Diagnosis and Management of Women with Hemolysis, Elevated Liver Enzymes, and Low Platelet Count (HELLP) Syndrome

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Hemolysis, abnormal results on liver function tests, and thrombocytopenia have been recognized as complications of preeclampsia-eclampsia for many years. In 1982, Weinstein[1] described 29 cases of severe preeclampsia-eclampsia complicated by thrombocytopenia, abnormal peripheral smear results, and abnormal liver function test results. Weinstein[1] suggested that these signs and symptoms constituted an entity separate from severe preeclampsia and termed the syndrome *HELLP syndrome:* "H" for hemolysis, "EL" for elevated liver enzyme levels, and "LP" for low platelet count. Since the recognition of HELLP syndrome, many articles describing this syndrome have appeared in the medical literature.

DIAGNOSIS

A literature review by Sibai et al[2] revealed considerable differences in the terminology, incidence, cause, diagnosis, and management of HELLP syndrome. The reported incidence rate ranges from 2% to 12%, which reflects the different diagnostic criteria and methods used. The time of onset and the type and degree of laboratory abnormalities that are diagnostic of HELLP syndrome vary considerably. Hemolysis, defined as the presence of microangiopathic hemolytic anemia, is the hallmark of HELLP syndrome; however, evidence of hemolysis was documented in few studies and the platelet count that defined the presence of thrombocytopenia ranged from less than 75,000/mm^3 to 150,000/mm^3. No consensus was reached in the medical literature regarding which abnormal results on liver function tests should be used to diagnose HELLP syndrome. Many physicians now advocate that lactate dehydrogenase levels and bilirubin levels be included in the diagnosis of hemolysis. The degree of abnormality in liver enzyme levels should be defined as a specific number of standard deviations from the normal values of a particular hospital. At the University of Tennessee Division of Maternal-Fetal Medicine (Memphis, TN), a cutoff value of more than three standard deviations above the mean is used to indicate abnormality. The diagnostic criteria for HELLP syndrome at this institution also include the laboratory findings listed in **Table 1**.

Disseminated Intravascular Coagulation

The role of disseminated intravascular coagulation (DIC) in preeclampsia is controversial. Most authors do not regard HELLP syndrome as a variant of DIC because coagulation parameters such as prothrombin time, partial thromboplastin time, and serum fibrinogen are normal in patients with HELLP syndrome. However, many patients with HELLP syndrome have laboratory values consistent with DIC when more sensitive determinants for this condition are used, such as antithrombin III, fibrinopeptide A, fibrin monomer, D-dimer, a_2 antiplasmin, plasminogen, prekallikrein, and fibronectin. Unfortunately, the tests for these determinants are time-consuming and not suitable for use in routine monitoring. Consequently, less sensitive parameters often are used in clinical practice. Sibai et al[2] defined DIC as the presence of thrombocytopenia, low fibrinogen levels (ie, plasma fibrinogen level of less than 300 mg/dL), and fibrin-degradation products of greater than 40 mg/mL. DIC was observed in 92 women (21%) of 442 patients with HELLP syndrome.[3]

Clinical Presentation

The incidence of HELLP syndrome in women with severe preeclampsia-eclampsia ranges from 2% to 30%

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Table 1. Laboratory Diagnostic Criteria for HELLP Syndrome*

Hemolysis
Abnormal peripheral smear
Total bilirubin level ≥ 1.2 mg/dL
Lactate dehydrogenase level ≥ 600 U/L
Elevated liver function test results
Serum aspartate aminotransferase level ≥ 70 U/L
Lactate dehydrogenase level ≥ 600 U/L
Low platelet count
Platelet count < 100,000/mm^3

*The laboratory diagnostic criteria used at the University of Tennessee Division of Maternal-Fetal Medicine (Memphis, TN).

HELLP = hemolysis, elevated liver enzymes, and low platelet count.

Table 2. Medical and Surgical Disorders with Signs and Symptoms Similar to HELLP Syndrome

Acute fatty liver of pregnancy
Appendicitis
Diabetes insipidus
Gallbladder disease
Gastroenteritis
Glomerulonephritis
Hemolytic uremic syndrome
Idiopathic thrombocytopenia
Peptic ulcer
Pyelonephritis
Systemic lupus erythematosus
Thrombotic thrombocytopenic purpura
Viral hepatitis

HELLP = hemolysis, elevated liver enzymes, and low platelet count

depending on the population studied and the criteria used to establish the diagnosis. The incidence of this syndrome is significantly increased among white middle-class and older multiparous women.

Women with HELLP syndrome may present with a variety of signs and symptoms that are not diagnostic of the syndrome. These signs and symptoms may also be seen in women with severe preeclampsia-eclampsia who do not have HELLP syndrome. Sibai et al[4] noted that women with HELLP syndrome usually present remote from term with complaints of epigastric or right upper-quadrant pain (90%). Some women with HELLP syndrome experience nausea or vomiting (50%), whereas other women with the syndrome experience nonspecific viral-syndrome–like symptoms. Most women with HELLP syndrome present with a history of malaise for the past few days prior to presentation (90%). The most common symptoms reported by Weinstein[1] were nausea and/or vomiting and epigastric pain. Right upper-quadrant or epigastric pain is thought to be caused by obstruction of blood flow in the hepatic sinusoids, which are blocked by intravascular fibrin deposits.

Women with HELLP syndrome usually have significant weight gain associated with generalized edema. In addition, a proteinuria value of greater than 1+ measured by dipstick is present in approximately 90% of women with HELLP syndrome; however, severe hypertension (ie, systolic blood pressure of 160 mm Hg or greater, diastolic blood pressure of 110 mm Hg or greater) is neither a constant nor a frequent finding in HELLP syndrome. Although 66% of the 112 women studied by Sibai et al[2] had a diastolic blood pressure of 110 mg Hg or greater, 14.5% had a diastolic blood pressure of less than 90 mm Hg. Thus, women with HELLP syndrome may present with various signs and symptoms, none of which are diagnostic of severe preeclampsia-eclampsia. As a result, these patients are often misdiagnosed as having other medical or surgical disorders (**Table 2**).

HELLP syndrome is occasionally associated with hypoglycemia that leads to coma, severe hyponatremia, and cortical blindness. A rare but interesting complication of HELLP syndrome is transient nephrogenic diabetes insipidus. Unlike central diabetes insipidus, which occurs because of diminished or absent secretion of arginine vasopressin by the hypothalamus, transient nephrogenic diabetes insipidus is characterized by a resistance to arginine vasopressin that is mediated by excessive vasopressinase.

Differential Diagnosis

The differential diagnoses of HELLP syndrome include acute fatty liver of pregnancy, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and acute renal failure.[5] The differential diagnoses for HELLP syndrome are listed in **Table 3**.

MANAGEMENT

Women with HELLP syndrome who are remote from term should be referred to a tertiary care center. The initial management of these patients should be the same as for any woman with severe preeclampsia(**Table 4**).[6] The first priority is to assess and stabilize the mother, with

Table 3. Clinical and Laboratory Findings of HELLP Syndrome and Common Differential Diagnoses

Finding	HELLP	Thrombotic Thrombocytopenic Purpura	Hemolytic Uremic Syndrome	Acute Fatty Liver of Pregnancy	Acute Renal Failure
Hypertension	80%	< 25%	50%–100%	25%–50%	100%
Proteinuria	±	±	+++	±	+++
Low platelet count (<100,000 cells/mm^3)	100%	100%	50% at onset	±	+
Lactate dehydrogenase	++	++++	++	++	+
Prothrombin time/ Partial prothrombin time	Normal	Normal	Normal	>	>
Fibrinogen	Normal	Normal	Normal	<	<
Fibrin degradation products	—	—	>	>	>
Bilirubin	+	++	+	+++	+
Ammonia	Normal	Normal	Normal	+++	Normal
Glycemia	Normal*	Normal	Normal	<70 mg/dL	Normal
Anemia	+	+++	+	±	Normal
Renal abnormalities	+	±	+++	+	++
Neural abnormalities	+	++	±	+	±
Fever	Normal	±	+	Normal	Normal
Skin lesions	+	++	—	Jaundice	+
Time of onset	Third trimester to postpartum	Second to third trimester	Postpartum	End of the third trimester	Second or third trimester to postpartum

— = Not present; ± = may be present; + = occasionally present; ++ = likely to be present; +++ = usually present; ++++ = always present; > = high level; < = low level; HELLP = hemolysis, elevated liver enzyme levels, and low platelet count.

* Normal range for glycemia, 80–120 mg/dL.

Adapted with permission from Sibai BM, Kustermann L, Velasco J: Current understanding of severe preeclampsia, pregnancy-associated hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, hemolysis, elevated liver enzymes, and low platelet syndrome, and postpartum acute renal failure: different clinical syndromes or just different names? *Curr Opin Nephrol Hypertens* 1994;3:436–445.

particular attention paid to coagulation abnormalities. The next step is to evaluate fetal well-being using nonstress testing or a biophysical profile. In addition, ultrasonographic biometry should be used for assessment of possible intrauterine growth restriction. A decision must be made regarding whether immediate delivery is indicated. Amniocentesis may be performed in these patients without risk of bleeding complications.

A review of the medical literature highlights the confusion surrounding the management of patients with HELLP syndrome. Some authors consider the presence of this syndrome to be an indication for immediate cesarean delivery, whereas other authors recommend a more conservative approach to prolong pregnancy in cases of fetal immaturity. Consequently, several therapeutic modalities to treat or reverse HELLP syndrome are described in the medical literature. Most of these modalities are similar to those used in the management of severe preeclampsia that occurs in women who are remote from term.

Conservative Management

Conservative management techniques are often associated with the use of inappropriately invasive procedures (eg, biopsy) and medical and surgical treatments. These confounding variables complicate the evaluation of any treatment modality proposed for HELLP syndrome. Occasionally, some women without true HELLP syndrome demonstrate antepartum reversal of hematologic abnormalities following bed rest,

Table 4. Management of Patients with Antepartum HELLP Syndrome

Assess and stabilize maternal condition
If disseminated intravascular coagulation is present, correct coagulopathy
Institute antiseizure prophylaxis with magnesium sulfate
Treat severe hypertension
If appropriate, transfer the patient to a tertiary care center
Perform imaging studies of the abdomen if subcapsular hematoma of the liver is suspected
Evaluate fetal condition
Perform nonstress testing
Obtain biophysical profile
Perform ultrasonographic biometry
Evaluate fetal lung maturity if fetus is younger than 34 weeks gestation
If lungs are mature, induce delivery
If lungs are immature, administer steroids followed by delivery

HELLP = hemolysis, elevated liver enzyme levels, and low platelet count

Table 5. Risks of Conservative Management of HELLP Syndrome

Abruptio placentae
Acute renal failure
Disseminated intravascular coagulation
Eclampsia
Fetal death
Intrauterine growth retardation
Maternal death
Perinatal asphyxia
Pulmonary edema
Ruptured liver hematoma

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use of steroids, or plasma volume expansion; however, a deterioration in either maternal or fetal condition occurs in most patients 1 to 10 days after conservative management is started. The potential risks associated with conservative management of HELLP syndrome are summarized in **Table 5**. Thus, instituting such a limited prolongation of pregnancy probably does not result in improved perinatal outcome, especially when the maternal and fetal risks are substantial.

Delivery as Management

If HELLP syndrome develops at 34 weeks' gestation or later or if evidence of fetal lung maturity or maternal jeopardy is present before this time, then delivery is the definitive therapy. In the absence of laboratory evidence of DIC and with absent fetal lung maturity, the patient can be given two doses of steroids to accelerate fetal lung maturation and the fetus can be delivered 48 hours after the second dose. The maternal and fetal condition should be assessed continuously during this time period.

Cesarean delivery. The presence of HELLP syndrome is not an immediate indication for cesarean delivery, which may prove detrimental for both the mother and the fetus. Women presenting with well-established labor should be allowed to deliver vaginally if they do not have obstetric contraindications. Labor may be initiated with oxytocin infusion in women with a cervix that is favorable for induction. In women with an unripe cervix, cervical ripening may be accomplished pharmaceutically with agents such as prostaglandin gel and hygroscopic dilators (eg, Dilapan [Gynotech, Inc., Middlesex, NJ], *Laminaria digitata*), mechanically with dilators such as a Foley catheter, or with an extra-alveolar saline infusion. Cesarean delivery should be performed only for women with HELLP syndrome who also have obstetric indications. **Table 6** lists the management protocol for patients with HELLP syndrome who require cesarean delivery.

Postpartum management. Following delivery, the mother should be monitored closely for at least 48 hours. Most women show evidence of resolution of the disease process within 48 hours of delivery. Some women, especially those with DIC, may demonstrate delayed resolution or even deterioration. These women require intensive monitoring for several days. In addition, these women are at risk for the development of pulmonary edema from transfusions of blood and blood products, fluid mobilization, and compromised renal function. A discussion of the management of the infant of a woman with HELLP syndrome is beyond the scope of this article.

Management of Complications

Liver rupture. Women who present with shoulder pain, in shock, or with evidence of massive ascites or pleural effusions should undergo ultrasonography or computed axial tomography of the liver to rule out the presence of subcapsular hematoma of the liver. Liver rupture is a rare but life-threatening complication of HELLP syndrome. In most cases, the rupture involves the right lobe and is preceded by the development of a parenchymal hematoma. A patient with liver rupture

Table 6. Management of Women with HELLP Syndrome Who Require Cesarean Delivery

Administer general anesthesia
Administer 10 units of platelets prior to surgery (if platelet count ≤ 50,000/mm^3)
Leave vesicouterine peritoneum (bladder flap) open
Insert subfascial drain
Perform secondary closure of skin incision or subcutaneous drain
Administer postoperative transfusions as needed
Perform intensive monitoring for 48 hours postpartum

HELLP = hemolysis, elevated liver enzyme levels, and low platelet count

Table 7. Management of Women with Documented Subcapsular Hematoma of the Liver

General considerations
Alert blood bank to the potential need for large amounts of fresh frozen plasma, packed erythrocytes, and platelet concentrate
Consult a general or vascular surgeon
Avoid direct or indirect manipulation of the liver
Closely monitor the patient's hemodynamic status
Unruptured hematoma
Perform surgical repair and evacuation
—OR—
Manage the patient conservatively with serial computed tomography scans or ultrasonography if hemodynamically stable
Ruptured hematoma
Perform massive transfusions
Perform immediate laparotomy
If bleeding is minimal:
Observe the patient
Drain the area
If the bleeding is severe:
Perform surgical ligation of the hemorrhaging hepatic segment
Embolize the hepatic artery to the involved liver segment
Apply laparotomy sponges as pressure packs
Loosely suture omentum or surgical mesh to the liver to improve integrity

usually presents with severe epigastric pain that may persist for several hours prior to circulatory collapse. The presence of a ruptured subcapsular liver hematoma resulting in shock is an indication for massive transfusions of blood, fresh frozen plasma, and platelets as well as immediate laparotomy. **Table 7** summarizes the management of women with documented subcapsular hematoma of the liver.

Survival depends on either successful immediate surgery or embolization of the hepatic artery to the involved liver segment. Even with appropriate treatment, maternal and fetal mortality is more than 50%. Surgical repair also has been recommended for hepatic hemorrhage without liver rupture; however, recent experience suggests that this complication can be managed conservatively in women who remain hemodynamically stable. Importantly, during conservative management, exogenous sources of trauma to the liver (eg, abdominal palpation, convulsion, emesis) must be avoided and care must be taken in transportation of the patient. Indeed, any sudden increase in intra-abdominal pressure could potentially cause rupture of the subcapsular hematoma.

Bleeding. Evidence of bleeding may be an indication for platelet transfusions, especially when the platelet count is less than 50,000/mm^3. Repeat platelet transfusions are not necessary because the transfused platelets are rapidly consumed and the effect is transient. Prior to intubation for a cesarean delivery, the policy at the University of Tennessee Division of Maternal-Fetal Medicine is to administer 10 units of platelets for women with a platelet count of less than 50,000/mm^3. Generalized oozing from the operative site is common. To minimize the risk of hematoma formation, the bladder flap should be left open and a subfascial drain should be used for 24 to 48 hours. The wound may be left open from the level of the fascia, or a subcutaneous drain may be placed and the skin closed. All wounds that are left open can be successfully closed within 72 hours.

Management of Postpartum HELLP Syndrome

HELLP syndrome may also develop during the postpartum period. In a review of 442 women with HELLP syndrome, Sibai et al[3] noted that 133 women (30%) only had postpartum manifestation of the syndrome. In these patients, the onset of clinical manifestations ranged from a few hours to 7 days; most clinical manifestations developed within 48 hours postpartum. Twenty-seven women (20%) had no evidence of preeclampsia before or during delivery. These women had increased blood pressure, proteinuria, and *de novo* laboratory abnormalities after delivery. Women with these signs are at increased risk for pulmonary edema and acute renal failure.

The management of patients with postpartum

HELLP syndrome is similar to the management of antepartum women with HELLP syndrome, including the need for antiseizure prophylaxis. Attempts to control hypertension may be more aggressive in patients with postpartum HELLP syndrome because compromising uteroplacental circulation is not a concern. The signs and symptoms of postpartum HELLP syndrome may share similar characteristics and overlap with several common obstetric and surgical disorders (Table 2).

In general, platelet counts may continue to decrease for the first few days after delivery. This drop is more marked following cesarean delivery and hypotension or after postpartum hemorrhage, and this decrease may continue for several days in some women. Platelet transfusions are unnecessary in such women except in the presence of significant maternal bleeding. The recovery of platelet counts to levels greater than 100,000/mm^3 may take several days and is usually related to the degree of thrombocytopenia. In contrast, maternal levels of aspartate transaminase and lactate dehydrogenase demonstrate improvement within 48 to 72 hours after delivery, except in women who sustain hypotensive episodes or require transfusions for postpartum hemorrhage.

Management of Delayed Resolution of HELLP Syndrome

The management of women with delayed resolution of HELLP syndrome, including persistent severe thrombocytopenia, is a clinical dilemma. Exchange plasmapheresis with fresh frozen plasma has been advocated as a treatment by some authors.[7,8] However, because most women with HELLP syndrome have spontaneous resolution of the disease, early initiation of plasmapheresis may be an unnecessary therapy. The question remains regarding how many women would spontaneously improve without the benefit of plasmapheresis. In the experience of these authors, all women demonstrate spontaneous resolution of HELLP syndrome without plasmapheresis.

MATERNAL OUTCOME AND COUNSELING

Pregnancies complicated by HELLP syndrome are associated with increased maternal mortality and morbidity. The reported maternal mortality rate ranges from 0% to 24%. Of the patients managed at the University of Tennessee Division of Maternal-Fetal Medicine by these authors during the past 15 years, five patients died among 442 patients with HELLP syndrome.[3] In addition, patients with HELLP syndrome are at increased risk for DIC, abruptio placentae, acute renal failure, pulmonary edema and pleural effusions, acute respiratory distress syndrome, liver infarcts, and ruptured liver hematomas. Thus, the development of HELLP syndrome in association with any of the previously mentioned complications is a frightening experience for both the patient and her family members. As a result, the managing obstetrician must be prepared to counsel these patients about the outcome in future pregnancies as well as any potential effects from HELLP syndrome or its complications.

Future Obstetric Complications

Women with HELLP syndrome should be considered at increased risk for obstetric complications (eg, preterm delivery, intrauterine growth retardation, abruptio placentae, perinatal death) in subsequent pregnancies. A study by Sibai et al,[9] however, showed that the risk of recurrent HELLP syndrome is only 4%. This study included longitudinal data on 341 women with HELLP syndrome in the index pregnancy. The findings of Sibai et al[9] are in contrast with Sullivan et al[10] who reported a recurrence risk of 25%. This difference in recurrence risk between these two studies may be attributed in part to the differences in the definition of the syndrome or in the populations studied. In addition, two patients who had ruptured liver hematomas had three subsequent pregnancies without complications. These findings should be used when counseling women who are considering future pregnancies.

The authors of this article recently studied 23 women with pure preeclampsia complicated by HELLP syndrome and acute renal failure (33% of these patients required dialysis). These women were followed for an average of 4.6 years and all patients had normal blood pressures and renal function on follow-up.[11]

Future Use of Oral Contraceptives

In another study by Sibai et al[9] of 98 women who were receiving oral contraceptive for varying periods of time, none had clinical or laboratory findings consistent with thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, or HELLP syndrome. Thus, the study concluded that there is no evidence that oral contraceptives are contraindicated after HELLP syndrome.[9]

SUMMARY

HELLP syndrome is a life-threatening complication of pregnancy. Optimal maternal and fetal outcome are dependent on prompt recognition and treatment of the disease process. **HP**

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