Diagnosis, Controversies, and Management of the Syndrome of Hemolysis, Elevated Liver Enzymes, and Low Platelet Count

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Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome has been recognized as a complication of preeclampsia–eclampsia for decades. Recognition of this syndrome in women with preeclampsia is increasing because of the frequency of blood test results that reveal unexpected thrombocytopenia or elevated liver enzymes. The diagnosis of HELLP syndrome requires the presence of hemolysis based on examination of the peripheral smear, elevated indirect bilirubin levels, or low serum haptoglobin levels in association with significant elevation in liver enzymes and a platelet count below 100,000/mm^3 after ruling out other causes of hemolysis and thrombocytopenia. The presence of this syndrome is associated with increased risk of adverse outcome for both mother and fetus. During the past 15 years, several retrospective and observational studies and a few randomized trials have been published in an attempt to refine the diagnostic criteria, to identify risk factors for adverse pregnancy outcome, and to treat women with this syndrome. Despite the voluminous literature, the diagnosis and management of this syndrome remain controversial. Recent studies suggest that some women with partial HELLP syndrome may be treated with expectant management or corticosteroid therapy. This review will emphasize the controversies surrounding the diagnosis and management of this syndrome. Recommendation for diagnosis, management, and counseling of these women is also provided based on results of recent studies and my own clinical experience. (Obstet Gynecol 2004;103:981–91. © 2004 by The American College of Obstetricians and Gynecologists.)

We have invited select authorities to present background information on challenging clinical problems and practical information on diagnosis and treatment for use by practitioners.

Intravascular hemolysis, elevated liver function tests, and thrombocytopenia have been described in women with severe preeclampsia–eclampsia for many decades.[1] In addition, physicians have recognized that the presence of these abnormalities is associated with adverse maternal outcome for the past 50 years.[2–4] In 1982, Weinstein[5] described 29 cases of severe preeclampsia–eclampsia complicated by thrombocytopenia, abnormal peripheral blood smear, and abnormal liver function test results. He suggested that this collection of laboratory abnormalities constituted an entity separate from traditional severe preeclampsia and coined the term HELLP syndrome (H = hemolysis; EL = elevated liver enzymes; and LP = low platelets). Since then, numerous reports claiming to describe this syndrome have appeared in the medical literature. In 1990, Sibai[1] reported that there is considerable disagreement in the medical literature regarding the terminology, incidence, diagnosis, and management of the HELLP syndrome During the past 15 years, numerous retrospective and observational studies as well as few randomized trials have been published in an attempt to refine the diagnostic criteria for this syndrome, to identify risk factors for adverse pregnancy outcome, and to reduce maternal and perinatal outcomes in women with this syndrome. Despite this recent literature, the diagnosis, management, and pregnancy outcome of HELLP syndrome remain controversial. In this review, I will describe the pathogenesis, diagnosis, and management of this syndrome based on data derived from the literature and from my own experience of treating more than 700 women with severe preeclampsia and eclampsia complicated by the HELLP syndrome.[6–8]

LABORATORY CRITERIA FOR DIAGNOSIS

The diagnostic criteria used for HELLP syndrome are variable and inconsistent. Hemolysis, defined as the presence of microangiopathic hemolytic anemia, is the hallmark of the triad of HELLP syndrome.[1] The classic findings of microangiopathic hemolysis include abnormal peripheral smear (schistocytes, burr cells, echinocytes), elevated serum bilirubin (indirect form), low serum haptoglobin levels, elevated lactate dehydrogenase (LDH) levels, and significant drop in hemoglobin levels. A significant percentage of published reports included patients who had no evidence of

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hemolysis; hence, these patients will fit the criteria for ELLP syndrome.[9–15] Even in studies in which hemolysis was mentioned, the diagnosis was based on the presence of abnormal peripheral smear (no description of type or degree of abnormalities)[16,17] or elevated LDH levels (threshold of 180–600 U/L).[18–23]

There is no consensus in the literature regarding whether the liver function test should be used or what degree of elevation in these test results should be used to diagnose elevated liver enzymes.[1] In the original report by Weinstein,[5] he mentioned abnormal serum levels of aspartate transaminase (AST), abnormal alanine transferase (ALT), and abnormal bilirubin values; however, levels were not stated. In addition, he made no mention of LDH as a diagnostic test of liver involvement. In subsequent studies in which elevated liver enzymes were mentioned (either AST or ALT), the values considered abnormal ranged from 17 to 72 U/L.[1] In clinical practice, many of these values are considered normal or slightly elevated. In essence, some of these studies included women with low platelets syndrome. Some of these women may have had severe preeclampsia with thrombocytopenia, gestational thrombocytopenia, or immune thrombocytopenic purpura.

Low platelet count is the third abnormality required to establish the diagnosis of HELLP syndrome. There is no consensus among various published reports regarding the diagnosis of thrombocytopenia. The reported cutoff values range from 75,000/mm^3 to 279,000/mm^3.[9–18] Therefore, some of the patients included in these studies will fit the criteria for "EL" (elevated liver enzymes) syndrome. In essence, these women had severe preeclampsia with mild elevation in liver enzymes.[10,12]

Despite well-intentioned efforts at making laboratory diagnosis of HELLP syndrome based on elevations in AST, ALT, LDH, and the presence of hemolysis, substantial interlaboratory differences remain a major problem. This is due in part to the different number of assays used to measure these tests as well as to the cutoff used to establish an abnormal test. Some studies used the upper limit for a particular test at their hospital laboratory, some used 2 standard deviations above the mean for that laboratory, whereas others used more than 2 times the upper limit in their laboratory. Therefore, clinicians should be familiar with the upper limit value for liver enzyme tests in their own laboratory when making the diagnosis of HELLP syndrome. For example, the upper limit for an LDH may range from 180 to 618 U/L depending on the assay being used. This is particularly important for patients referred from level I hospitals to tertiary care facilities where different assays are used to measure these tests.

Many authors[13–15,18–23] have used elevated total LDH (usually more than 600 U/L) as a diagnostic criterion for hemolysis. There are 5 different isoforms of LDH, and only 2 of them, LDH_1 and LDH_2, are released from ruptured red blood cells. In the majority of women with severe preeclampsia–eclampsia, the elevation in total LDH is probably caused mostly by liver ischemia. Therefore, many authors advocate that elevated bilirubin values (indirect form), abnormal peripheral smear, or a low serum haptoglobin level should be part of the diagnostic criteria for hemolysis.[1,5,24–27]

Time of Onset and Maternal Condition at Diagnosis

Another point of confusion includes the time of onset and the clinical condition of the patient at the time of diagnosis of the syndrome. Some studies included patients who had the abnormalities on admission,[1–6,24–26] others included patients who developed the abnormalities during expectant management of preeclampsia remote from term,[10–12,16] and others included patients who developed the abnormalities in the postpartum period.[6,20–23,28–30] Even among the latter group, some had preeclampsia before delivery, some had no clinical evidence of preeclampsia before delivery, some were diagnosed during the first 48 hours postpartum,[20–23,29,30] and others were diagnosed for the first time at or beyond 3 days postpartum.[6,28] It is important to recognize that maternal and perinatal outcomes of women who are referred to a tertiary care facility because of HELLP syndrome (usually remote from term or complicated cases) are expected to be different from the respective outcome in women who had the diagnosis made because of serial evaluation of liver enzymes and platelet count during expectant management of preeclampsia. In addition, both maternal and perinatal outcomes are expected to be substantially worse in those patients in whom HELLP syndrome develops in the second trimester and who require emergency cesarean delivery because of nonreassuring fetal testing than in women in whom severe preeclampsia develops at term and have spontaneous vaginal delivery and subsequently had the diagnosis of HELLP syndrome made because of frequent evaluation of liver enzymes and platelet count during labor and immediately postpartum.

CLINICAL FINDINGS

One of the major problems with early detection of HELLP syndrome lies in its clinical presentation, because patients may present with nonspecific symptoms or subtle signs of preeclampsia. Patients with this syndrome may present with various signs and symptoms, none of which are diagnostic of preeclampsia and all of which may be found in patients with severe preeclampsia–eclampsia without HELLP syndrome.[1,5,9,21,24] Pa-

Table 1. Signs and Symptoms in Women With HELLP Syndrome

	Weinstein[17] (n = 57)	Sibai et al[6] and Audibert et al[7] (n = 509)	Martin et al[21] (n = 501)	Rath et al[26] (n = 50)
Right upper quadrant or epigastric pain	86	63	40	90
Nausea or vomiting	84	36	29	52
Headache	Not reported	33	61	Not reported
Hypertension	Not reported	85	82	88
Proteinuria	96	87	86	100

HELLP = hemolysis, elevated liver enzymes, and low platelets.
Data are presented as percentage.

tients frequently will have right upper quadrant or epigastric pain, nausea, or vomiting ranging in frequency from 30% to 90% (Table 1).[6,7,17,21,26] Most patients will give a history of malaise for the past few days before presentation, and some will have nonspecific viral-syndrome–like symptoms,[1] which led one investigator to suggest performing laboratory investigation (completed blood count and liver enzymes) in all pregnant women with suspected preeclampsia having these symptoms during the third trimester.[1] Headaches are reported by 33–61%[6,7,21] of the patients whereas visual changes are reported in approximately 17%.[7] A subset of patients with HELLP syndrome may present with symptoms related to thrombocytopenia such as bleeding from mucosal surfaces, hematuria, petechial hemorrhages, or ecchymosis.

Although the majority of patients will have hypertension (82–88%, Table 1), it may be only mild in 15–50% of the cases,[1–5] and absent in 12–18% (Table 1). The majority of the patients (86–100%) will have proteinuria by dipstick examination; however, it was reported to be absent in 13% of cases in the 2 largest series.[6,7,21]

DIFFERENTIAL DIAGNOSIS

The presenting symptoms, clinical findings, and many of the laboratory findings in women with HELLP syndrome overlap with a number of medical syndromes, surgical conditions, and obstetric complications. Therefore, the differential diagnosis of HELLP syndrome should include any of the conditions listed in the Box. Because some patients with HELLP syndrome may present with gastrointestinal, respiratory, or hematologic symptoms in association with elevated liver enzymes or low platelets in the absence of hypertension or proteinuria, many cases of HELLP syndrome will initially be misdiagnosed as upper respiratory infection, hepatitis, cholecystitis, pancreatitis, acute fatty liver of pregnancy, or immune thrombocytopenic purpura.[1] Conversely, some conditions such as thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, systemic lupus erythematosus sepsis, or catastrophic antiphospholipid antibody syndrome may be erroneously diagnosed as HELLP syndrome.

In addition, in some patients preeclampsia may be superimposed on one of these disorders, further contributing to the diagnostic difficulty. Because of the remarkably similar clinical and laboratory findings of these disease processes, even the most experienced physician will face a difficult diagnostic challenge. Therefore, an effort should be made to attempt to identify an accurate diagnosis given that management strategies may differ among these conditions. The clinical and laboratory findings, as well as the management of the conditions that mimic the HELLP syndrome, are beyond the scope of this report. For detailed discussion of differential diagnosis and management of these syndromes, several recent reviews have been written (Egerman RS, Sibai BM. Recognizing and managing HELLP syndrome and its imitators. Contemp Ob Gyn 1997; October:129–49).[31–34]

Differential Diagnosis in Women With HELLP Syndrome

Acute fatty liver of pregnancy (AFLP)
Thrombotic thrombocytopenic purpura (TTP)
Hemolytic uremic syndrome (HUS)
Immune thrombocytopenic purpura (ITP)
Systemic lupus erythematosus (SLE)
Antiphospholipid syndrome (APS)
Cholecystitis
Fulminant viral hepatitis
Acute pancreatitis
Disseminated herpes simplex
Hemorrhagic or septic shock

MATERNAL AND PERINATAL OUTCOME

The presence of HELLP syndrome is associated with an increased risk of maternal death (1%)[6,7,23] and increased rates of maternal morbidities such as pulmonary edema

(8%),[7,21] acute renal failure (3%),[7,21] disseminated intravascular coagulopathy (DIC, 15%),[7] abruptio placentae (9%),[7] liver hemorrhage or failure (1%), adult respiratory distress syndrome (ARDS), sepsis, and stroke (< 1%).[7,21] Pregnancies complicated by HELLP syndrome are also associated with increased rates of wound hematomas and the need for transfusion of blood and blood products.[1–8,21,23] The rate of these complications will depend on the population studied, the laboratory criteria used to establish the diagnosis, and the presence of associated preexisting medical conditions (chronic hypertension, lupus) or obstetric complications (abruptio placentae, peripartum hemorrhage, fetal demise, eclampsia). The development of HELLP syndrome in the postpartum period also increases the risk of renal failure and pulmonary edema.[35,36] The presence of abruptio placentae increases the risk of DIC, need for blood transfusions, pulmonary edema, and renal failure.[6,8,35,36] Patients who have large volume ascites will have a high rate of cardiopulmonary complications.[37] Finally, patients who meet all the criteria reported by the author will have higher rates of maternal complications than those who have partial HELLP or elevated liver enzymes only.[7]

There is general agreement that perinatal mortality and morbidities are substantially increased in pregnancies complicated by the HELLP syndrome. The reported perinatal death rate in recent series ranged from 7.4% to 20.4%.[21,25,38–40] This high perinatal death rate is mainly experienced at very early gestational age (less than 28 weeks), in association with severe fetal growth restriction or abruptio placentae.[38–40] It is important to emphasize that neonatal morbidities in these pregnancies are dependent on gestational age at time of delivery and they are similar to those in preeclamptic pregnancies without the HELLP syndrome.[25,38–40] The rate of preterm delivery is approximately 70%, with 15% occurring before 28 weeks of gestation.[6,25,33,39] As a result, these infants have a high rate of acute neonatal complications such as respiratory distress syndrome, bronchopulmonary dysplasia, intracerebral hemorrhage, and necrotizing enterocolitis.[38]

EXPECTANT MANAGEMENT OF (H)ELLP SYNDROME

The clinical course of women with true HELLP syndrome is usually characterized by progressive and sometimes sudden deterioration in the maternal condition.[6,21] Because the presence of this syndrome has been associated with increased rates of maternal morbidity and mortality, some authors consider its presence an indication for immediate delivery.[5,26] There is also a consensus of opinion that prompt delivery is indicated if the syndrome develops beyond 34 weeks of gestation, or earlier if there is multiorgan dysfunction, DIC, liver infarction or hemorrhage, renal failure, suspected abruptio placentae, or nonreassuring fetal status.[6,8]

However, there is considerable disagreement about the treatment of women with HELLP syndrome at or before 34 weeks of gestation when the maternal condition is stable except for mild-to-moderate abnormalities in blood test results and a reassuring fetal condition. In such patients, some authors recommend the administration of corticosteroids to accelerate fetal lung maturity followed by delivery after 24 hours,[1,13,14,19] whereas others recommend prolonging pregnancy until the development of maternal or fetal indications for delivery or until achievement of fetal lung maturity or 34 weeks of gestation.[11,12,16,25,40] Some of the measures used in these latter cases have included one or more of the following: bed rest, antihypertensive agents, chronic parenteral magnesium sulfate, antithrombotic agents (low-dose aspirin, dipyridamole), plasma volume expanders (crystalloids, albumin, fresh frozen plasma), and steroids (prednisone, dexamethasone, or betamethasone).

There are few case reports and few large case series describing expectant management of women with true HELLP, partial HELLP, or severe preeclampsia with elevated liver enzymes only.[9–12,16,25,40] In general, these reports suggest that transient improvement in laboratory values or pregnancy prolongation from a few days to a few weeks is possible in a select group of women with "HELLP" syndrome. It is important to note that most of the patients included in these studies were delivered within a week after expectant management.

Recently, investigators from the Netherlands reported that expectant management is possible in women with "HELLP" syndrome before 34 weeks of gestation. Visser and Wallenburg[25] reported the use of plasma volume expansion utilizing invasive hemodynamic monitoring and vasodilators in 128 women with HELLP syndrome before 34 weeks of gestation. Magnesium sulfate and steroids were not used in such women. Twenty-two of the 128 patients were delivered within 48 hours; the remaining 102 patients had pregnancy prolongation for a median of 15 days (range, 3–62 days). Fifty-five of these 102 women had antepartum resolution of HELLP syndrome with a median pregnancy prolongation of 21 days (range, 7–62 days). There were no maternal deaths or serious maternal morbidity; however, 11 pregnancies (8.6%) resulted in fetal death at 25–34.4 weeks of gestaion, and there were 7 (5.5%) neonatal deaths at 27–32 weeks of gestation.[25]

Van Pampus et al[39] reported the use of bed rest, antihypertensive medication, and salt restriction in 41 women with HELLP syndrome before 35 weeks of

gestation. Fourteen women (34%) were delivered within 24 hours; in the remaining 27 women, pregnancy was prolonged a median of 3 days (range, 0–59 days). Fifteen of these 27 women showed complete normalization of the laboratory abnormalities. There were no serious maternal morbidities; however, there were 10 fetal deaths at 27–35.7 weeks of gestation.

The results of these studies suggest that expectant management is possible in a very select group of patients with alleged HELLP syndrome before 34 weeks of gestation. However, despite pregnancy prolongation in some of these cases, the overall perinatal outcome was not improved compared with cases at similar gestational age who were delivered within 48 hours after the diagnosis of HELLP syndrome.[38] Therefore, such management remains experimental in absence of randomized trials.

USE OF CORTICOSTEROIDS TO IMPROVE PREGNANCY OUTCOME IN WOMEN WITH HELLP SYNDROME

It is well established that antenatal glucocorticoid therapy reduces neonatal complications and neonatal mortality in women with severe preeclampsia at or before 34 weeks of gestation.[41] The recommended regimens of corticosteroids for the enhancement of fetal maturity are betamethasone (12 mg intramuscularly every 24 hours, 2 doses) or dexamethasone (6 mg intramuscularly every 12 hours, 4 doses).[42] These regimens have been identified as the most appropriate for this purpose because they readily cross the placenta and have minimal mineralocorticoid activity. However, it is unclear whether the same or different regimens are safe and effective in women with HELLP syndrome.

Corticosteroids have been suggested as safe and effective drugs for improving maternal and neonatal outcome in women with HELLP or partial HELLP syndrome.[18–23] A review of the literature reveals substantial differences in methodology, time of administration, and drug selection among investigators who advocate the use of corticosteroids in women with HELLP syndrome. Different regimens of steroids have been suggested for preventing respiratory distress syndrome as well as to accelerate maternal recovery in the postpartum period. The regimens of steroids used included intramuscular betamethasone (12 mg/12 hours or 24 hours apart on 2 occasions) or intravenous dexamethasone (various doses at various time intervals) or a combination of the two.[13–15,18–23] Some studies used steroids in the antepartum period only (for 24 hours, 48 hours, repeat regimens, or chronically for weeks until delivery).[11,15,18,19] Those who used steroids for long intervals recommend tapering them over 4–6 weeks.[11,12] In other studies, steroids were given for 48 hours before delivery and then continued for 24–48 hours postpartum,[14,15,22,23] whereas others recommend their administration in the postpartum period only.[29,30]

There are few case reports describing the potential maternal–neonatal benefit of antenatal corticosteroid therapy in women with (H)ELLP syndrome. Heyborne et al[11] described 5 cases of HELLP syndrome at 24–30 weeks of gestation in which temporary reversal of the HELLP syndrome was achieved with low-dose aspirin and corticosteroids. However, only 1 of the 5 women had true HELLP syndrome when dexamethasone was used, and she was delivered within 48 hours of dexamethasone administration. Two of the remaining 4 women had ELLP syndrome, and the other 2 had elevated liver enzymes only (platelet counts of more than 100,000). Eclampsia with DIC developed in 1 of these 4 women, and 2 of the 5 neonates died.

Heller and Elliott[12] described 4 women with high-order multiple pregnancies complicated by ELLP syndrome who were treated with long-term corticosteroids. None of these women had hemolysis, 3 had elevated liver enzymes only (platelet count more than 100,000), and 1 had thrombocytopenia only when steroids were allegedly used to treat HELLP syndrome. Two of these women developed pulmonary edema with such therapy. The authors reported that dexamethasone resulted in stabilization of laboratory values and prolongation of gestation by 6–41 days.[12]

There are 5 randomized trials comparing the use of high-dose dexamethasone with either no treatment[19,20,29,30] or with betamethasone[43] in women who had presumed HELLP syndrome (Table 2). The results of these studies demonstrated improved laboratory values and urine output in patients receiving dexamethasone, but no differences in serious maternal morbidity. In addition, the number of patients studied was limited, and neither of these studies used a placebo.

In summary, the available evidence suggests that standard-dose corticosteroids (as recommended by the National Institutes of Health Consensus Development Panel) improve perinatal outcome when used in women with HELLP syndrome before 34 weeks of gestation.[14,19,38] In addition, in some of these women, there is transient improvement in maternal platelet counts, which makes them eligible to receive epidural anesthesia.[13,15] There is also some evidence suggesting improved laboratory values with the use of higher doses of dexamethasone in women with postpartum "HELLP" syndrome.[14,22,23,29,30] The doses of dexamethasone considered "high dose" in these reports was 10 mg of dexamethasone administered intravenously every 6 to 12 hours for 2 doses followed by 5–6-mg intravenous doses

Table 2. Randomized Trials of Corticosteroids in Women With ELLP or HELLP Syndrome

Authors	Dexamethasone (n)	Control (n)	Key finding
Magann et al[19]	12*	13	Improved platelet, ALT, LDH values in dexamethasone group
Magann et al[20]	20†	20	Improved platelet, AST, LDH, urine output, mean arterial pressure in dexamethasone group
Vigil-De Gracia[29]	17†	17	Improved platelet counts only with dexamethasone
Yalcin et al[30]	15†	15	Improved platelet, AST, mean arterial pressure and urine output with dexamethasone
Isler et al[43]	19*	21‡	Improved AST, LDH, mean arterial pressure and urine output with dexamethasone

ELLP = elevated liver enzymes and low platelets; HELLP = hemolysis, elevated liver enzymes, and low platelets; ALT = alanine amino transferase; LDH = lactic dehydrogenase; AST = aspartate amino transferase.

* Antepartum.

† Postpartum.

‡ Received intramuscular betamethasone.

given 6 to 12 hours later for 2 additional doses.[14,22,23,29,30] However, it must be emphasized that most of the patients included in these studies had partial HELLP only. In addition, none of these studies reported improvement in clinically important maternal morbidity such as the need for platelet transfusion or pulmonary, renal, or hepatic complications. Therefore, there is a definite need for placebo-controlled, randomized trials in women with postpartum HELLP syndrome. Until then, the use of high-dose dexamethasone to improve maternal outcome in women with HELLP syndrome beyond 34 weeks of gestation or in the postpartum period remains experimental.

RECOMMENDED MANAGEMENT

The clinical course of women with HELLP syndrome is usually characterized by progressive and sometimes sudden deterioration in maternal and fetal conditions. Therefore, patients in whom HELLP syndrome is suspected should be hospitalized immediately and observed in a labor and delivery unit. Such patients should be treated for severe preeclampsia and should initially receive intravenous magnesium sulfate as prophylaxis against convulsions and antihypertensive medications to keep systolic blood pressure below 160 mm Hg or diastolic blood pressure below 105 mm Hg or both.[44] This can be achieved with a 5-mg bolus dose of hydralazine, to be repeated as needed every 15–20 minutes for a maximum dose of 20 mg per hour. Blood pressure is recorded every 15 minutes during therapy and every hour once the desired values are achieved. If hydralazine does not lower blood pressure adequately or if maternal side effects such as tachycardia or headaches develop, another drug such as labetalol or nifedipine can be used.

The recommended dose of labetalol is 20–40 mg intravenously every 10–15 minutes for an hourly maximum of 220 mg, and the dose of nifedipine is 10–20 mg orally every 30 minutes for an hourly maximum dose of 50 mg. During the observation period, maternal and fetal conditions are then assessed.

The recommended regimen of magnesium sulfate is a loading dose of 6 g given over 20 minutes, followed by a maintenance dose of 2 g per hour as a continuous intravenous solution. Magnesium sulfate is initiated at the beginning of the observation period and then continued during labor and for at least 24 hours postpartum.

The next step in management is to confirm or exclude the diagnosis of HELLP syndrome from other conditions listed in the Box. Blood tests should include a complete blood count with platelet count, a peripheral smear, coagulation studies, serum AST, creatinine, glucose, bilirubin, and LDH levels. My diagnosis of HELLP syndrome requires the presence of all the following: platelet count less than 100,000/mm^3, an AST level greater than 70 IU/L (more than 2 times the upper limit of normal values), abnormal peripheral smear, and an LDH level greater 600 IU/L (more than 2 times the upper limit of normal), or bilirubin (more than 1.2 mg/dL). Those who do not have all these parameters are considered to have partial HELLP syndrome.[7]

In its early presentation, acute fatty liver of pregnancy may be difficult to differentiate from HELLP syndrome. Patients with acute fatty liver of pregnancy typically present with nausea, vomiting, abdominal pain, and jaundice; however, hypertension and proteinuria are usually absent.[31] In addition, most patients with acute fatty liver of pregnancy will have prolonged prothrombin and partial thromboplastin times with low fibrinogen and low serum glucose values (Egerman RS, et al. Contemp Ob Gyn 1997;October:129–49). These latter abnormalities (other than low glucose values) are rarely present in patients with HELLP syndrome without ab-

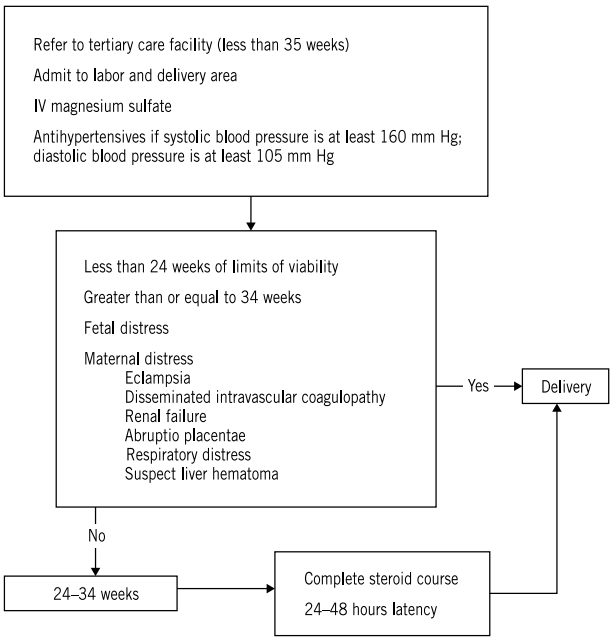

Figure 1. Management of HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome.

Sibai. Diagnosis and Management of HELLP syndrome. Obstet Gynecol 2004.

ruptio placentae (Egerman RS, et al. Contemp Ob Gyn 1997;October:129–49). Thrombotic thrombocytopenic purpura is an extremely rare condition during pregnancy characterized by neurological dysfunction, fever, severe thrombocytopenia, and severe hemolysis. These patients will usually have very low hematocrit, markedly abnormal peripheral smear, and normal or slightly elevated liver enzymes (Egerman RS, et al. Contemp Ob Gyn 1997;October:129–49). In contrast, patients with HELLP syndrome and acute fatty liver of pregnancy usually have normal-to-elevated hematocrit values and significantly higher liver enzymes values. Patients with hemolytic uremic syndrome usually present with renal failure, and most cases (95%) develop in the postpartum period (Egerman RS, et al. Contemp Ob Gyn 1997; October:129–49). Patients with immune thrombocytopenic purpura will have thrombocytopenia but rarely associated with hypertension or abnormal liver enzymes.

Once the diagnosis of HELLP syndrome is confirmed, a decision is made regarding the need for delivery (Figure 1). Patients with HELLP syndrome who are at less than 35 weeks of gestation should be referred to a tertiary care facility if the maternal condition is stable. The first priority is to assess and stabilize the maternal condition, particularly blood pressure and coagulation abnormalities. The next step is to evaluate fetal status with the use of fetal heart rate testing, biophysical profile, or Doppler assessment of fetal vessels. Finally, a decision must be made as to whether delivery should be initiated or delivery could be delayed for 48 hours for corticosteroid benefit. It is my policy to initiate delivery in all patients with true HELLP syndrome except in those with a gestational age between 24 to 34 weeks with stable maternal and fetal conditions. These latter patients are given 2 doses of either betamethasone 12 mg intramuscularly every 12 hours or dexamethasone 12 mg intravenously every 12 hours, and then delivered within 24 hours after the last dose of corticosteroids. Maternal and fetal conditions are assessed continuously during this time period. In some of these patients, there may be transient improvement in maternal laboratory tests; however, delivery is still indicated despite such improvement.

INTRAPARTUM MANAGEMENT

The presence of HELLP syndrome is not an indication for immediate cesarean delivery. Such an approach might prove detrimental for both mother and fetus. The decision to perform cesarean delivery should be based on fetal gestational age, fetal conditions, presence of labor, and cervical Bishop score. My policy is to recommend elective cesarean delivery for all women with HELLP syndrome before 30 weeks of gestation who are not in labor and whose Bishop score is below 5. I also recommend elective cesarean delivery to those with HELLP syndrome plus fetal growth restriction and/or oligohydramnios if the gestational age is below 32 weeks in the presence of an unfavorable cervical Bishop score.

Patients having labor or rupture of membranes are allowed to deliver vaginally in the absence of obstetric complications. When labor is indicated, it is initiated with either oxytocin infusions or prostaglandins in all patients with a gestational age at or above 30 weeks, irrespective of the extent of cervical dilatation or effacement. A similar approach is used for those at or before 30 weeks of gestation if the cervical Bishop score is at least 5.

Maternal pain relief during labor and delivery can be provided by intermittent use of small doses of systemic opioids. Local infiltration anesthesia can be used for all vaginal deliveries in case of episiotomy or laceration repair. The use of pudendal block is contraindicated in these patients because of the risk of bleeding and hematoma formation into this area. Epidural anesthesia is also contraindicated, particularly if the platelet count is less than 75,000/mm^3. Therefore, general anesthesia is the method of choice for cesarean delivery in such patients. O'Brien et al[15] assessed the impact of glucocorticoid administration on the rate of epidural anesthesia use in 37 women with partial HELLP syndrome who had a platelet count below 90,000/mm^3 before steroid administration. The authors found that administration of corticosteroids in these patients increased the rate of epi-

Table 3. Pregnancy Outcome After HELLP

	Normotensive women			
	Women (n)	Pregnancies (n)	HELLP (%)	Preeclampsia (%)
Sibai et al[47]	139	192	3	19
Sullivan et al[45]	122	161	19	23
Van Pampus et al[49]	77	92	2	16
Chames et al[50]*	40	42	6	52

HELLP, hemolysis, elevated liver enzymes, and low platelets.
* HELLP at or before 28 weeks of gestation in a previous pregnancy.

dural anesthesia use, particularly in those who achieved a latency period of 24 hours before delivery (8 of 14 in steroid group versus 0 of 10 in no steroids, $P = .006$).[15]

Platelet transfusions are indicated either before or after delivery in all patients with HELLP syndrome in the presence of significant bleeding (ecchymosis, bleeding from gums, oozing from puncture sites, wound, intraperitoneal, etc.), and in all those with a platelet count of less than 20,000/mm^3. Repeated platelet transfusions are not necessary because of the short half-life of the transfused platelets in such patients. Correction of thrombocytopenia is also important before any surgery. My policy is to administer 6 U of platelets in all patients with a platelet count less than 40,000/mm^3 before intubation if cesarean delivery is needed. Generalized oozing from the surgical site can occur during surgery or in the immediate postpartum period because of the continued drop in platelet count in some of these patients. The risk of hematoma formation at these sites is approximately 20%. Therefore, my policy is to use a subfascial drain and to keep the skin incision open for at least 48 hours in all patients requiring cesarean delivery.[1]

POSTPARTUM MANAGEMENT

After delivery, patients with HELLP syndrome should receive close monitoring of vital signs, fluid intake and output, laboratory values, and pulse oximetry for at least 48 hours. My policy is to continue intravenous magnesium sulfate prophylaxis for 48 hours, and to use antihypertensive drugs if the systolic blood pressure is at least 155 mm Hg or if the diastolic pressure is at least 105 mm Hg. In general, the majority of patients will show evidence of resolution of the disease process within 48 hours after delivery. However, some patients, especially those with abruptio placentae plus DIC, those with severe thrombocytopenia (platelet count less than 20,000/mm^3), and those with severe ascites or significant renal dysfunction may show delayed resolution or even deterioration in their clinical condition.[35–37] Such patients are at risk of the development of pulmonary edema from transfusion of blood and blood products, fluid mobilization, and compromised renal function. These patients are also at risk of acute tubular necrosis and need for dialysis,[35,36] and may require intensive monitoring for several days. Some authors suggested that such patients might benefit from plasmapheresis or plasma transfusions.[28] However, my experience indicates that these patients will recover with supportive therapy only.

The clinical and laboratory findings of HELLP syndrome may develop for the first time in the postpartum period.[6,22,23] In these patients, the time of onset of the manifestations ranges from a few hours to 7 days, with the majority developing within 48 hours postpartum.[6] Hence, all postpartum women and health care providers should be educated and be aware of the signs and symptoms of HELLP syndrome. The treatment of patients with postpartum HELLP syndrome should be similar to that in the antepartum period, including the use of magnesium sulfate. The differential diagnosis in these patients should include many of the conditions listed in the Box.

Some authors recommend the administration of high-dose dexamethasone for patients with postpartum HELLP syndrome.[22,23,29,30] These authors suggest that such therapy results in accelerated recovery and shorter hospital stay as compared with a historical group not receiving such therapy. My policy is not to give dexamethasone to such patients because such therapy remains experimental.

SUBSEQUENT PREGNANCY OUTCOME AND REMOTE PROGNOSIS

Pregnancies complicated by HELLP syndrome may be associated with life-threatening complications for both the mother and her infant. Therefore, clinicians should be able to answer questions regarding subsequent pregnancy outcome and long-term prognosis. Women with a history of HELLP syndrome are at increased risk of all forms of preeclampsia in subsequent pregnancies (Table 3). In general, the rate of preeclampsia in subsequent pregnancies is approximately 20%, with significantly higher rates if the onset of HELLP syndrome was in the

second trimester. The rate of recurrent HELLP syndrome ranges from 2% to 19%. My policy is to give these women a recurrence risk of less than 5%.[46–48] Because of these risks, these women are informed that they are at increased risk for adverse pregnancy outcome (preterm delivery, fetal growth restriction, abruptio placentae, and fetal death) in subsequent pregnancies. Therefore, they require close monitoring during subsequent gestations. Currently, there is no preventive therapy for recurrent HELLP syndrome. Liver function tests were studied in 54 women at a median of 31 months (range 3–101 months) after pregnancies complicated by HELLP syndrome.[49] Serum levels of AST, LDH, and conjugated bilirubin were found to be normal. However, total bilirubin levels were elevated in 11 (20%) of the studied women. The authors of this report suggested the possibility that a dysfunction of the bilirubin-conjugating mechanism represents a risk factor for the development of this syndrome.[49]

There are 2 reports describing long-term renal function after HELLP syndrome.[36,50] One of the reports included 23 patients whose pregnancies were complicated by HELLP syndrome and acute renal failure: 8 of these women had 11 subsequent pregnancies, with 9 resulting in term gestation.[35] All 23 women also had normal blood pressures and renal function at an average follow-up of 4.6 years (range 0.5–11 years). The other study compared renal function after at least 5 years after HELLP syndrome in 10 patients with the respective findings in 22 patients with previous normotensive gestation.[50] There were no differences in renal function tests between the 2 groups. These findings suggest that the development of HELLP syndrome with or without renal failure does not affect long-term renal function.

SUMMARY

The presence of HELLP syndrome is associated with life-threatening maternal and fetal complications. Despite the voluminous literature on this subject, there is an urgent need for a uniform definition and diagnostic criteria for this syndrome. Pregnancies complicated by this syndrome require a well-formulated management plan. The potential benefits of expectant management in those remote from term and the use of corticosteroids to improve maternal outcome remain experimental.

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