

Review

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Severe hepatic dysfunction in pregnancy

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Summary

Acute liver disease in pregnancy may have fatal consequences. Pre-eclampsia, HELLP syndrome and acute fatty liver of pregnancy form a spectrum of disease that range from mild symptoms to severe life-threatening multi-organ dysfunction. Early recognition of signs and prognostic indicators

may enable prompt referral to specialist centres providing the multidisciplinary support required to reduce maternal and perinatal morbidity and mortality. We review the common causes of acute hepatic failure associated with pregnancy, and current management practices.

Introduction

Pregnancy induces physiological, hormonal and physical changes. These changes may be responsible for the incidence of acute hepatic failure (AHF) in pregnancy both pre- and post-partum. Acute fatty liver of pregnancy (AFLP), pre-eclampsia and HELLP (haemolysis, elevated liver enzymes, and low blood platelet count) syndrome have been demonstrated as being the main causes of severe hepatic failure in pregnancy. They are thought to represent a spectrum of the same pathological process. They are described as being specific to the trimester in which they appear, but this is not always the case. We will be concerned with the pathological processes taking place that specifically affect the liver during pregnancy, increasing morbidity and mortality in both mother and fetus.

Pre-eclampsia, HELLP syndrome and AFLP are significant causes of maternal and perinatal morbidity and mortality. Several retrospective studies indicate an incidence of 1 in 13 000 pregnancies for AFLP compared to 1–6 per 1000 deliveries for the HELLP syndrome. Pre-eclampsia occurs in 5% of all pregnancies usually occurring in the second or third

trimester. These processes may be involved with rarer complications, including veno-occlusive disease, hepatic rupture, haematoma, and haemorrhage, and are associated with significant mortality. In a recent case-control study, risk factors were identified as: age over 34 years, non-White ethnic group, past or current hypertension, previous postpartum haemorrhage, delivery by emergency caesarean section, antenatal admission to hospital, multiple pregnancies, social exclusion, and taking iron or anti-depressants at antenatal booking, which were all independently associated with morbidity after adjustment.¹ Prior to 1980, the mortality associated with AFLP was in excess of 80%, and > 25% for the HELLP syndrome. Mortality has since been reduced, which is thought to be due to earlier recognition, prompt effective treatment, and referral to specialist centres when required. Hyperemesis gravidarum and cholestasis of pregnancy will not be reviewed, as they are usually benign conditions that do not cause severe hepatic impairment.

The thrombophilias are a distinct group of abnormalities that induce a pro-coagulant state.

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These may present with recurrent spontaneous miscarriages, venous and arterial thrombosis during the course of pregnancy, affecting hepatic vessels, causing hepatic failure and threatening the pregnancy.² Amongst the pro-coagulant disorders are, hereditary conditions such as protein S, protein C, and anti-thrombin III deficiency; mutations and polymorphisms for factor V Leiden, methylenetetrahydrofolate reductase (MTHFR), angiotensin-converting enzyme and prothrombin genes; hyperhomocysteinaemia; and combinations of these pathologies.^{3,4} Other pro-coagulant disorders commonly seen are those associated with systemic lupus erythematosus (SLE). SLE is associated with anticardiolipin antibodies, lupus anticoagulant, and anti- β 2-glycoprotein antibodies (anti- β 2-GPI), which are all associated with the antiphospholipid syndrome, and hepatic abnormalities that arise from hepatic infarction and venous embolisms.⁵

Other causes of hepatic abnormality in pregnancy include the viral hepatitis. These are rare in the UK and more commonly seen in the Far East, although there has been increasing awareness the risks of contracting of hepatitis C (HCV) in pregnancy and the rates of vertical carriage to the child upon delivery. One study examined hepatitis markers in 127 pregnant females: 73/127 (57.5%) had hepatitis E (HEV) infection, and 58% of these HEV-infected pregnant females developed acute hepatic failure (AHF). Hepatitis B infection (HBV) was observed in 19%, and 20% remained non-reactive for seromarkers of HAV-HEV. Mortality during the pregnancy was highest (56%) among HEV-infected AHF cases during third trimester of pregnancy.⁶ This study is not typical of the UK.

Normal liver in pregnancy

Physiological changes that take place in pregnancy have effects on all organs in the body. The increase in plasma volume has been well-documented as increasing by about 40%, and this is associated with an increase in the cardiac output and heart rate which peaks at 32 weeks. The blood flow in the liver itself remains the same or in some studies decreases (35% of the cardiac output in non-pregnant females and 28% of cardiac output in pregnant females).

Abnormal or 'normal for pregnancy' laboratory tests have been recognized. In 1997, a prospective analysis of AST, ALT, bilirubin and GGT in 430 pregnant women found that these tests were about 20% lower in pregnant women compared to laboratory reference ranges. Lunzer and others have found increased alkaline phosphatase (ALP), triglycerides, cholesterol, caeruloplasmin,

transferrin, and α_1 - and α_2 -globulins, and reduced serum albumin, urea and uric acid concentrations in the third trimester.^{7,8}

Significant changes also occur in the haematological adaptation to pregnancy. The increased plasma volume may indicate a spurious anaemia. Anaemia seen in pregnancy is usually associated with a raised mean corpuscular volume, and is macrocytic with a normoblastic bone marrow. The platelet count and mean platelet volume remain unchanged during the gestational period.^{9,10} In normal pregnancy, the coagulation cascade is in a state of activation, based on the increased concentrations of clotting factors and raised high-molecular-mass fibrinogen complexes. The measured prothrombin time and partial thromboplastin times remain unchanged. Levels of anti-thrombin III and protein C are essentially unchanged in normal pregnancy, in contrast with the level of protein S, which serves as a cofactor to activated protein C. This decreases to levels similar to those of congenital protein S deficiency.^{4,11}

Pre-eclampsia/eclampsia

Pre-eclampsia is characterized by the presence of hypertension, proteinuria and non-dependent oedema. It affects about 5–7% of all women during pregnancy and a subset of these patients (as high as 65% in one series¹²) may also have HELLP syndrome. Pre-eclampsia usually occurs in the second and third trimesters, but is also seen, less frequently, before 20 weeks gestation. Complications include maternal hypertensive crises, renal impairment, hepatic rupture, infarction and neurological complications including seizures, cerebro-vascular accidents and increased perinatal morbidity and mortality.^{8,13}

Aetiology

The available evidence suggests that there are several distinct origins of pre-eclampsia, each with its own pathological characteristics and natural history, but placental ischaemia offers a unifying hypothesis.

Uteroplacental ischaemia

Changes in the uteroplacental circulation transform the vascular supply to a low-pressure high-flow system. Disturbed penetration of the trophoblast into the spiral arteries leads to hypoperfusion and local hypoxia, activating the endothelium with abnormal expression of integrins, cadherins and other immunoglobulin superfamily members,

which are involved in the pathophysiology of pre-eclampsia.¹⁴

Endothelial dysfunction

Placental hypoperfusion leads to activation of the endothelium, with alteration of vasomotor tone, initiation of the coagulation cascade, increased adhesiveness to platelets and greater thrombogenicity.^{15,16} Nitric oxide has a critical role in vasomotor homeostasis and upregulation of the nitric oxide synthase pathways has been demonstrated in normal pregnancy.^{17,18}

Cytotoxic factors

Uterine tissue from pre-eclamptic patients has higher levels of thromboxanes, isoprostanes and lipid peroxides and reduced prostacyclin (PGI₂).¹⁹ Maladaptation has been described in pre-eclamptic women, with an imbalance of the PGI₂:thromboxane ratio facilitating increased vascular sensitivity, increased systemic resistance, reduced plasma volume and reduced cardiac output.²⁰

Genetic

Studies have demonstrated a familial association in the occurrence of pre-eclampsia. Several studies have demonstrated increased risk of pre-eclampsia amongst sisters, daughters and grandparents. More recently human leukocyte antigen (HLA-DR) analysis of compatibility between pre-eclamptic women and their partners showed a statistically highly significant increase of the female-to-male compatibility ($p=0.0003$) and a lower but significant male-to-female compatibility in comparison with controls ($p=0.014$). This suggests that HLA-DR homozygosity and reduced antigenic disparity are associated with a major risk of pre-eclampsia.²¹

Histopathology

The liver in pre-eclampsia shows peri-portal fibrin deposition, haemorrhage and hepatocellular necrosis. This may be due to focal segmental hepatic vasospasm. AFLP and pre-eclampsia have similar histological patterns, and both develop microvesicular steatosis.¹²

Clinical course

Most patients present following routine screening where they have been found to be either hypertensive and or passing protein in the urine. Magann *et al.* (Table 1) demonstrated that nausea, vomiting and epigastric pain in association with admission laboratory values in excess of the cut-offs for lactate dehydrogenase, aspartate aminotransferase, and

Table 1 Risk factors for severe pre-eclampsia and HELLP syndrome³⁴

Clinical	Laboratory tests
Epigastric pain	Platelets <50 000/mm ³
Nausea	Creatine phosphokinase >200 IU/l
Vomiting	Lactate dehydrogenase >1400 IU/l
	Aspartate transaminase >150 IU/l
	Alanine transaminase >100 IU/l
	Uric acid >7.8 mg/dl
	Serum creatinine >100 mg/dl
	4+ Dipstick urine

uric acid concentrations, predict high morbidity in patients with severe pre-eclampsia.¹³ These factors are independent of, and additive with, the rising maternal risk associated with decreasing platelet counts.²² Uric acid remains one of the best markers for assessing disease severity and progression, and this will increase as gestation proceeds.

The use of aspirin in prevention of pre-eclampsia is controversial; however, a recent meta-analysis concluded that low-dose aspirin therapy reduced the incidences of pre-eclampsia among women with poor obstetric histories and among high-risk nulliparous women, but was ineffective among women with underlying medical illness. It was marginally effective among low-risk nulliparous women, and benefit for women with multiple gestations remained unclear. The differential effects of low-dose aspirin therapy in the various risk groups are probably a result of varying roles in the groups of abnormal arachadonic acid metabolism in mediating pre-eclampsia.^{23,24}

More recently, a meta-analysis examined the use of antiplatelet drugs in pre-eclampsia in 39 trials (30 563 women). Use of antiplatelet drugs was associated with a 15% reduction in the risk of pre-eclampsia, and an 8% reduction in the risk of preterm birth. There were no significant differences in other measures of outcome. The authors concluded that antiplatelet drugs, largely low-dose aspirin, have low-to-moderate benefits when used for prevention of pre-eclampsia.²⁵

Hypertension

Control of hypertension reduces the morbidity and mortality associated with this condition for both mother and fetus. Commonly used anti-hypertensives include methyldopa and beta-blockers, of which labetalol is commonly used (combined α - and β -blocker, also reduces vasoconstriction).²⁶

Calcium channel blockers (nifedipine) were recently recommended as possible first-line

agents. However, careful clinical observation is required when administering magnesium sulphate, which may result in profound hypotension. Hydralazine is used for acute management of hypertensive emergencies, reducing peripheral resistance, and improving cardiac output. Resistant hypertension, severe proteinuria and hyperemesis will require admission to hospital.^{7,27,28}

Seizures

These may be related to focal cerebral vasospasm and cerebral hypoperfusion. The incidence of seizures in pre-eclampsia is 4.9/10 000 maternities, in the UK. Pereira *et al.* reported that 25% of the pre-eclamptic patients admitted in the King's series had seizures; all were treated with anticonvulsant therapy, including diazepam, phenytoin and magnesium sulphate.²⁹ In the Collaborative Eclampsia trial, magnesium sulphate was superior to phenytoin and/or diazepam at preventing seizures.³⁰ Patients treated with magnesium sulphate also demonstrated a lower incidence of mechanical ventilation, pneumonia and fewer neonatal intensive care admissions. It is thought to act as a membrane stabilizer, reducing intracerebral ischaemia. Care should be taken to monitor levels of magnesium sulphate; high plasma concentrations (e.g. in renal failure) may cause respiratory arrest with paralysis of respiratory muscles. Other side-effects include areflexia, weakness, nausea, flushes, somnolence, diplopia and slurred speech.

Renal dysfunction

This occurs in two stages. The first involves impairment of tubular function, and is reflected by a reduction in uric acid clearance and development of hyperuricaemia. The second involves the impairment of glomerular filtration, with resulting intermediate selectivity proteinuria (albumin, transferrin, γ -globulin). Gross proteinuria occurs late in the pregnancy and (at >0.5 g/day) may lead to mandatory delivery. The systemic consequences are hypoalbuminaemia and reduced plasma oncotic pressure. The loss of the selectivity of the glomerular tubules resolves after delivery. Acute renal failure may result from placental abruption reducing renal blood flow.^{13,31}

Haematological factors

Thrombocytopenia and an increase in the mean platelet volume have been described.⁹ Several studies have also demonstrated increased platelet activation in pre-eclampsia, and this has been correlated with proteinuria and a raised serum

creatinine, suggesting a link between platelet activation and renal microvascular damage.

Increased levels of factor-VIII-related antigen and fibrinopeptides may encourage platelet aggregation and clot formation, as has been demonstrated in pre-eclamptic women. Anti-thrombin III, protein C and protein S are all reduced in pre-eclampsia, exacerbating the hypercoagulable state.^{11,32,33} The prothrombin time and the partial thromboplastin time may remain normal.

Liver function tests

These are abnormal in 20–30% of patients with pre-eclampsia,¹² and are thought to reflect liver dysfunction resulting from vasoconstriction of the hepatic vascular bed, as demonstrated by Doppler studies in pre-eclamptic women. Alkaline phosphatase, which is often elevated in pregnancy, may be further increased, likewise the transaminases. In severe cases of pre-eclampsia, with or without HELLP syndrome, abnormal transaminases may be present.³⁴

Indications for delivery

After 36 weeks, fetal maturity can be assumed and continuation of the pregnancy has no benefit. Mode of delivery will be dictated by clinical circumstances, but vaginal delivery is the preferred route.²⁹

Severe pre-eclampsia may require early delivery due to the increased risk to both mother and fetus (see Figure 1a and b). Premature delivery is associated with increased fetal mortality due to inadequate lung maturation. Sibai *et al.*³⁵ investigated the possibility of 'buying time' or 'expectant' management of patients at 28–32 weeks with severe pre-eclampsia. Ninety-five women were randomized to 'expectant management' or 'prepared for delivery'. It was possible to prolong the pregnancy for an average of 2.6 days to 15.4 days in the expectant group by optimization of hypertension, coagulopathy and the use of corticosteroids to enhance fetal lung maturity. This significantly improved neonatal mortality without significantly increasing maternal mortality. Similar improvement has been seen in the pre-term delivery of patients with HELLP syndrome.^{36–38}

Intrapartum care

Meticulous fluid resuscitation may require the need for central venous monitoring. Pre-eclamptic patients have increased sensitivity to volume shifts, due to low plasma oncotic pressure, raised hydrostatic pressure due to hypertension, and increased



Figure 1. CT scans pre- (a) and post- (b) contrast of a 25-year-old woman presenting with pre-eclampsia. Following an elective caesarian section, she became encephalopathic and developed acute liver failure. Contrast-enhanced CT shows extensive necrosis throughout the right lobe with patchy necrosis also in the left lobe.

capillary permeability reflecting endothelial dysfunction, increasing susceptibility to pulmonary oedema. Central venous pressure >10 cm of water indicates a risk of pulmonary oedema. More complex patients will require admission to intensive care for invasive intravascular haemodynamic monitoring.

Postpartum care

In severe pre-eclampsia, intensive monitoring, correction of coagulopathy and thrombocytopenia should continue for 24–72 h after delivery, as patients are still susceptible to seizures, haemorrhage and other complications including renal

failure, hepatic infarction, rupture and multi-organ failure.

HELLP syndrome

The haemolysis (H), elevated liver enzymes (EL) and low platelets (LP) syndrome is a severe form of pre-eclampsia that threatens the patient and her fetus. Early reports described pre-eclampsia associated with microthrombi, thrombocytopenia, coagulopathy and a poor prognosis.³⁹ It may appear from mid-second trimester until several days postpartum. One study reports that two-thirds of patients will be diagnosed antepartum, of which 10% will be identified before 27 weeks, 20% in pregnancies

beyond 37 weeks and the majority between (70%) 27 and 37 weeks. One third will develop HELLP syndrome postpartum.⁴⁰ There is an increased incidence of HELLP in White women and multiparas, which differs from pre-eclampsia. There is, however, an overlap, with a 4–12% incidence of HELLP complicating pre-eclamptic disease. Pereira *et al.*²⁹ reported that all their patients with HELLP also had pre-eclampsia.

Aetiology

The pathophysiology of normal pregnancy and pre-eclampsia are discussed above. HELLP syndrome and pre-eclampsia may well be part of the same spectrum of disease, with a common aetiology. Key abnormalities include vasoconstriction, increased vascular tone, platelet aggregation and an alteration of the thromboxane:prostacyclin ratio. These changes can be partly explained by the activation of complement and the coagulation cascade causing multi-organ endothelial and microvascular injury, and resulting in microangiopathic haemolytic anaemia, elevated liver enzymes (periportal and hepatic necrosis) and thrombocytopenia.⁴¹

Clinical course

The presentation can often be non-specific with subtle signs: most frequently nausea, epigastric pain, or right upper quadrant pain, ranging in frequency from 36–86%. A subset of patients with severe pre-eclampsia present with symptoms of headache and visual changes. Hypertension may be present (16%) or absent (15%), and proteinuria may be absent (6%) or just 1+ on dipstick (9%). The majority of patients will present with hypertension and more severe signs and symptoms.⁴² Mortality amongst patients with HELLP has been investigated: among 54 maternal deaths, 60% had class 1 disease, 35.6% had class 2 disease, and 4.4% had class 3 disease. Events associated with maternal deaths included cerebral haemorrhage (45%), cardiopulmonary arrest (40%), disseminated intravascular coagulopathy (39%), adult respiratory distress syndrome (28%), renal failure (28%), sepsis (23%), hepatic haemorrhage (20%), and hypoxic ischaemic encephalopathy (16%). Delay in diagnosis of HELLP syndrome was implicated in 22 of 43 deaths (51.1%).⁴³

Several studies have tried to define the HELLP syndrome based on laboratory parameters (Table 2).^{42,44} Most classifications have attempted to combine the elevation in hepatic enzymes and the low platelet count. These parameters have also been analysed to identify increased risk factors associated with severe disease.

Care must be taken to exclude other causes of haemolysis that may appear clinically similar, or that present laboratory data similar to HELLP. The differential diagnosis should include idiopathic thrombocytopenic purpura, systemic lupus erythematosus, haemolytic uraemic syndrome, and AFLP (Table 3). HELLP syndrome carries a significant risk to mother and fetus: about 1–3.5% for the mother, with increased incidence of multi-organ failure, DIC and acute lung syndrome.^{45,46} The haematological abnormalities increase the risk of spontaneous and post-partum haemorrhage, and the need for blood products is 10–50% for correction of thrombocytopenia and coagulopathy. Sibai *et al.*⁴² reported eclampsia in 8% of patients, and in other series this had been as high as 30%. Other complications include pulmonary oedema and acute renal failure, which are more common in patients who develop HELLP postpartum.

HELLP syndrome will affect the microvasculature of the kidney and may lead to acute

Table 2 Two systems used to classify HELLP syndrome

Mississippi 3 Class System ⁴⁰	Tennessee System ⁷⁵
<i>Class 1</i> Platelets < 50 000/mm ³	<i>Complete syndrome</i> AST and /or ALT > 40 IU/l
<i>Class 2</i> Platelets 50 000–100 000/mm ³	Platelets < 100 000 mm ³
<i>Class 3</i> Platelets 100 000–150 000/mm ³ Haemolysis + elevated liver enzymes LDH > 600 IU/l	LDH > 600 IU/l AST > 70 IU/l <i>Incomplete syndrome</i> Any one or two of the above

Table 3 The differential diagnoses when considering HELLP syndrome

Differential diagnosis of HELLP syndrome
<i>Thrombotic disorders</i> Thrombotic thrombocytopenic purpura Haemolytic uraemic syndrome Sepsis and disseminated intravascular coagulopathy (DIC) Drug-induced haemolytic anaemias
<i>Consumptive disorders</i> Acute fatty liver of pregnancy Sepsis and DIC Haemorrhage
<i>Others</i> Connective tissue disease Systemic lupus erythematous (SLE) Antiphospholipid syndrome Procoagulant disorders

tubular necrosis. This may be reversible; however, more permanent damage has been recorded with severe cortical necrosis. Renal lesions are similar to that described in pre-eclampsia with glomerular enlargement, mesangial thickening and capillary narrowing. Patients may require temporary haemofiltration, or in the long term, haemodialysis.³¹

HELLP and AFLP both affect the liver, HELLP being more common, (1:5000 deliveries vs. AFLP 1:13–16 000 deliveries).²⁹ AFLP usually occurs later in gestation and causes a reduction in the synthetic function of the liver, resulting in hypoglycaemia, elevated ammonia, and an increased coagulopathy. Disseminated intravascular coagulopathy is common to both AFLP and HELLP, but abnormal liver transaminases are commoner in HELLP. Histologically, periportal necrosis and vascular microthrombi are present, as the disease progresses there are more extensive areas of necrosis that may lead to haematomas and eventually to hepatic rupture. This commonly occurs in the anterior aspect of the right lobe of the liver and have been recorded as early as 16 weeks gestation to 3 days postpartum.

Hepatic rupture has been reported as a spontaneous event, but is more frequent in the presence of HELLP or severe eclampsia/pre-eclampsia (Figure 2). Sibai *et al.*⁴⁷ recorded an incidence of 1% and this occurred in the setting of abruptio placentae, leading to massive haemorrhage and shock in four patients. This requires emergency surgical treatment, and Pereira *et al.*²⁹ suggested that this may be an indication for liver transplantation. Hepatic infarction, subcapsular haematomas and intraparenchymal haemorrhage have also been recorded. The severity of complications has led authors to recommend early referral to specialist liver centres where adequate imaging, surgical and transplantation facilities are available. The fetus is also at risk, with a perinatal mortality rate of 56–367 per 1000 births. The onset of HELLP is before term, and so the greatest risk is prematurity. Mortality is due to early-onset HELLP on the verge of viability or due to placental abruption.

Several groups have attempted to study prognostic indicators to assess the severity of disease, and to predict at an early stage those with a poor outcome. Martin *et al.*^{40,48} examined the platelet nadir: on this basis, patients were classified as class 1 (platelets <50 000/mm³), class 2 (platelets 50 000–100 000/mm³) and class 3 (platelets 100 000–150 000/mm³). Class 1 and class 2 had a higher incidence of postpartum haemorrhage and a longer, more complicated recovery. Prophylactic platelet infusions did not reduce complications. Patients who developed superadded

DIC were at greater risk of complications. More recently, Haddad *et al.*⁴⁴ found that among women with HELLP syndrome, African–American race was a risk factor for eclampsia. Both acute renal failure and abruptio placentae were associated with disseminated intravascular coagulopathy. Laboratory parameters of HELLP syndrome were not independent risk factors for adverse maternal outcome.

Pereira *et al.*²⁹ described 17 patients out of 32 with AFLP, two of whom had HELLP, all with evidence of DIC. Barton *et al.*⁴⁹ examined the correlation between abnormal liver function tests and severity of disease. There appeared to be no strong correlation between liver function tests, histopathology and radiological investigations, the only finding being that patients with thrombocytopenia were at a higher risk of subcapsular haemorrhage and hepatic rupture. There are case reports illustrating massive elevation of liver function tests in association with hepatic rupture, infarction and subcapsular haematomas.^{50,51}

The natural history of HELLP is similar to that of severe pre-eclampsia: the disease becoming progressively more severe until delivery. Experience from patients treated expectantly has illustrated that some in this group may be stabilized and delivered days later, reducing fetal morbidity. Pereira *et al.*²⁹ described seven patients in their series of 46 women admitted to the Kings College Hospital. All seven also had pre-eclampsia, with demonstrated encephalopathy, jaundice, renal failure, median platelet count of 39 000/mm³ (range 19–89 000/mm³) and a median platelet count nadir of 31 000/mm³ (range 6–66 000/mm³) 2 days after admission. The correlation of deteriorating platelet counts and the liver function tests suggests rapid disease progression. Following delivery, most patients got worse for a short period, followed by clinical improvement with platelet counts returning to normal. Martin *et al.*⁴⁰ demonstrated that the postpartum period sees a nadir in platelet counts 24–48 h after delivery.

Maternal risk

Management of HELLP syndrome will incorporate the investigative and supportive care that has already been described for pre-eclampsia. Although these conditions may be part of the same spectrum of disease, HELLP syndrome is more common among older multiparous women, whereas pre-eclampsia is commoner in young nulliparous women. Therefore it is important to be aware of and recognize maternal risk factors that may increase maternal and perinatal morbidity and mortality. Approximately 80% of patients

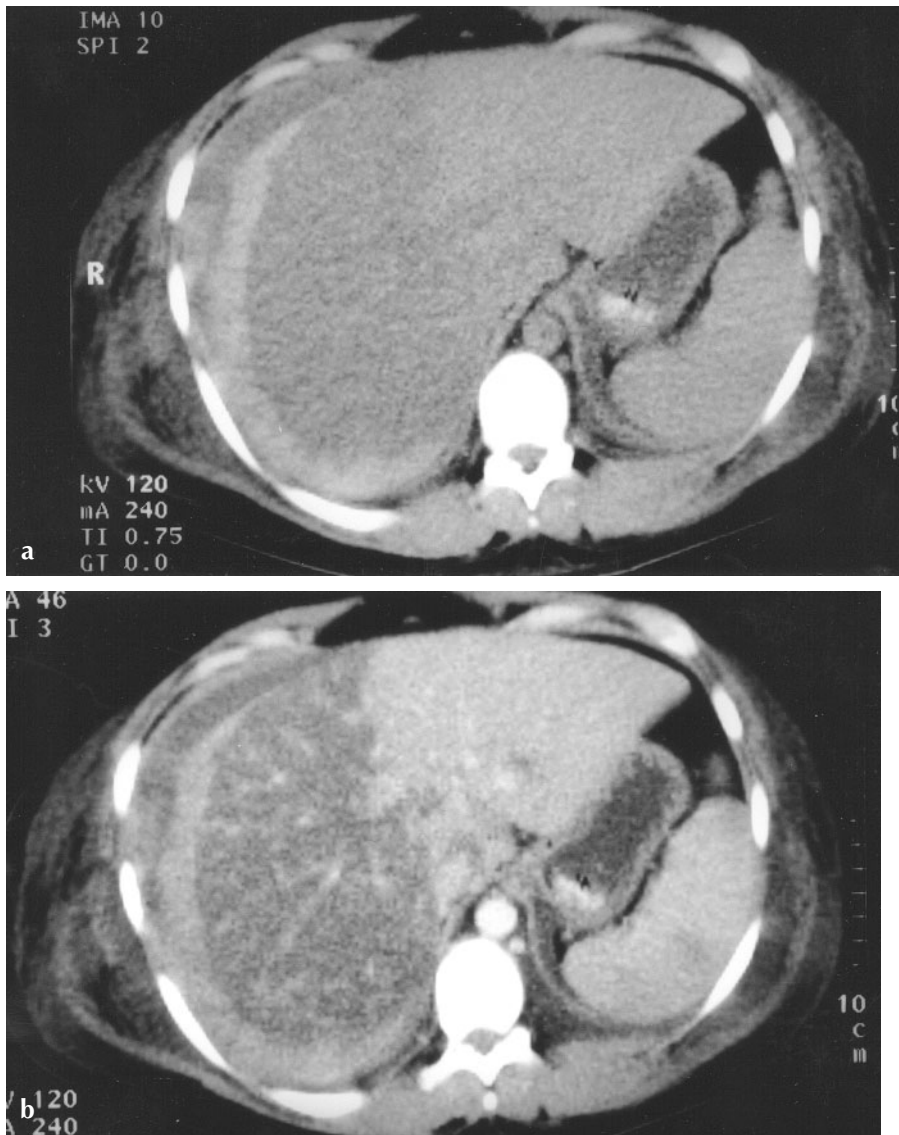


Figure 2. Plain abdominal CT scan (a) and contrast-enhanced CT scan (b) of the liver. These are from a patient presenting in her third trimester with severe pre-eclampsia. Following an emergency caesarian section, she developed severe right upper quadrant pain and deteriorated rapidly. Contrast-enhanced CT (b) confirmed the presence of a large area of arterial infarction, a secondary right subcapsular haematoma and segmental Budd-Chiari syndrome. She had a successful liver transplant 2 days later.

with HELLP and or pre-eclampsia will have hypertension, which requires pharmacological intervention. Prevention of seizures with magnesium sulphate as an infusion should be commenced. This may also have an effect in reducing platelet clumping by relaxing central and peripheral vasculature. If magnesium sulphate is contraindicated, then phenytoin is the drug of choice.

Laboratory investigations

Once the physician is aware of the diagnosis, initial laboratory investigations can be appropriately ordered and interpreted. Modest changes

in the hepatic transaminases, platelet counts and also the lactate dehydrogenase may be exhibited in the early phase, and these will mandate further investigations to exclude other differential diagnoses. Disseminated intravascular coagulopathy must be excluded, with decreased fibrinogen and fibrin degradation products not usually appearing until the platelet count is below between 50 000–100 000/mm³ (Table 4).

Fetal risk

Having established and assessed maternal risk, fetal risk must also be examined. Severity of the maternal

Table 4 Some of the differences seen in early and late HELLP syndrome and acute fatty liver of pregnancy

HELLP syndrome	Acute fatty liver of pregnancy
<i>Early</i>	
Platelets 50 000–150 000/mm ³	Platelets > 100 000/mm ³
LDH 600–1400 IU/l	LDH normal
Bilirubin normal	Bilirubin high +
Prothrombin time normal	Prothrombin time prolonged +++ Uric acid high +++
<i>Late</i>	
Platelets < 50 000/mm ³	Platelets < 100 000/mm ³
LDH > 1400 IU/l	LDH < 600 IU/l
Prothrombin time increased	Prothrombin time prolonged +++
Bilirubin increased	

and fetal condition will influence where and when delivery should take place. Once assessed, if gestational age is >34 weeks and the mother displays the criteria for Class 1 HELLP syndrome, delivery should take place within 24 h.

Corticosteroids

These have been advocated to accelerate fetal maturity in deliveries of all pregnancies between 24–34 weeks except in specified cases. This is the same protocol as in pre-eclampsia. This may provide a 24–48 h period of transient improvement in the maternal condition and would then also allow for maturation of the fetal lungs prior to delivery.^{37,52} A retrospective study found a significant reduction in the number of neonatal episodes of intubation and mechanical ventilation. Maternal haematological status also improved, with improvement or stabilization of platelet counts, lactate dehydrogenase and liver function tests in those treated with steroids. The improvement of platelet counts were maintained if steroids were also administered after delivery to the mother; this avoided a rebound thrombocytopenia with associated complications.^{53,54}

Fluid management

Multi-organ endothelial injury, increased vaso-motor tone and relative hypoalbuminaemia make the mother less tolerant to volume shifts and results in a predisposition to pulmonary oedema. Careful fluid management is needed to prevent a reduced intravascular volume exacerbating pre-renal renal

failure; in contrast, overzealous resuscitation may lead to pulmonary oedema, ascites and peripheral oedema. Good management may be achieved by central venous pressure monitoring and, if required, more invasive haemodynamic monitoring in the setting of an intensive care unit. Daily evaluation of electrolyte status will influence fluid choices.⁵⁵

Thrombocytopenia

Thrombocytopenia will increase the risk of spontaneous bleeding, and may also complicate both vaginal and caesarean deliveries. Platelet transfusion will be required for mothers with platelet counts <50 000/mm³ prior to delivery or any surgical procedure that may take place, and a platelet count <30 000/mm³ will also require transfusion to reduce the risks of spontaneous haemorrhage. This must be continued after the delivery has taken place, as retroperitoneal, abdominal, subcapsular hepatic haematomas and hepatic rupture may occur in the postpartum period.

Labour

The natural history of HELLP syndrome is of rapid deterioration following hospital admission, careful assessment of maternal and fetal risk is needed. Once assessed, corticosteroids may be administered, and delivery will follow quickly. Provision for neonatal care is needed, especially if gestation is <34 weeks. Infants may require ventilation and resuscitation, because of their immature lung development. Intraventricular haemorrhage and necrotising enterocolitis have also been reported.⁵⁵

Vaginal delivery is the preferred route; however, as described in the pre-eclampsia section, this may not always be possible, and caesarean section may be needed. The caesarean section rate is high with HELLP syndrome: one study reported a rate of 68% at a gestational age of 30–34 weeks.⁵⁶ Complications of caesarean delivery include haemorrhage, haematomas, wound infection and dehiscence. Rarer complications are seen in patients who present with ascites.⁵⁷ Patients with large-volume ascites will be at increased risk of congestive heart failure, infection, acute lung injury and adult respiratory distress syndrome in the postpartum period.⁴⁶ Admission to the intensive care unit, invasive haemodynamic monitoring and judicious fluid replacement will be required in this small subset of patients.

Hepatic haemorrhage and rupture may occur in the peri- and postpartum period. This may present as right upper quadrant pain and hypotension.

As the liver ruptures, epigastric and right upper quadrant pain get worse, with radiation to the back, followed by signs of shock. The physician must be aware that this condition has a high mortality rate, and that the patient will require intensive care and referral to a specialist liver centre. The fetus must be delivered once the mother has been resuscitated, but there is a very significant perinatal mortality. Computer tomography with contrast studies are effective in assessing damage to the liver, and angiography and embolization may be used to control hepatic bleeding if present. Haematoma formation may also impair venous outflow. Based on the mother's clinical condition, supported by laboratory and radiological investigations, it may be appropriate to refer the mother for liver transplantation.⁵⁸

Postpartum care

Patients with severe HELLP will require ongoing supportive care in a high-dependency/intensive-care setting. Care must be applied to the haemodynamic status of the patient as well as regular monitoring and supplementation of electrolytes and blood products. Treatment of hypertension, seizure prophylaxis and the administration of corticosteroids should continue and until laboratory investigations show a trend towards normal. The physician must always be aware of the possibility of deterioration postpartum.

The recurrence of HELLP in subsequent pregnancies has been investigated, and this information will be important in counselling parents with regards to family planning. Two studies showed an increased risk of hypertension and pre-eclampsia in subsequent pregnancies, with a rate approaching 20% in one and 42–43% in the other. The risk of recurrent HELLP is thought to be 3–27%. However, if the previous pregnancy ended before 32 weeks, the risk of recurrence of pre-eclampsia and another premature gestation was 61%.^{42,45,59}

Acute fatty liver of pregnancy (AFLP)

This is an uncommon, potentially fatal disorder that occurs in the third trimester of pregnancy. The first clinical descriptions came from Stander and Cadden, who described 'acute yellow atrophy of the liver', a rare and fatal complication of pregnancy, in 1934.⁶⁰ The histological appearance of a microvesicular fatty infiltrate, the clinicopathological process and a mortality of 70% was soon described.^{61,62} In 1984, ten patients with AFLP

were reported by Pockros *et al.*,⁶³ who illustrated the clinical course, and found a mortality of 10% where patients were given careful clinical support.

Most studies have estimated the incidence of AFLP as 1:10 000–15 000 pregnancies, with mortality 10–20%. Castro and colleagues⁶⁴ performed a retrospective analysis of pregnancies at their institution from 1982 to 1997: only 28 cases were reported amongst 199 767 births, giving an incidence of 1:6659 births. It is commoner in twin pregnancies and male births and also in nulliparous mothers.³⁴

Aetiology

Recent molecular advances suggest that AFLP may result from mitochondrial dysfunction. The mitochondria fatty acid β -oxidation spiral consists of a series of multiple transport steps and four enzymic reactions. Fatty acids are transported to the mitochondrial inner membrane by special carrier transporters. Beyond the inner membrane, they are then broken down by a series of four enzymes. The third enzyme is long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHA), deficiency of which results in the increased excretion and accumulation of medium- and long-chain fatty acids. Children born with this defect fail to thrive and are prone to hepatic failure (microvesicular steatosis), hypoglycaemia and death.⁶⁵

This defect has been localized to a G1528C mutation in the exon α -subunit leading to inactivation of the catalytic domain.⁶⁶ The prevalence of this mutation E474Q has been investigated in population screening studies performed in Finland. This demonstrated a carrier rate of 1:150–200. Further mutations have also been found, but E474Q accounts for 65–90% of the LCHAD patients. Evidence of clinical correlation between LCHAD and AFLP came in 1991, Schoeman *et al.*⁶⁷ reporting an association between recurrent maternal AFLP. In 1993, Wilcken *et al.*⁶⁸ and Treem *et al.*⁶⁹ reported six families of children who had failure of fatty acid oxidation, which by now had been localized to the long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD) in mitochondria. All these children had been born to mothers who suffered from AFLP or HELLP syndrome during pregnancy. Further retrospective studies have suggested an association between LCHAD and AFLP.⁷⁰

Alternatively, pregnancy may itself affect mitochondrial function. Animal studies demonstrate reduced FAO and activity of the decarboxylic cycle in late-term rats and mice. Other hypotheses favour above-normal (for pregnancy) level of oestrogens potentiating the effects of an otherwise

tolerable hormonal insult to mitochondria in the third trimester.

Clinical course

Clinical

Onset is between the 30th and 38th weeks of gestation. It is sometimes preceded by a prodromal illness, but classically presents with malaise, nausea, vomiting, malaise, abdominal pain (right upper quadrant), fever, headaches and pruritus. Often jaundice is only noticed after delivery has taken place. Patients will require supportive care, fluid resuscitation, nutrition, correction of coagulopathies and thrombocytopenia and hypertension an seizure treatments.

Biochemistry

The biochemical changes have some similarity to those in HELLP syndrome, and careful distinction should be made (Table 4). Elevated serum transaminases may also be associated with raised serum ammonia, amino acid levels and lactic acidosis, uric acid, hyperbilirubin and hypoglycaemia. The prothrombin and the partial thromboplastin times are prolonged.

Histology

Microvesicular steatosis with sparing of zone 1. Hepatocytes have a foamy appearance with centrally dense nuclei. There is little inflammation and necrosis and the liver architecture remains intact. In more severe cases, hepatocyte necrosis may be seen. Liver ultrasounds are frequently normal, since the fat is microvesicular in nature.

Among 28 patients with AFLP in a series described by Castro *et al.*⁶⁴ the commonest cause for admission was labour and hepatitis. The diagnosis of AFLP was made in ten patients 48 h after admission and in another ten 48 h after birth. Almost all patients had abnormal liver function tests, with elevated total bilirubin and prothrombin. Mean gestational age was 37.5 weeks (range 31–42) and there was no reported maternal mortality.

This study contrasts with that of Pereira *et al.*²⁹ who performed a retrospective analysis of pregnant women admitted to the Liver Failure Unit at King's College Hospital. They reported 46 women (median age 30 years, range 17–41) admitted with severe liver impairment during pregnancy of whom 32 had AFLP. Thirteen developed hepatic encephalopathy and other complications, including hypoglycaemia (55%), renal insufficiency (50%) requiring haemofiltration, coagulopathy (96%) and disseminated

intravascular coagulopathy (55%) and pre-eclampsia (50%). Four of the 32 with AFLP died due to complications, including severe haemorrhage, sepsis, multi-organ failure and hepatic rupture and subcapsular haematoma. The reported maternal mortality rate was 12.5% (see Figure 3).

Sepsis leads to significant morbidity and mortality, as demonstrated by Pereira *et al.*,²⁹ and the early use of broad-spectrum antibiotics is suggested. Surgical procedures and/or haemorrhagic complications require correction of the coagulopathy with vitamin K, fresh frozen plasma and cryoprecipitate. In both series, most haemorrhagic complications resulted from surgical trauma that led to intra-abdominal and retroperitoneal bleeding and haematomas.

The use of liver transplantation in AFLP is controversial. Case reports suggest some benefit in specific cases, but in the majority this will not be required. The deterioration of parameters such as transaminases and prothrombin time and concurrent disseminated intravascular coagulopathy may be explained by concomitant sepsis. Castro *et al.*⁶⁴ suggested that patients often deteriorated in the postpartum period and then began to improve. Pereira *et al.*²⁹ suggested that transplantation should be reserved for 'those with liver rupture complicated by hepatic necrosis, as indicated by computer tomographic findings, the presence of hepatic encephalopathy, and a severe metabolic acidosis, together with worsening coagulopathy, and/or increasing fresh frozen plasma requirements'.

It is uncommon for AFLP to recur in subsequent pregnancies; to date, four cases are reported in the literature.^{71,72} This may be an under-representation, as following the first occurrence of this syndrome, many women may refrain from having further pregnancies, undergo sterilization, or die before they can become pregnant again.

Conclusions

The three pathological processes described appear to overlap, and are regarded by many as representing a spectrum of the same disease. Clearly, all three have specific characteristics, but their close clinical correlation supports this hypothesis. Recent reports suggest that the fetal inborn error of metabolism, long-chain fatty3-hydroxylacyl-coenzyme-A dehydrogenase deficiency in mitochondria, leading to a failure of β -oxidation, may be responsible for the development of AFLP and possibly pre-eclampsia. Initial high reported mortality rates of 70%⁶² have been reduced to zero mortality in the Castro series.⁶⁴ No specific treatments have been developed for AFLP, and so this improvement

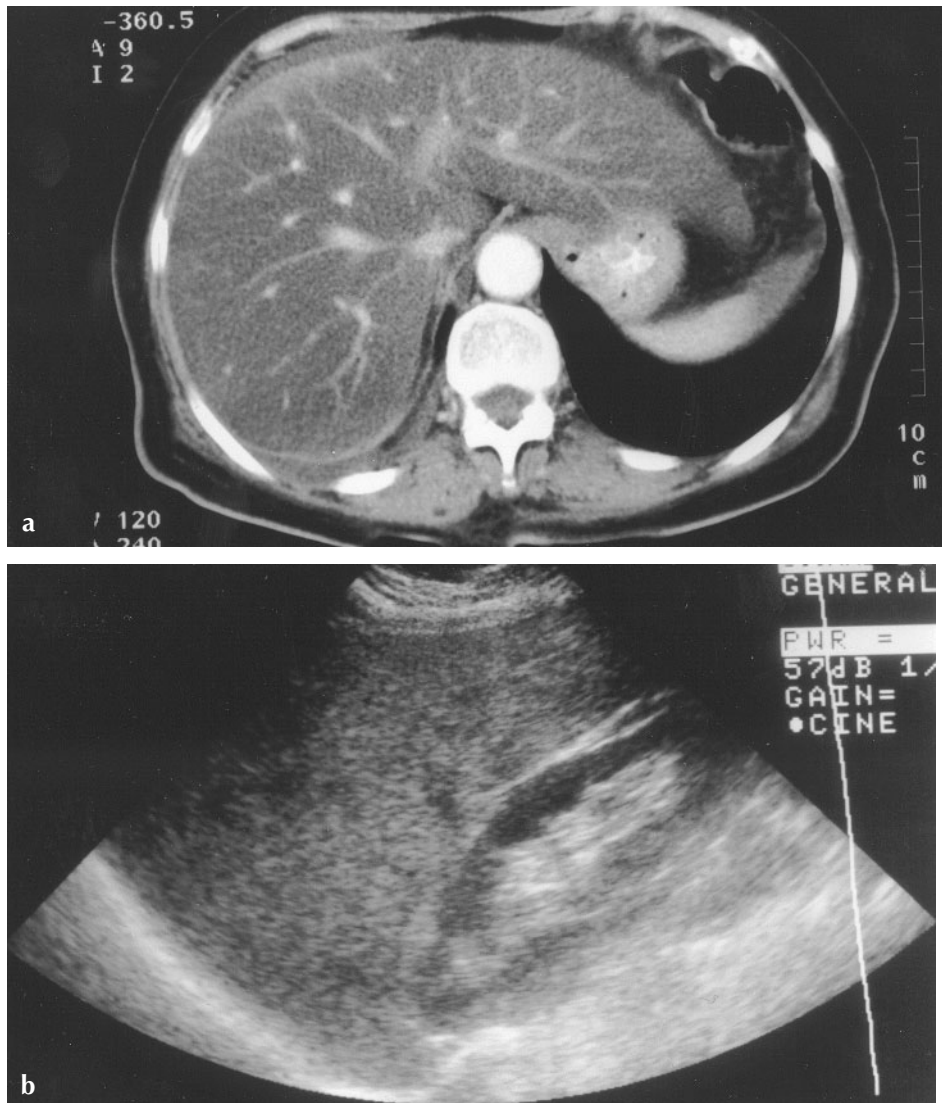


Figure 3. CT scan (a) and an ultrasound examination (b) of the liver of a pregnant woman who presented with obstructive jaundice. The CT scan shows generally low attenuation, however, the ultrasound examination shows marked parenchymal reflectivity consistent with fatty infiltration of the liver. Percutaneous liver biopsy confirmed acute fatty liver of pregnancy.

in mortality is due to improved awareness, early fetal monitoring, and fetal and maternal supportive care. Early recognition of patients who may be at high risk of severe liver impairment will allow counselling for future family planning.

The pathogenesis of pre-eclamptic liver disease remains unclear, but is related in part to sympathetic over-activity and a marked increase in peripheral vascular resistance, which in turn causes increased blood pressure. The role of nitric oxide has been thought to be central to the pathogenesis of pre-eclampsia; however, recent clinical studies of NO donors in pre-eclampsia have yielded conflicting results.^{73,74} Severe pre-eclampsia requires specific treatment of hypertension, prevention of seizures and careful obstetric management, optimizing both mother and fetus till

birth. HELLP syndrome also carries significant fetal and maternal morbidity and mortality.

Patients with severe AFLP, pre-eclampsia and HELLP should be treated in tertiary centres that are prepared for all maternal and fetal complications. All three conditions will require the obstetric management to be optimized with a view to timing and choice of route of delivery. Close supervision of these patients providing careful and judicious supportive care may avoid many of the reported complications. Early referral to a specialist unit is also recommended, as deterioration is rapid and specialist radiological, surgical, and transplantation facilities may be required.

Several investigators have reported the use of liver transplantation in grave situations of severe hepatic impairment. This must be interpreted with

caution. Several larger series of patients with AFLP have shown that often these patients will demonstrate deteriorating liver function tests for up to one week post-partum and will then make a recovery. Similarly, computer tomographic studies have demonstrated that as a part of the natural history of this disease the liver volume will also decrease, recovering some time post-partum. In the case of HELLP and or pre-eclampsia, Pereira *et al.*²⁹ have suggested that hepatic rupture in association with gross physiological derangement may be an indication for early listing for liver transplantation.

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