HELLP syndrome: mechanisms and management

Joanne Ellison, Naveed Sattar, Ian Greer

Effective management of HELLP syndrome depends on swift recognition of a condition which often masquerades as other pathology. This article reviews clinical aspects of HELLP syndrome and outlines recent advances in our comprehension of what may be the underlying pathophysiology.

Weinstein first coined the acronym 'HELLP' in 1982, to describe a syndrome of haemolysis, elevated liver enzymes and low platelets, that occurs during pregnancy. Its features had been described in the literature over a century before, but the underlying pathogenic mechanisms remained enigmatic. Goodlin (1982) described the syndrome as EPH (oedema, proteinuria, hypertension) gestosis type B, McKenna et al (1983) considered it to be misdiagnosed pre-eclampsia, and not a unique variant of the condition proposed by Weinstein, while others thought that it represented mild disseminated intravascular coagulation (DIC) that had been missed because of technical inadequacy.

More recently it has become apparent that this condition represents one extreme of a spectrum of disease, ranging from mild pre-eclampsia to the rare but life-threatening condition known as acute fatty liver of pregnancy (AFLP). Recent work by our group has shown that dysfunctional lipid metabolism plays an integral role in the pathogenesis of pre-eclampsia (Sattar et al, 1997), and we have proposed possible metabolic disturbances that may effect the observed perturbations in blood lipids that precede clinical onset of the disease.

Extrapolation of such concepts gives an explanation for the pathological abnormalities characteristic of HELLP syndrome. This article discusses the presentation, diagnosis and management of HELLP syndrome, and proposes a pathogenic mechanism for its development.

DIAGNOSTIC CRITERIA

While superficially the symptomatic triad of haemolysis, elevated liver enzymes and low platelets during pregnancy implies a diagnosis of HELLP syndrome, considerable differences exist between groups regarding the degree of laboratory abnormality constituting a diagnosis of HELLP. Hence the terminology is confusing and results are often inconsistent or even contradictory.

Sibai (1990), whose group has considerable experience in managing the HELLP syndrome, suggest the following definition, which correlates well with maternal and perinatal outcome and effectively identifies candidates warranting expeditious delivery:

- Haemolysis — characteristic blood smear with the presence of burr cells and schistocytes (*Figure 1*) and serum lactate dehydrogenase >600 U/litre. This is thought to result from the passage of erythrocytes through small vessels with damaged intima and fibrin deposition, leading to the appearance seen in *Figure 1*
- Elevated liver enzymes — serum aspartate transaminase >70 U/litre
- Low platelets — platelet count <100 000/μl.

Others have used less strict criteria (McKenna et al, 1983; Clark et al, 1986; Martin et al, 1990, 1991) and have consequently included in their studies women who by the above definition would only qualify as having partial HELLP syndrome (i.e. ELLP or HEL). As a result, the poor prognosis associated with HELLP syndrome has been challenged by some authors.

Martin et al (1990) invented the Mississippi Triple Class System, which further subdivided HELLP by the severity of thrombocytopenia. By this system, a platelet nadir <50 000/μl is class I HELLP, 50 000–100 000/μl class II, and class III is 100 000–150 000/μl. Platelet levels have been shown to be a useful indicator of disease severity and time to recovery, and also correlate well (better than liver enzymes) with the degree of hepatic abnormality detected by both imaging and histological assessment. However, this system has yet

Dr Joanne Ellison is Clinical Research Fellow and **Professor Ian A Greer** is Professor of Obstetrics and Gynaecology in the University Department of Obstetrics and Gynaecology, and **Dr Naveed Sattar** is Specialist Registrar in the Department of Pathological Biochemistry, Glasgow Royal Infirmary University NHS Trust, Glasgow G31 2ER

Correspondence to: Dr J Ellison

to prove its value in terms of management and is currently restricted to classification and audit.

Other laboratory tests (plasma glutathione S-transferase alpha 1–1 and hyaluronic acid as indices of hepatocellular damage, and haptoglobin as a marker for haemolysis) may have greater sensitivity in detecting HELLP, and facilitate earlier diagnosis (Knapen et al, 1988). However, a lack of consideration of HELLP syndrome by clinicians is currently the main impediment to swift diagnosis, and it is unlikely that use of these investigations would alter management or improve outcome. More beneficial in improving outcome would be a standard definition using routine laboratory tests, enabling meaningful comparisons of different treatments, and development of an optimal management strategy. Understanding of this disorder will remain stunted until standard diagnostic criteria are widely accepted.

PATHOGENESIS

Similarities between pre-eclampsia, HELLP and AFLP suggest that these disorders form a spectrum of disease with common clinical and laboratory abnormalities. Hepatic dysfunction is a common feature of each of these conditions, ranging from mild elevations in the plasma concentrations of liver enzymes, to more serious forms associated with clinical jaundice and gross hepatic impairment. It has been proposed that the poorly perfused placenta, secondary to defective placental invasion of the maternal circulation, is the origin of blood-borne material(s) that, directly or indirectly, activate maternal endothelial cells, setting up a vicious circle of endothelial dysfunction and vascular damage (Roberts and Redman, 1993).

There is increasing evidence that in addition to endothelial activators, such as cytokines and lipid peroxidases, marked perturbations in lipid and lipoprotein metabolism may be of fundamental importance in the pathogenesis certainly of pre-eclampsia, and probably of HELLP syndrome and AFLP (Endersen et al, 1992; Lorentzen et al, 1994; Sattar et al, 1997). There is a growing body of evidence that dysfunctional lipid metabolism may represent a key link in the pathogenic chain, leading to pre-eclampsia, HELLP or ultimately AFLP (Minakami et al, 1988; Kaaja et al, 1995).

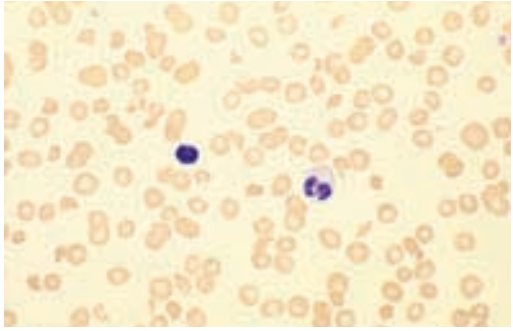

Figure 1. Haemolysis leads to this appearance on peripheral blood smear of triangular cells, echinocytes or burr cells (crenated, contracted erythrocytes with spiny projections along the periphery that are characteristic of cell membrane changes), and schistocytes (small, irregularly shaped erythrocyte fragments that reflect microangiopathic haemolysis).

Potential role of altered lipid metabolism in pre-eclampsia/HELLP/AFLP

Normally, free fatty acids (FFAs) released from adipocytes by the action of hormone-sensitive lipase (HSL) are taken up by the liver and subject to two alternative routes of metabolism: one is their reassimilation into triglyceride molecules, and the other is oxidation by mitochondrial β-oxidative pathways, which results in generation of energy and synthesis of ketones (*Figure 2a*).

In the late second trimester of human pregnancy, increased flux of FFAs is promoted by a combination of stimulation of HSL by human placental lactogen and relative resistance to insulin (which normally suppresses FFA release from adipose tissue). Studies in mice suggest that late pregnancy is also associated with a mild impairment in β-oxidative function. The net result of these changes is an increase in circulating FFAs coupled with a reduced capacity of the liver to clear this excess.

The delivery of FFAs as substrate for triglyceride synthesis is known from cell culture work to be the major determinant of very low-density lipoprotein (VLDL) secretion. As total hepatic lipids remain unchanged, it appears that in normal pregnancy this decreased oxidation of fat in the liver is compensated for by increased secretion of VLDL, in agreement with studies in animal models (*Figure 2b*). Recently, in a single human case study, oestrogen was shown to inhibit hepatic lipid oxidation, with a resultant increase in serum triglyceride concentration (O'Sullivan et al, 1995).

Women with pre-eclampsia have shown an increased flux of FFAs over and above that seen in normal pregnancy, which significantly is observed long before the onset of clinical disease. In pre-eclampsia it is tempting to postulate that, as has been shown in animal models, increased FFA flux, along with impaired β-oxidation in late pregnancy, promotes excessive synthesis of hepatic triglyceride and thus VLDL hypersecretion. Plasma triglyceride concentrations are significantly raised in women with pre-eclampsia compared with unaffected controls matched for gestational age, and raised plasma triglyceride concentrations precede the onset of clinical disease.

This correlates with earlier work and with findings from our laboratory of a specific accu-

mulation of large triglyceride-rich VLDL in the circulation of pre-eclamptic women (Sattar et al, 1997). β-oxidation may also be further impaired in subjects with pre-eclampsia, since ketonaemia is not a feature despite fatty acid levels being increased. In AFLP there is more direct evidence for inhibition of fatty acid oxidation (see below).

It is likely that when the liver's ability to produce VLDL is saturated, triglycerides accumulate in hepatocytes. Significant amounts of microvesicular fat droplets have been shown in cases of pre-eclampsia with and without liver dysfunction (*Figure 2c*), increasing in density in HELLP syndrome (*Figure 2d*), and maximal in cases of AFLP. Density of hepatocellular fat correlated positively with plasma urate concentration, and negatively with platelet count, established markers of severity and progression of pre-eclampsia.

Data on plasma triglyceride and high density lipoprotein cholesterol concentrations in HELLP syndrome and AFLP are currently lacking. However, supportive evidence for the above theory exists in the pathogenic parallels with animal models, and in the similarity of features seen in human diseases with identical pathogenic processes.

LCHAD deficiency and other abnormalities of hepatic metabolism

Pregnancies with a long chain 3-hydroxyacyl-coenzyme A (LCHAD)-deficient fetus have a high frequency of pre-eclampsia-related conditions, e.g. HELLP syndrome or AFLP (Tyni et al, 1998). These complications are exceptionally severe in LCHAD carriers, and they can not be attributed to primigravidity or age of the mother, as in the normal population, supporting the causative role of LCHAD deficiency in their development.

LCHAD is a mitochondrial trifunctional protein that catalyses the last three steps of a single β-oxidation cycle for long chain fatty acids. The complications of LCHAD deficiency during pregnancy have been postulated to be associated with the accumulation of intermediates from abnormal β-oxidation of fatty acids. In pregnancies with an LCHAD-deficient fetus, increased FFA serum concentration may result from accumulation of intermediates in the fetus with abnormal β-oxidation and the slightly impaired β-oxidative capacity of the carrier mother. This is consistent with the theory that aberrant lipoprotein and fatty acid metabolism play a decisive role in the pathogenesis of pre-eclampsia.

Other examples to support the role of impaired hepatic function in the pathogenesis of HELLP include observation of an increased incidence of pre-eclampsia, eclampsia and other abnormalities of pregnancy in two Norwegian families who carry a genetic abnormality of mitochondrial function (Torbergsen et al, 1989). An association between Gilbert's syndrome and HELLP has been described. At long-term follow-up after an episode of HELLP syndrome, 20% of women had impairment of the bilirubin-conjugating mechanism, despite other parameters of liver function being within normal limits, suggesting that these women may represent the subpopulation of adult women who have Gilbert's syndrome (Knapen et al, 1998). This requires further verification.

Cytokines

Increased plasma cytokine concentrations, particularly tumour necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6 have been implicated in the pathophysiology of pre-eclampsia. Such cytokine perturbances can induce adipocyte lipolysis (TNF-α, IL-1), promote de novo hepatic fatty acid synthesis (TNF-α, IL-1, IL-6), and impair hepatic fatty acid oxidation and ketogenesis (IL-1, TNF-α), resulting in increased hepatic triglyceride synthesis. The significantly higher TNF-α and TNF receptor levels in patients with HELLP syndrome support a role for TNF-α in liver dysfunction.

Oxidative stress

A role for oxidative damage in the pathogenesis of HELLP has been postulated, although evidence remains indirect and circumstantial (Hubel et al, 1989; Wang et al, 1991). It was postulated that antioxidants selectively inhibit release of

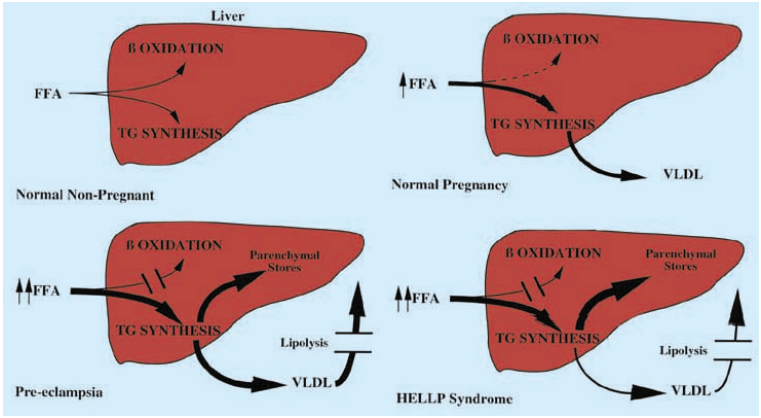

Figure 2. a. Normally free fatty acids (FFAs) entering the liver have two routes of metabolism; they are either subjected to β-oxidation resulting in CO_2 (and a small amount of ketones) or they are esterified and secreted as triglycerides (TGs) in very low-density lipoprotein (VLDL). b. Late pregnancy is associated with an increased flux of FFAs and impaired fatty acid oxidation. The net effect is increased delivery of FFAs into TG synthesis. However, in normal pregnancy this increased TG synthesis is compensated for by increased secretion of VLDL. Consequently, hepatic TG content remains unchanged. c. In pre-eclampsia, FFA flux is further enhanced and β-oxidation may be further impaired. The liver responds by increasing secretion of VLDL, but eventually this mechanism becomes saturated resulting in the deposition of TGs within the parenchyma. d. In HELLP syndrome this situation is further exaggerated, resulting in the accumulation of microvesicular fat droplets within the hepatocytes, leading to significant hepatic steatosis.

TNF, because they control the oxidation-reduction status of glutathione, an endogenous modulator of TNF production (Peristeris et al, 1992).

In mitochondria, TNF subverts part of the electron flow to release oxidizing free radicals, with subsequent formation of lipid peroxidases. If these are not removed with efficient reduction of the oxidized glutathione, serious toxic effects ensue, because persisting toxic lipid peroxidases and oxidized glutathione further enhance TNF production. It may be that the pro-oxidative environment in pre-eclampsia and HELLP syndrome induces the rise in TNF seen in these conditions, and thereby indirectly effects development of the pathological features of HELLP by the mechanisms described above. This is supported by various animal models in which a HELLP-like syndrome has been observed following the injection of cytokines.

Possible haematological risk factors

Brenner et al (1995) reported two cases of HELLP syndrome occurring in patients heterozygous for the factor V R506Q (Leiden) mutation. The R506Q mutation is a heritable thrombophilia associated with a variety of thrombotic states. Pregnancy itself is associated with a transient increase in the activated protein C (APC) sensitivity ratio, and this may be further augmented during pregnancy in subjects with the R506Q mutation. Recent observations have suggested a higher incidence of the R506Q mutation in patients with pre-eclampsia. As HELLP syndrome is considered to be a variant of severe pre-eclampsia, it would be interesting to know whether the R506Q mutation is associated with HELLP, and the authors suggest that APC resistance should be checked in all patients with HELLP syndrome.

INCIDENCE AND EPIDEMIOLOGY

The reported incidence of HELLP syndrome in women with pre-eclampsia/eclampsia ranges from 4% to 12%, because of different diagnostic criteria (McKenna et al, 1983; Thiagarajah et al, 1984; Moodley and Pillay, 1985). The mean maternal age at presentation is 24 years and HELLP mainly affects white multiparous women with a poor past obstetric history. The incidence is very low among black women (Sibai et al, 1993). Up to one-quarter of patients who developed HELLP in a previous pregnancy will have a subsequent recurrence (McKenna et al, 1983; Sibai, 1990; Sullivan et al, 1994), and pre-eclamptic women with delayed diagnosis or delivery are particularly at risk.

While 13% of HELLP patients have pre-existing chronic hypertension, it is important to note that on presentation, hypertension and proteinuria may be absent or only slight. Although the majority of cases occur antenatally, a significant minority (31%) occur postpartum (Sibai et al, 1993). One in five postnatal cases have no evidence of pre-eclampsia before or during delivery, yet this postpartum subgroup have a significantly greater risk of developing severe complications such as pulmonary oedema and acute renal failure (ARF) compared with antenatal cases (Sibai et al, 1993).

This situation is akin to findings in the recent Report on Confidential Enquiries into Maternal Deaths in the UK 1994–1996 (Department of Health, 1998), which suggests that pre-eclampsia complicated by HELLP syndrome carries a markedly increased risk of developing acute respiratory distress syndrome (ARDS), the most common preterminal complication in women with hypertensive pregnancy disorders in that triennia.

CLINICAL PRESENTATION AND COMPLICATIONS

The presenting symptoms of HELLP syndrome are often vague, hence the average delay in achieving a correct diagnosis is 8 days. This underscores the need for vigilance and awareness of presenting features among clinicians. Most women with HELLP syndrome will have felt ill for only a few days, if at all (Sibai et al, 1986); hypertension and proteinuria may be absent or slight (Sibai, 1990). Normotensive patients presenting with any of the symptoms below merit investigation by full blood count, serum urea and electrolytes, and liver enzyme level estimation. HELLP syndrome may develop during treatment of pre-eclampsia, and regular monitoring of the above laboratory parameters is essential. Most antenatal cases develop before 37 weeks' gestation (82%), with 2.5% developing at 17–20 weeks (Sibai et al, 1993).

The symptoms most commonly associated with HELLP syndrome are epigastric or right upper quadrant (RUQ) pain, thought to be caused by swelling and distension of Glisson's capsule, reported in 90% of cases (Sibai, 1990). This often misleads clinicians to diagnoses such as biliary colic, cholecystitis, perforated peptic ulcer, hiatus hernia, gastroenteritis, hepatitis, pancreatitis, appendicitis, idiopathic thrombocytopenic purpura, haemolytic uraemic syndrome, pyelonephritis or renal colic. Resulting inappropriate medical or surgical interventions and invasive diagnostic procedures associated with significant morbidity (laparotomy, biopsy of bone marrow, liver, kidney and intestine) further complicate the issue, and more importantly further delay accurate diagnosis.

Alternative presentations include vague symptoms such as malaise, vague non-specific viral symptoms or a flu-like illness (Sibai et al, 1993; Tomsen, 1995), and 50% of cases experience

nausea and vomiting (Sibai et al, 1993). Rarer presentations include convulsions, jaundice, gastrointestinal bleeding, gingival bleeding, renal angle pain, pain in the chest or shoulder, hypoglycaemia leading to coma, severe hyponatraemia causing mental confusion, cortical blindness or nephrogenic diabetes insipidus, all recognized complications of pre-eclampsia.

MANAGEMENT

In addition to these diagnostic difficulties, the variable presentation has made it difficult to evaluate proposed treatments. Patients diagnosed with HELLP syndrome should be managed in a tertiary care centre. The priority is to establish maternal stabilization (with particular regard to coagulation status) and fetal wellbeing (cardiotocography, biophysical profile and assessment of fetal growth), and a decision must then be made about delivery. The excessively high maternal and perinatal mortality observed in 'true HELLP' syndrome (Sibai, 1990) provides a compelling argument for expeditious delivery irrespective of gestational age.

Some patients without true HELLP syndrome may have antepartum reversal of haematological abnormalities after bedrest, use of steroids or plasma volume expansion. However, either maternal or fetal condition will deteriorate within 1–10 days of conservative management in most of these patients. Some also develop abruption, fetal distress and fetal death during conservative management, particularly as many have intrauterine growth retardation (IUGR), so it is doubtful that limited pregnancy prolongation will improve perinatal outcome, especially where maternal and fetal risks are substantial. Thus at gestation over 34 weeks or so, there seems little to be gained from conservative treatment and delivery is the best option. At premature gestation initial conservative treatment will allow steroid administration and promote fetal lung maturation. Maternal deterioration requires delivery regardless of gestation.

Steroids have also been tried to reduce maternal disease severity and progression. Thiagarajah et al (1984) found that antenatal corticosteroid administration to facilitate fetal lung maturation was often coincidentally accompanied by partial or complete resolution of the thrombocytopenia and disturbances of liver enzymes seen in HELLP syndrome. Magann et al (1994), in their prospective study of the use of antenatal steroids in HELLP syndrome, found that steroid administration significantly delayed delivery compared with control groups, but only by a mean of 41 hours — time to facilitate maternal stabilization, transfer to a tertiary referral centre, and permit fetal lung maturation, but certainly not a long-term therapeutic strategy. They also found that antepartum steroid therapy reduced the need for maternal transfusion of blood products and reduced neonatal morbidity or mortality from multiple systemic effects.

Patients given antenatal steroids often have postpartum deterioration of HELLP syndrome following cessation of steroids (this may result in part from the natural course of HELLP, with a disease nadir 24–36 hours postpartum.) Use of intravenous dexamethasone for postpartum HELLP is associated with a shorter disease course, faster recovery, reduced morbidity and diminished requirement for other interventionalist therapy. This may prove to be a useful treatment in patients with postpartum HELLP syndrome who fail to respond to supportive management (Martin et al, 1997).

Mode of delivery should be determined by fetal condition and cervical state (Sibai, 1990). Epidural and pudendal anaesthesia are usually contraindicated if coagulation tests are disturbed or thrombocytopenia severe (Sibai, 1990). Evidence of DIC should be aggressively treated with fresh frozen plasma, and a platelet count <20 000/μl necessitates platelet transfusion. Repeat transfusions are unnecessary as consumption occurs rapidly and the effect is transient (Sibai, 1990).

Some authors recommend delayed closure in caesarean deliveries to minimize the cited 20% risk of haematoma formation (Sibai, 1990). This is not common practice in the UK; however, the risk of haematoma formation may be avoided by use of drains in both the peritoneal cavity and the rectus sheath and/or midline closure.

Patients should undergo intensive monitoring postpartum in an intensive care unit for at least 48 hours. There is a substantial risk of developing pulmonary oedema and ARDS from transfusions, immobilization and compromised renal function. Some patients, especially those with DIC, may have a delayed deterioration in their condition. Schwartz and Brenner (1983) suggest that exchange plasmapheresis may be helpful in such patients, but the majority will resolve with supportive treatment alone. This procedure is costly and may risk transmission of a potentially fatal infectious disease. Postpartum there is a significant risk of deep venous thrombosis formation. Heparin is contraindicated in the presence of coagulopathy, and graduated compression stockings should be used until coagulation has normalized, when thromboprophylaxis with low molecular weight heparin should be instituted.

COMPLICATIONS, MATERNAL AND FETAL OUTCOME

Pregnancies complicated by HELLP syndrome are associated with a poor outcome for mother and

infant. Six studies have specifically looked at maternal mortality associated with HELLP syndrome, with a quoted range of 1.1–24.2% (Lopez-Llera et al, 1976; Weinstein, 1982; Sibai et al, 1986, 1993; Reubinoff and Schenker, 1991; Abroug et al, 1992), and reported 29 maternal deaths out of 746 cases (3.9%). The reported perinatal mortality is 77–370/1000, and may relate to prematurity or be secondary to maternal complications such as abruption (Geary, 1997). Maternal complications, e.g. DIC, placental abruption and ARF, are common and often life-threatening. Other complications include eclampsia, cerebral haemorrhage, adult respiratory distress syndrome and hypovolaemic shock. Haematoma, infarction and rupture of the liver have also been reported.

DIC is the most common maternal complication, with a reported frequency of 4–38% depending on the definition applied. It is likely that DIC exists to some extent in all cases of HELLP, but its detection depends on the sensitivity of the diagnostic test used. Using a crude definition of DIC (thrombocytopenia, prolonged prothrombin time and activated partial thromboplastin time, and low fibrinogen), Sibai et al (1993) found that DIC occurred in 20% of the 442 pregnancies they reviewed. However, most of these had had an antecedent abruption, postpartum haemorrhage or subcapsular liver haematoma, and excluding these cases the incidence of DIC occurring de novo was less than 5%. Audibert et al (1996) also noted this association and concurred that if frank (decompensated) DIC is detected in women with HELLP, the presence of an additional inciting condition, e.g. abruptio placentae, liver haematoma or sepsis, should be specifically sought.

Abruption is strongly associated with the development of DIC, ARF, pulmonary oedema and effusions. Bleeding in the gravid patient is related to more than platelet count alone. However, patients with platelet counts >40 000/μl maintained intrapartum are unlikely to have clinically significant bleeding, and those with intrapartum platelet counts <40 000/μl are at significant risk of postpartum bleeding. Prophylactic platelet transfusion does not significantly reduce the risk of postpartum haemorrhagic complications and so active management and close observation are critical, although use of ergometrine (including syntometrine) should be avoided, as it can induce an acute rise in blood pressure. Thus acute management of the third stage is with oxytocin alone.

Subcapsular liver haematoma is a rare but life-threatening complication. Large hyaline deposits of fibrin-like material in the hepatic sinusoids are associated with periportal or focal parenchymal necrosis. These deposits lead to sinusoidal obstruction, distension of the liver and RUQ pain. If intrahepatic pressure exceeds the ability of Glisson's capsule to distend, rupture occurs, indicating massive transfusion of blood, fresh frozen plasma and platelets, and immediate laparotomy.

Some evidence suggests that unruptured subcapsular haematomas may be managed conservatively, provided patients receive regular imaging to monitor progress (Barton and Sibai, 1996). However, this is a high-risk situation and in the UK would usually lead to delivery.

Liver enzymes abnormalities correlate poorly with histopathology and degree of disease severity. However, diagnostic imaging (computed tomography scan or magnetic resonance imaging) identifies hepatic complications, and should be performed on patients complaining of RUQ pain, neck pain, shoulder pain or demonstrating relapsing hypotension. Barton and Sibai (1996) found hepatic abnormalities on diagnostic imaging in almost half of patients with these symptoms, six of whom required emergency laparotomy.

In Sibai et al's (1993) review of 442 pregnancies, 33 were complicated by ARF. All of these were complicated by one of abruption, intrauterine death, DIC, hypotensive shock or sepsis. This highlights the need for aggressive blood and fluid replacement. A strong correlation between pulmonary oedema and ARF was also noted.

MATERNAL COUNSELLING

It is prudent to advise women with pre-eclampsia, both antenatally and those discharged soon after delivery, to report to hospital if they develop symptoms such as RUQ or epigastric pain, as one-third of HELLP cases occur postpartum.

The recurrence rate for HELLP syndrome in subsequent pregnancies varies from 3.4% to 27% in different studies (McKenna et al, 1983; Sibai, 1990; Sullivan et al, 1994). Risk is considered to be at the lower end of this range. However, apart from HELLP, these women are at increased risk of other obstetric complications, such as pre-eclampsia, IUGR and abruption in subsequent pregnancies, and there is a need for continued vigilance.

Patients developing this syndrome may subsequently receive combined oral contraceptives without any problems. Although pre-eclampsia has been associated with increased cardiovascular disease in later life, it is unclear whether HELLP syndrome influences the risk.

CONCLUSION

The importance of HELLP syndrome lies not in its name, but in its associated high maternal and perinatal mortality. It is essential that clinicians are alert to the many facets of the condition and its

presentation. Expeditious delivery is the most prudent management. The pathogenic mechanisms proposed in this review require verification by further studies of blood lipid profiles in women with HELLP syndrome. This would represent a significant advance in our understanding of this disorder, and may allow the development of improved monitoring techniques and new therapies. HM

Abroug F, Boujdaria R, Nouira S et al (1992) Hellp syndrome: incidence and maternal fetal outcome — a prospective study. *Intens Care Med* **18:** 274–7

Audibert E, Friedman SA, Frangieh AY, Sibai B (1996) Clinical utility of strict diagnostic criteria for the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. *Am J Obstet Gynecol* **175:** 460–4

Barton JR, Sibai B (1996) Hepatic imaging in HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count). *Am J Obstet Gynecol* **174:** 1820–7

Brenner B, Lanir N, Thaler I (1995) HELLP syndrome associated with factor V R506Q mutation. *Br J Haematol* **92:** 999–1001

Clark SL, Phelan JR, Allen SH, Golde SR (1986) Antepartum reversal of haematological abnormalities associated with the HELLP syndrome. *Obstet Gynecol* **31:** 70–2

Department of Health (1998) *Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1994–1996.* HMSO, London

Endersen MJ, Lorentzen B, Henriksen T (1992) Increased lipolytic activity and high ratio of free fatty acids to albumin in sera from women with pre-eclampsia leads to triglyceride accumulation in cultured endothelial cells. *Am J Obstet Gynecol* **167:** 440–7

Hubel CA, Roberts JM, Taylor RN et al (1989) Lipid peroxidation in pre-eclampsia: new perspectives on pre-eclampsia. *Am J Obstet Gynecol* **161:** 1025–34

Geary M (1997) The HELLP syndrome. *Br J Obstet Gynaecol* **104:** 887–91

Goodlin RC (1982) Beware the great imitator — severe pre-eclampsia. *Contemp Obstet Gynaecol* **20:** 215

Kaaja R, Tikkanen M, Vinikka L, Ylikorkala O (1995) Serum lipoproteins, insulin and urinary prostanoid metabolites in normal and hypertensive women. *Obstet Gynecol* **85:** 353–6

Knapen MCFM, Mulder TPJ, Bisseling JGA, Penders RHMJ, Peters WHM, Steegers EAP (1988) Plasma glutathione S-transferase alpha 1-1: a more sensitive marker for hepatocellular damage than serum alanine aminotransferase in hypertensive disorders of pregnancy. *Am J Obstet Gynecol* **178:** 161–5

Knapen MFCM, van Altena AM, Peters WHM et al (1998) Liver function following pregnancy complicated by the HELLP syndrome. *Br J Obstet Gynaecol* **105:** 1208–10

Lopez-Llera M, Espinosa M, De Leon MD, Linares UR (1976) Abnormal coagulation and fibrinolysis in eclampsia, A clinical and correlation study. *Am J Obstet Gynecol* **124:** 680

Lorentzen B, Endersen MJ, Clausen T Henriksen T (1994) Fasting serum free fatty acid and triglycerides are increased before 20weeks of gestation in women who later develop pre-eclampsia. *Hypertens Pregnancy* **13:** 103–9

Magann EF, Bass D, Chauhan SP, Sullivan DL, Martin RW, Martin JN (1994) Antepartum corticosteroids: disease stabilization in patients with the syndrome of hemolysis, elevated liver enzymes and low platelets (HELLP). *Am J Obstet Gynecol* **171:** 1148–53

Martin JN, Blake PG, Lowry SL, Perry KG, Files JC, Morrison JC (1990) Pregnancy complicated by pre-eclampsia — eclampsia with the syndrome of hemolysis, elevated liver enzymes, and low platelet count: how rapid is postpartum recovery? *Obstet Gynecol* **76:** 737–41

Martin JN, Blake PJ, Perry KG, McCaul JF, Hess LW, Martin RW (1991) The natural history of HELLP syndrome: patterns of disease progression and regression. *Am J Obstet Gynecol* **164:** 1500–13

Martin JN, Perry KG, Blake PG, May WA, Moore A, Robinette L (1997) Better maternal outcomes are achieved with dexamethasone therapy for postpartum HELLP (hemolysis, elevated liver enzymes, and thrombocytopenia) syndrome. *Am J Obstet Gynecol* **177:** 1011–17

McKenna J, Dover NL, Brame RG (1983) Preeclampsia associated with the syndrome of haemolysis, elevated liver enzymes and low platelets in severe preeclampsia-eclampsia. *Obstet Gynecol* **62:** 751

Minakami H, Oka N, Sato T, Tamada T, Yasuda Y, Hirota N (1988) Pre-eclampsia: a microvesicular fat disease of the liver? *Am J Obstet Gynecol* **159:** 1043–7

Moodley J, Pillay M (1985) The HELLP syndrome in severe hypertensive crisis of pregnancy: does it exist? *S Afr Med J* **67:** 246

O'Sullivan AJ, Hoffman DM, Ho KKY (1995) Estrogen, lipid oxidation and body fat. *N Engl J Med* **333:** 669–70

Peristeris P, Clark BD, Gatti S et al (1992) N-acetylcysteine and glutathione as inhibitors of tumour necrosis factor production. *Cell Immunol* **140:** 390–9

Reubinoff BE, Schenker JG (1991) HELLP syndrome - a syndrome of hemolysis, elevated liver enzymes and low platelet count — complicating preeclampsia-eclampsia. *Int J Gynecol Obstet* **36:** 95–102

Roberts JM, Redman CWG (1993) Pre-eclampsia: more than pregnancy-induced hypertension. *Lancet* **341:** 1447–51

Sattar N, Bendomir A, Berry C, Shepherd J, Greer IA, Packard CJ (1997) Lipoprotein subfraction concentrations in preeclampsia: pathogenic parallels to atherosclerosis. *Obstet Gynecol* **89:** 403–8

Schwartz ML, Brenner WE (1983) Pregnancy-induced hypertension with life-threatening thrombocytopaenia. *Am J Obstet Gynecol* **146:** 756–9

Sibai SM (1990) The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets): much ado about nothing? *Am J Obstet Gynecol* **162:** 311–16

Sibai BM, Taslimi MM, El Nazer A et al (1986) Maternal-perinatal outcome associated with the syndrome of hemolysis, elevated liver enzymes and low platelets in severe preeclampsia-eclampsia. *Am J Obstet Gynecol* **155:** 501–9

Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA (1993) Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). *Am J Obstet Gynecol* **169:** 1000–6

Sullivan CA, Magann EF, Perry KG, Roberts EW, Blake PG, Martin JN (1994) The recurrence risk of the syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP) in subsequent gestations. *Am J Obstet Gynecol* **171:** 940–3

Thiagarajah S, Bourgeouis FJ, Harbert GM, Caudle MR (1984) Thrombocytopenia in preeclampsia: associated abnormalities and management principles. *Am J Obstet Gynecol* **150:** 1–7

Tomsen T (1995) HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) presenting as generalized malaise. *Am J Obstet Gynecol* **172:** 1876–80

Torbergsen T, Øian P, Mathiesen E, Borud O (1989) Pre-eclampsia - a mitochondrial disease? *Acta Obstet Gynecol Scand* **68:** 145–8

Tyni T, Ekholm E, Pihko H (1998) Pregnancy complications are frequent in long chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency. *Am J Obstet Gynecol* **178:** 603–8

Wang Y, Walsh SW, Guo J, Zhang J (1991) The imbalance between thromboxane and prostacyclin in pre-eclampsia is associated with an imbalance between lipid peroxidases and vitamin E in maternal blood. *Am J Obstet Gynecol* **165:** 1695–700

Weinstein L (1982) Syndrome of haemolysis, elevated liver enzymes and low platelet count: a severe consequence of hypertension in pregnancy. *Am J Obstet Gynecol* **142:** 159–67

KEY POINTS

- Pre-eclampsia, HELLP (haemolysis, elevated liver enzymes and low platelets) and acute fatty liver of pregnancy form a spectrum of disease with a common pathogenic basis.
- In HELLP syndrome, dysfunctional lipid metabolism leads to hepatic steatosis, with accumulation of microvesicular fat droplets in the hepatocytes. This may precede clinical manifestation of the syndrome.
- A widely accepted definition for HELLP syndrome is currently lacking, but Sibai et al's (1993) criteria correlate with need for intervention and final outcome.
- HELLP syndrome may present with vague, non-specific symptoms, and clinician awareness is of paramount importance in its detection.
- HELLP syndrome is associated with high maternal and perinatal morbidity and mortality, and expeditious delivery is currently the only definitive management.