradually until at lowest maintenance dose that controls symptoms</li> </ul>	<ul style="list-style-type: none"> <li>▶ Metoclopramide</li> <li>▶ Ondansetron</li> <li>▶ Trimethobenzamide (only recommended if dehydration not present)</li> </ul>	<ul style="list-style-type: none"> <li>▶ Ondansetron</li> <li>▶ Glucocorticoids</li> </ul>
Fourth line		<ul style="list-style-type: none"> <li>▶ Chlorpromazine</li> <li>▶ Methylprednisolone orally or intravenously for 3 days. Taper over 2 weeks to lowest effective dose. If beneficial, limit total duration of use to 6 weeks.</li> </ul>	

ACOG, American College of Obstetricians and Gynecologists; EASL, European Association for the Study of the Liver; RCOG, Royal College of Obstetricians and Gynaecologists.

is often mild with bilirubin <100 µmol/L. Raised GGT is rare. Prothrombin time (PT) is normal unless there is vitamin K malabsorption. Liver biopsy is generally not indicated.<sup>21</sup>

The American College of Gastroenterology (ACG) advises that liver ultrasonography should be performed in all cases to rule out cholelithiasis, whereas AASLD and RCOG recommend only in select cases.<sup>9 26 29</sup> RCOG advises screening for viral hepatitis and autoimmune liver disease according to individual risk factors.<sup>29</sup> AASLD advise that all women should be tested for hepatitis C, if not done previously, given the higher prevalence of hepatitis C in IHCP.<sup>9 23 30</sup> Pre-eclampsia and AFLP should be considered in atypical cases.<sup>21</sup>

### Management

Ursodeoxycholic acid (UDCA) is the first-line treatment recommended for IHCP by ACG, ACOG, AASLD and EASL.<sup>9 21 26 31</sup> ACG and AASLD advise UDCA at a dose of 10–15 mg/kg of maternal body weight per day.<sup>9 26</sup> ACOG advises starting at 10–15 mg/kg/day in 2–3 daily doses, which can be uptitrated to a maximum of 21 mg/kg/day.<sup>31</sup> EASL advises 10–20 mg/kg/day, which can be uptitrated to 25 mg/kg/day.<sup>21</sup> Despite the largest trial of UDCA identifying no benefit in maternal symptoms,<sup>32</sup> a

recent systematic review and meta-analysis has detected a reduction in stillbirth and preterm birth with UDCA.<sup>33</sup>

Second-line therapies include S-adenosyl-methionine (recommended by AASLD, RCOG, ACOG and EASL), rifampicin (recommended by AASLD, ACOG and EASL) cholestyramine (recommended by AASLD and ACOG) and dexamethasone (recommended by RCOG).<sup>9 21 29 31</sup> All of these therapies lack robust evidence for improvement in pruritus.<sup>9 29</sup> EASL do not advise dexamethasone on the basis that it is an inadequate treatment for IHCP.<sup>21</sup> Antihistamines (diphenhydramine and hydroxyzine suggested by ACOG, chlorphenamine suggested by RCOG) can be used for sedation at night but do not improve pruritus.<sup>9 29 31</sup> Topical emollients are also safe for use.<sup>21 29 31</sup> Vitamin K supplementation at 5–10 mg daily is recommended if the PT is prolonged, with more frequent monitoring of PT in women taking cholestyramine.<sup>9 29</sup>

Delivery at 37 weeks prevents stillbirth after this point. RCOG advises that a discussion regarding the induction of labour after 37 weeks should be made with the patient.<sup>29</sup> ACOG advises delivery at 36 weeks if bile acids are ≥100 µmol/L or between 36 and 39 weeks if bile acids are <100 µmol/L.<sup>31</sup> Monitoring of the disease as advised by the RCOG includes weekly measurements of LFTs.<sup>29</sup>

ACOG advises repeated bile acid measurements to guide timing of delivery, but does not recommend weekly testing.<sup>31</sup>

### Prognosis

Biochemical tests and antenatal fetal monitoring are poor predictors of adverse fetal outcome including fetal death.<sup>29</sup> However, high bile acid concentrations >40 µmol/L show some correlation with adverse fetal outcomes which include fetal distress, preterm birth and meconium-stained amniotic fluid.<sup>34 35</sup> A small additional risk of stillbirth is associated with serum bile acids >100 µmol/L.<sup>36</sup>

Symptoms and LFTs generally resolve within 4–6 weeks after delivery.<sup>21</sup> LFTs and serum bile acid concentrations should be checked at 6 weeks after delivery.<sup>29</sup> If there are persistent symptoms or deranged LFTs post-delivery, other liver diseases such as primary biliary cholangitis and primary sclerosing cholangitis should be excluded.<sup>9 21 26 29</sup> For severe disease with persistence post-delivery, genetic analysis should be considered for mutations associated with paediatric familial cholestatic disorders such as *ABCB4* (encoding the multidrug resistance protein 3), *ABCB11* (ATP binding cassette subfamily B encoding the Bile Salt Export Pump), *ATP8B1* (ATPase class 8B member 1 encoding a phosphatidyl serine flippase), *ABCC2* (the multidrug resistance-associated protein 2), and *TJP2* (encoding tight junctional proteins).<sup>37</sup>

IHCP has a high rate of recurrence of up to 90% of subsequent pregnancies.<sup>24</sup> It is also associated with an increased risk of cholestasis with the use of the combined OCP,<sup>24</sup> higher rates of cholelithiasis<sup>23</sup> and a slightly increased risk of developing hepatobiliary cancer.<sup>38</sup>

### HYPERTENSION-RELATED LIVER DISEASES IN PREGNANCY

Hypertension in pregnancy is defined as a blood pressure of greater than 140/90 mm Hg on at least two occasions. Hypertension-related liver diseases in pregnancy include pre-eclampsia, eclampsia, HELLP syndrome and hepatic haematoma, rupture and infarction.

### PRE-ECLAMPSIA AND ECLAMPSIA

Pre-eclampsia is defined as the development of hypertension after 20 weeks of gestation with proteinuria (>300 mg/24 hours), other maternal organ dysfunction or fetal growth restriction.<sup>39 40</sup> It develops in 3%–5% of all pregnancies.<sup>41</sup> It is a multisystem disorder, where placental ischaemia leads to endothelial dysfunction and coagulation activation.<sup>42</sup> The presence of seizures with no other explanation differentiates eclampsia from pre-eclampsia. There is hepatic involvement in 20%–30% of cases of pre-eclampsia, thought to be secondary to vasoconstriction of the hepatic vascular bed.<sup>43</sup>

### Prevention

High-risk factors for developing pre-eclampsia include<sup>40</sup>:

- ▶ Hypertensive disease during a previous pregnancy.

- ▶ Chronic kidney disease.
- ▶ Autoimmune disease such as systemic lupus erythematosus (SLE), antiphospholipid syndrome or autoimmune liver diseases.
- ▶ Type 1 or 2 diabetes.
- ▶ Chronic hypertension.

Factors denoting moderate risk:

- ▶ First pregnancy.
- ▶ Age 40 years or older.
- ▶ Pregnancy interval of more than 10 years.
- ▶ Body mass index of 35 kg/m<sup>2</sup> or more at first visit.
- ▶ Family history of pre-eclampsia.
- ▶ Multifetal pregnancy.

A large randomised controlled trial has shown low-dose aspirin to reduce the incidence of preterm pre-eclampsia in women with high risk factors.<sup>44</sup> Women with one high risk factor or more than one moderate risk factor should be advised to take low-dose aspirin (75–150 mg daily) from 12 weeks of pregnancy until delivery.<sup>40 45</sup>

### Diagnosis

Symptoms of liver involvement are non-specific and include right upper quadrant or epigastric pain (due to stretching of Glisson's capsule from hepatic swelling), nausea, vomiting and headaches.<sup>26</sup> Elevations of AST and ALT can be up to 10 times the ULN (table 2). AST is typically increased to a greater extent than ALT which can be helpful in differentiating pre-eclampsia from other liver diseases.<sup>45</sup> Bilirubin and albumin usually remain within the normal range.

### Management

There is no specific medical treatment for liver involvement in pre-eclampsia. Abnormal LFTs with abdominal pain meets the criteria for severe pre-eclampsia and immediate delivery is required if beyond 34 weeks gestation, and considered at earlier gestations.<sup>40 45</sup> Prior to delivery, tight control of maternal blood pressure should be achieved with labetalol, nifedipine or hydralazine.<sup>40 45</sup> Intravenous magnesium sulphate should be administered for seizure prophylaxis if delivery is planned within 24 hours.<sup>45</sup> Monitoring of LFTs should be performed until results return to the normal range.<sup>40</sup>

### Prognosis

Liver-related maternal complications include liver infarction, rupture and haemorrhage. Other maternal complications include pulmonary oedema, renal dysfunction and cerebral haemorrhage. The severity of LFT derangement can help to predict adverse maternal but not fetal outcomes.<sup>46</sup> Fetal complications include preterm delivery, intrauterine growth restriction and intrauterine death.<sup>40</sup>

Post-delivery, LFTs usually normalise within 2 weeks. There is significant evidence to suggest that women who have had pre-eclampsia have a higher long-term risk of developing cardiovascular disease, type 2 diabetes and renal disease in later life.<sup>47–49</sup>



**Table 4** Mississippi and Tennessee systems for diagnosis of HELLP syndrome

Mississippi system	Tennessee system
Class 1 (severe): ▶ AST or ALT > 70 U/L ▶ LDH > 600 U/L ▶ Platelets < 50 × 10 <sup>9</sup> /L Class 2 (moderate): ▶ AST or ALT > 70 U/L ▶ LDH > 600 U/L ▶ Platelets 50–100 × 10 <sup>9</sup> /L Class 3 (mild) ▶ AST or ALT > 40 U/L ▶ LDH > 600 U/L ▶ Platelets 100–150 × 10 <sup>9</sup> /L	▶ AST > 70 U/L ▶ LDH > 600 U/L ▶ Platelets < 100 × 10 <sup>9</sup> /L Complete HELLP syndrome: all three criteria met Partial HELLP syndrome: 1–2 criteria met

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HELLP, haemolysis, elevated liver enzymes, low platelets; LDH, lactate dehydrogenase.

## HELLP SYNDROME

HELLP syndrome was first described by Weinstein and constitutes an important and severe sub-section of pre-eclampsia.<sup>50</sup> HELLP syndrome occurs in 10%–20% of women with severe pre-eclampsia, but can also develop in women without pre-eclampsia.<sup>51</sup> Overall incidence is up to 0.9% of pregnancies.<sup>52–53</sup> Risk factors are advanced maternal age, nulliparity, multiple pregnancy and previous pre-eclampsia or HELLP syndrome.<sup>54</sup>

## Diagnosis

HELLP syndrome usually presents between 28 and 36 weeks of gestation but may develop in the first week post partum. Patients may be asymptomatic or have non-specific symptoms including right upper quadrant or epigastric pain, nausea, vomiting, headache, and malaise.<sup>52</sup> Hypertension and proteinuria are present in up to 85% of cases.<sup>26</sup>

Diagnostic criteria for HELLP syndrome, such as the Tennessee and Mississippi criteria (table 4), include the triad of haemolysis, thrombocytopenia and deranged LFTs.<sup>55–57</sup> When the triad is not fulfilled, it is termed incomplete HELLP or ELLP syndrome.<sup>56–58</sup> There is typically a moderate increase in aminotransferases and a mild elevation in unconjugated bilirubin (table 2). Other features include an elevated lactate dehydrogenase (LDH), schistocytosis on peripheral smear and an elevated uric acid.<sup>56</sup> PT can be raised in severe liver injury or disseminated intravascular coagulation (DIC). The elevation of aminotransferases is much greater in HELLP syndrome than in pre-eclampsia. Elevation of aminotransferases, rising LDH and uric acid in severe pre-eclampsia might indicate progression to HELLP syndrome which is important to recognise because of the potentially life-threatening nature of this syndrome. Liver biopsy is not indicated for diagnosis of HELLP syndrome and would be hazardous because of the risk of bleeding.<sup>19</sup>

Other differential diagnoses to consider include haemolytic uraemic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) and AFLP.<sup>59</sup>

## Management

Women with HELLP syndrome generally require care in a high-dependency setting because of the risk of complications of bleeding, DIC, hepatic encephalopathy, hepatic rupture and acute renal dysfunction.<sup>40</sup> Tight blood pressure control is crucial.<sup>40–45</sup> Magnesium sulphate infusion is advised by ACOG, whereas the National Institute of Health and Care Excellence (NICE) advise consideration of magnesium sulphate.<sup>40–45</sup> Platelet transfusion is advised by ACG and ACOG to maintain platelet counts above 40 000–50 000 cell/μL if bleeding or when invasive procedures, such as Caesarean section, are planned.<sup>26–60</sup> It has been thought that corticosteroids would treat the proinflammatory component of HELLP syndrome. However, a Cochrane review found that despite improved platelet counts, dexamethasone did not improve maternal morbidity and mortality or perinatal death,<sup>61</sup> and so is not recommended by NICE.<sup>40</sup> ACOG also note that there is insufficient evidence for usage of steroids.<sup>45</sup> Delivery is the only curative therapy and should take place as soon as the maternal condition has been stabilised.<sup>45</sup>

Laboratory results should be performed every 12 to 24 hours postpartum.<sup>45</sup> AASLD advise that HELLP syndrome resulting in hepatic rupture or acute liver failure (ALF) should warrant transfer to a liver transplant centre for assessment.<sup>9</sup> Indications for liver transplantation include persistent bleeding from a hepatic haematoma, hepatic rupture or ALF.<sup>62–63</sup>

## Prognosis

Maternal mortality rate ranges between 1% and 3%.<sup>64</sup> Liver-related complications include hepatic haematoma, rupture or infarction. Other maternal complications include stroke, acute kidney injury (AKI), DIC, placental abruption and pulmonary oedema.<sup>52</sup> Fetal prognosis is related to gestational age at delivery, birth weight and neonatal condition at birth. Perinatal mortality is estimated to be between 8% and 34%.<sup>58</sup>

LFTs should start to resolve within 48 hours postpartum.<sup>52</sup> Recurrence rate of HELLP syndrome in future pregnancies is probably in the region of 2%–6%.<sup>65</sup> However, at least 20% of those with HELLP syndrome will develop some form of pre-eclampsia in a subsequent pregnancy.<sup>65</sup>

## LIVER HAEMATOMA, RUPTURE, INFARCTION

Liver-related complications of both pre-eclampsia and HELLP syndrome include subcapsular haematoma, rupture and infarction. Development of a subcapsular haematoma is thought to complicate 0.9%–1.6% of cases of HELLP syndrome.<sup>66</sup> Haematomas can remain contained or can rupture and haemorrhage into the peritoneal cavity, which is one of the most life-threatening complications of HELLP syndrome. Because of the rarity

of these complications, the literature is limited to case reports.

### Diagnosis

Subcapsular liver haematomas usually develop in the late second or third trimester. Patients can present with epigastric or right upper quadrant pain radiating to the right shoulder, nausea, vomiting and hypotension.<sup>65</sup> When hepatic rupture occurs, patients develop abdominal distension from haemoperitoneum and hypovolaemic shock.<sup>67</sup> Bloods typically show a severe thrombocytopenia and moderate elevations of aminotransferase concentrations, but elevations to 4000–5000 IU/L have been reported.<sup>65</sup> Imaging should be performed in any patient with HELLP syndrome or pre-eclampsia with right upper quadrant pain, shoulder pain or shock, regardless of the LFTs as they do not correlate with findings on imaging.<sup>68</sup> CT or MRI of the liver confirm the diagnosis. CT is the imaging of choice, as it is faster and safer for the unstable patient.<sup>66</sup>

Hepatic infarction is less common than hepatic haematoma but can also complicate pre-eclampsia and HELLP syndrome.<sup>69</sup> Infarction can present with right upper quadrant pain and fever, associated with severe elevations in aminotransferases (1000–2000 IU/L or higher) and leukocytosis.<sup>65</sup> The diagnosis is also confirmed with liver imaging, where infarction is typically seen in a peripheral location of the right liver.<sup>70</sup>

### Management

Contained subcapsular haematomas with haemodynamic stability should be managed conservatively with close observations and repeat imaging to monitor the size of the haematoma.<sup>1 71</sup> Blood transfusions and coagulation support should be used as required and prophylactic antibiotics considered.<sup>1 9</sup> Patients with hepatic rupture should be transferred to a transplant centre.<sup>9</sup>

Haemodynamic instability suggests active bleeding and urgent hepatic angiography should be performed.<sup>9</sup> Haemostasis can be achieved by embolisation of the hepatic artery or surgical methods, such as packing of the liver, hepatic artery ligation or resection of the affected liver.<sup>71 72</sup> Transplant should be considered in cases of refractory haemorrhage or rapidly progressing ALF and has been successful in case reports.<sup>62 63</sup>

### Prognosis

Consequences can be severe and the maternal mortality rate is thought to be 17%–59% for a haematoma, depending on whether it ruptures, when it is diagnosed and availability of therapy.<sup>66</sup> Complications in the acute period include hypovolaemic shock, AKI and acute respiratory distress syndrome (ARDS). For conservatively managed haematomas, complete resolution can take up to several months.<sup>66</sup> Infarctions also typically resolve on imaging after delivery.<sup>69</sup>

### ACUTE FATTY LIVER DISEASE OF PREGNANCY

AFLP is a serious and rare pregnancy-related liver disease. AFLP resulting in hepatic failure is a medical

and obstetric emergency. Incidence varies from 1:7000 to 1:20000 pregnancies.<sup>73 74</sup> It is most strongly linked with a fetal homozygous mutation for the long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD).<sup>74 75</sup> This leads to the accumulation of fatty acid metabolites in the placenta, which are then shunted into the maternal circulation and accumulate in the maternal liver. The mother is typically heterozygous for this mutation, and also has reduced fatty acid oxidation.<sup>76</sup> However, women who are negative for the mutation can still develop AFLP.<sup>77</sup> Other risk factors include multiple pregnancy and male fetus.<sup>73 76</sup>

### Diagnosis

AFLP may present with non-specific symptoms such as nausea, vomiting, headache, anorexia and abdominal pain. Some women will rapidly progress to liver failure with hepatic encephalopathy, jaundice, hypoglycaemia and coagulopathy. Symptoms almost always develop in the third trimester; however, cases have been reported in the late second trimester or postpartum period.<sup>73</sup> There is also an association with pre-eclampsia but the reason for this is not well understood.

Biochemical tests often show a raised AST, ALT, bilirubin, creatinine, ammonia, lactate and serum uric acid (table 2).<sup>78</sup> Aminotransferases are usually in the range of 300–500 IU/L. Haematological tests typically demonstrate a leukocytosis, low to normal platelets and a normocytic normochromic anaemia. The coagulopathy is usually severe, with a prolonged PT, hypofibrinogenaemia and elevated D-dimer.<sup>76 79</sup> Coagulopathy or DIC occur in approximately 70% of cases.<sup>78</sup> The role of liver ultrasound is unclear, as a prospective study showed that only 25% of women had the classic echogenic findings.<sup>73</sup> CT scan is more sensitive, however, only 50% of cases show typical features on CT scan.<sup>80</sup> Liver biopsy is not required to confirm the diagnosis but can be useful in indeterminate cases to guide the need for an early delivery.<sup>9 81</sup>

AFLP can be challenging to distinguish from HELLP syndrome, as they share many clinical and laboratory features. Women with AFLP are more likely to have synthetic liver dysfunction with coagulopathy, hypofibrinogenaemia, lower cholesterol levels, higher bilirubin levels, hypoglycaemia, hepatic encephalopathy, hyperammonaemia, DIC and more severe AKI.<sup>82 83</sup> Other differentials include HUS, TTP, paracetamol toxicity, exacerbation of SLE and overlap with pre-eclampsia and HELLP syndrome.<sup>59</sup>

The Swansea criterion (box 1) is a validated system to help diagnose AFLP but only in the absence of other liver diseases, such as HELLP syndrome, thus limiting its application.<sup>84 85</sup> One recent study found that the Swansea criteria were fulfilled in women presenting with any cause of ALF.<sup>86</sup>

### Management

Delivery is the only curative treatment as liver failure will continue until the fetus has been delivered.<sup>9 26 76</sup> Before

**Box 1 Swansea criteria for diagnosis of AFLP**

Vomiting.  
 Abdominal pain.  
 Polydipsia/polyuria.  
 Encephalopathy.  
 Elevated bilirubin >14 µmol/L.  
 Hypoglycaemia <4 mmol/L.  
 Elevated urea >340 µmol/L.  
 Leukocytosis >11×10<sup>6</sup> cells/L.  
 Elevated transaminases (AST or ALT)>42 U/L.  
 Elevated ammonia >47 µmol/L.  
 Renal impairment; creatinine >150 µmol/L.  
 Coagulopathy; PT >14 s or APTT>34 s.  
 Ascites or bright liver on ultrasound scan.  
 Microvesicular steatosis on liver biopsy.

(Six or more criteria are required in the absence of another explanation.)  
 AFLP, acute fatty liver of pregnancy; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; PT, prothrombin time.

delivery, maternal stabilisation should be achieved with correction of hypoglycaemia, coagulopathy and hypertension.<sup>76 87</sup> Maternal intensive supportive care in a multidisciplinary team is required following the delivery. Six-hourly LFTs, renal function and haematological parameters should be performed within the first 24–48 hours after delivery.<sup>76 78</sup> In non-randomised trials, plasma exchange has been associated with hastening hepatic improvement and decreasing intensive care stay, but not with improved maternal mortality.<sup>88 89</sup>

Patients with ongoing deterioration in liver function after emergency delivery or patients who develop hepatic rupture should be transferred to a liver transplant centre for assessment.<sup>9</sup> Transplantation should be considered in cases of ALF or hepatic rupture.<sup>9</sup> Elevated lactate with hepatic encephalopathy appeared to be best predictors of maternal death or need of liver transplantation in one retrospective study.<sup>90</sup>

**Prognosis**

Maternal mortality has improved to <10% in recent years from as high as 80%–90% in the 1980s.<sup>73 78</sup> This improvement is likely secondary to advances in obstetric care and earlier diagnosis. However, life-threatening complications remain including ALF, DIC, postpartum haemorrhage, acute renal failure and gastrointestinal bleeding.<sup>91 92</sup> Cases of hepatic rupture and hepatic infarction in AFLP have also been documented in the literature.<sup>93</sup>

Fetal mortality rates are estimated to be up to 20%.<sup>78</sup> All children of mothers with AFLP should be longitudinally monitored for symptoms of LCHAD deficiency.<sup>26</sup> AASLD and ACG recommend that all children of mothers with AFLP should be screened at birth for LCHAD deficiency.<sup>9 26</sup> The long-term outcomes in LCHAD deficiency are variable as most symptoms resolve with sufficient energy supply while some studies have reported the

development of retinopathy, cardiomyopathy, metabolic crises, hypotonia and muscle pains.<sup>26 94 95</sup>

LFTs typically begin to fall within 1–2 days after delivery.<sup>96</sup> Cholesterol and bilirubin levels lag by 3–4 days.<sup>97</sup> Transaminases continue to decline to <100 IU/L, where they may plateau for up to 4 weeks.<sup>96</sup> Complete normalisation of LFTs is expected in the majority of women, with no signs of chronic liver disease or major adverse events at 54 months postdelivery.<sup>98</sup> In those who required liver transplantation, survival is comparable to liver transplantation for other causes of ALF.<sup>99</sup> Recurrence of AFLP occurs in a minority of women in future pregnancies and may take a milder course.<sup>100</sup>

**CONCLUSION**

Pregnancy-related liver diseases are challenging for both the physician and the obstetrician. This review has focused predominantly on the diagnostic challenges facing the physician and the management options available. Early diagnosis and initiation of appropriate management with a multidisciplinary approach are important for preventing maternal and fetal morbidity and mortality.

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