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HELLP Syndrome: The State of the Art

Jason K. Baxter, MD,* and Louis Weinstein, MD†

*Clinical Instructor, Department of Obstetrics and Gynecology, Fellow, Division of Maternal–Fetal Medicine, †Paul A. and Eloise B. Bowers Professor and Chairman of Obstetrics and Gynecology, Thomas Jefferson University, Philadelphia, Pennsylvania

Preeclampsia/eclampsia has been recognized for centuries and continues to plague both the patient and the obstetrician. A severe variant, the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP), has been recognized for 50 years. Although much new data has been elucidated about the condition, only several observations have withstood the test of time. These are the uniqueness of the disease to humans, the progressive nature of the disease, and the fact that delivery is the sole therapy.

Target Audience: Obstetricians & Gynecologists, Family Physicians

Learning Objectives: After completion of this article, the reader should be able to outline the history of HELLP syndrome and describe the pathophysiology of HELLP syndrome, to summarize the clinical presentation and differential diagnosis of HELLP syndrome, and to list the various management options.

The association between hemolysis, thrombocytopenia, and liver dysfunction was first described in association with a severe form of preeclampsia 50 years ago. In 1954, Pritchard and colleagues described 3 cases of eclampsia associated with intravascular hemolysis, thrombocytopenia, and clotting defects, including evidence of hepatic dysfunction in 2, with only 1 survivor (1). In 1972, McKay reviewed 4 cases of the syndrome occurring in eclamptic patients, including 2 liver ruptures and 1 maternal death (2). Kitzmiller et al.'s review of the coagulation system in 31 patients with preeclampsia noted significant thrombocytopenia in 4 patients, 3 of whom had evidence of microangiopathic hemolytic anemia (3). In 1975, Killam et al. reported 5 cases of preeclampsia with classic hemolysis, elevated liver enzymes, and low platelet syndrome. They concluded that the entity was more common than realized, prompt delivery is mandated regardless of gestational age, and hypertension does not have to be severe to see the hemolysis, elevated liver enzymes, and low platelet syndrome (4). Pritchard et al.'s 1976 report of 95 cases of eclampsia noted that 29% had thrombocytopenia and 2% had overt hemolysis. They concluded that the coagulation changes in these patients were markedly different than that seen in patients who experience a thromboplastin release (5). Goodlin has reported 16 patients with severe preeclampsia, thrombocytopenia, and abnormal liver enzymes. He called severe preeclampsia "another great imitator," because all of those patients were misdiagnosed as having disorders unrelated to pregnancy (6). In a later report, Goodlin et al. described 8 patients with thrombocytopenia and abnormal liver enzymes with a perinatal mortality rate of 44% (7).

The term HELLP syndrome, an acronym for hemolysis, elevated liver enzymes, and low platelets, was first coined by Weinstein in 1982 (8). He initially presented a series of 29 patients evaluated over

Address correspondence to: Jason K. Baxter, MD, Suite 400, 834 Chestnut Street, Philadelphia, PA 19107. E-mail: Jason.Baxter@jefferson.edu.

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30 months with the disorder, and then followed up with a series of 57 patients who presented with the syndrome at a single center over 5 years (9). HELLP syndrome was initially proposed as the sixth criterion that independently constituted a diagnosis of severe preeclampsia. HELLP syndrome was termed a severe variant of preeclampsia, part of the spectrum of the disease process involved in preeclampsia/eclampsia. Although others have argued against the existence of such an entity as HELLP syndrome, that it is only preeclampsia associated with a coexisting medical or surgical condition (10,11), it is now widely accepted that HELLP syndrome is a clinical entity that obstetricians must know how to recognize and treat in a similar manner to severe preeclampsia.

PATHOPHYSIOLOGY

Preeclampsia has been called the disease of theories, and as a severe variant of that disease, the etiology of HELLP syndrome remains elusive. Preeclampsia is a disease whose clinical findings usually manifest in the second half of pregnancy and is associated with incomplete trophoblastic invasion of the maternal vessels early in pregnancy. Preeclampsia and HELLP syndrome are associated with endothelial injury, fibrin deposition in the vessel lumen, and increased platelet activation with platelet consumption. Platelet activation results in the release of thromboxane A_2 and serotonin, both vasoconstrictors. Platelet aggregation damages the endothelium and impairs the production of prostacyclin, a potent vasodilator. The alteration of the prostacyclin/thromboxane A_2 ratio is present in preeclampsia and is altered by delivery.

Hemolysis

Hemolysis, defined as the presence of microangiopathic hemolytic anemia, is a hallmark of HELLP syndrome. It is confirmed by the sensitive, but not specific, observation of burr cells (crenated, contracted, distorted red blood cells with spiny projections along the periphery), schistocytes (small, irregularly shaped red blood cell fragments), and polychromasia on peripheral blood smear examination. Red blood cell fragmentation occurs secondary to passage through small blood vessels with intimal damage and fibrin deposition. Hemolysis is more common than realized, as automated technology has resulted in a decrease of manual examination of peripheral smears. Lactic dehydrogenase levels and measurements of indirect bilirubin have also been used as additional markers of evidence for hemolysis.

Liver

The classic hepatic lesion associated with HELLP syndrome is periportal or focal parenchymal necrosis, in which hyaline deposits of fibrin-like material can be seen in the hepatic sinusoids. The fibrin obstruction of the hepatic sinusoids causes hepatocellular injury, which is manifested by elevated liver enzymes and pain localized to the right upper quadrant or midepigastric region. Swelling of the liver with distension of Glisson's capsule causes pain. With a continued increase in intrahepatic pressure and the presence of subcapsular hematomas, the ability of Glisson's capsule to distend is exceeded and the patient experiences rupture of the liver.

A debate has ensued regarding the differences between HELLP syndrome and acute fatty liver of pregnancy (AFLP). Minakami et al. reviewed 41 liver specimens taken from 41 preeclamptic women and showed the importance of staining with oil red O to show microvesicular fat droplets in the hepatocytes that do not show with the usual hematoxylin–eosin stain. The authors concluded that it was impossible to differentiate histologically among AFLP, HELLP syndrome, and preeclampsia, suggesting that they are all variants of the same disorder (12). Barton and colleagues studied liver biopsies taken at the time of cesarean section from 11 patients with HELLP syndrome. They showed no correlation between the severity of the histologic findings and the clinical laboratory findings (13).

Platelets

The decrease in circulating platelets is secondary to an increased rate of consumption at the sites of the damaged vascular endothelium. Often this is an early finding in the development of preeclampsia (14). Bone marrow aspiration demonstrates an increased number of megakaryocytes and circulating megakaryocytes are noted. The resultant thrombocytopenia is secondary to increased platelet turnover, reduced mean platelet lifespan, and adherence of platelets to exposed collagen at damaged vascular sites. These patients do not have clinical disseminated intravascular dissemination (DIC), and coagulation studies are not needed for clinical management of the patient with severe preeclampsia unless an abruption or other complicated clinical condition is present.

DIAGNOSIS

Incidence

The incidence of HELLP syndrome among patients with severe preeclampsia or eclampsia has a range of 10% to 20% (15). When preeclampsia is present, the incidence of HELLP syndrome varies from 2% to 12% (16).

Clinical Presentation

In the 2 largest series from the Universities of Tennessee and Mississippi, the majority of patients with HELLP syndrome were black, young, and nulliparous (15,17). A higher percentage were white, multiparous, and older (25 years old vs. 19 years old) when compared with the baseline population of patients with severe preeclampsia (18). The onset of symptoms occurs in the majority (67%) of patients during the early third trimester (27–37 weeks). Approximately 25% of patients demonstrate the disease for the first time in the postpartum period, many of whom (79%) have had an antepartum diagnosis of preeclampsia.

The clinical presentation is variable with symptoms of malaise, fatigue, and nonspecific complaints reported by 90% of patients. Each of the individual symptoms of nausea with or without vomiting, headaches, abdominal pain, and edema are seen in more than half of the patients presenting with HELLP syndrome. Although approximately two thirds of patients with HELLP syndrome present with blood pressure >160/110 mm Hg, others have blood pressures in the range of 140–160/90–110 mm Hg, and a minority (15%) have diastolic blood pressure <90. Proteinuria of 2+ or more on dipstick is present in 85% of patients with 1+ proteinuria seen in 9% and none in 6% (18). Clinicians must be aware that HELLP syndrome can occur in patients with normal or minimally elevated blood pressures and no proteinuria. It has been suggested to check a complete blood with platelet count and liver enzymes in any pregnant patient presenting with right upper quadrant or epigastric pain (18).

Laboratory Presentation

Various investigators have defined HELLP syndrome differently. Confusion regarding terminology and diagnosis, and a lack of consensus regarding which liver function tests and what extremes of divergence from normal should be used to diagnose the syndrome, hampered earlier study of the syndrome. Martin et al. defined hemolysis as evidenced by a falling hematocrit, lactic dehydrogenase (LDH) >164, or a bleeding diathesis, elevated liver enzymes as evidenced by an AST >48 and ALT >24, and thrombocytopenia as platelets <100 K (17). These investigators at the University of Mississippi have also divided the diagnosis of HELLP syndrome into classes based on the severity of the thrombocytopenia (19). Platelets less than or equal to 50 K constitutes class 1, between 50 and 100 K class 2, and greater than 100 K class 3. We do not agree with this classification because class 3 (platelets over 100 K) is not consistent with most definitions of HELLP syndrome. The definition used at the University of Tennessee in Memphis defined HELLP syndrome as hemolytic anemia (LDH >600 U/L), elevated liver enzymes (AST >70 U/L), and thrombocytopenia (PLTS <100 K) (18). The level of abnormal liver enzymes was set at >3 standard deviations over the laboratory's mean.

PARTIAL HELLP SYNDROME

Patients that have manifested 1 or 2, but not all 3, of the components of HELLP syndrome test the decision-making ability of the clinician. Audibert et al. have demonstrated that the prognosis and outcome for "partial," or evolving, HELLP syndrome is better than that seen with complete HELLP syndrome (20). The evolving picture of HELLP syndrome follows that of preeclampsia, whereby the natural progression of the disease is to worsen over time. Although conservative management of preeclampsia may be appropriate, the diagnosis of severe preeclampsia should prompt efforts toward an expeditious delivery.

DIFFERENTIAL DIAGNOSIS

Preeclampsia and HELLP syndrome have been misdiagnosed as other disease processes. The concept of preeclampsia as "another great imitator" was presented in 1975. Preeclampsia and probable HELLP syndrome were misdiagnosed as viral hepatitis, cholangitis, systemic lupus erythematous, immune thrombocytopenic purpura (ITP), detached retina, and gastric ulcer (6). Since the term HELLP syndrome has been coined and recognized as a clinical entity, it continues to be both over- and underdiagnosed. Goodlin presented 11 case histories of significant medical and surgical problems initially diagnosed as HELLP syndrome or preeclampsia. These included misdiagnosed cases of actual cardio-

myopathy, dissecting aortic aneurysm, cocaine abuse, chronic renal disease, acute fatty liver, gangrenous gallbladder, ruptured bile duct, glomerulonephritis, immune thrombocytopenia, systemic lupus erythematous, and pheochromocytoma (21). In these cases, delivery may actually aggravate the clinical course of the patient's illness, and appropriate therapy may be delayed while dealing with the maternal condition.

It has been suggested that severe preeclampsia, HELLP syndrome, pregnancy-associated hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), acute fatty liver of pregnancy (AFLP), and postpartum acute renal failure are diseases that are part of a spectrum of the same illness. Endothelial cell injury, with subsequent vasospasm, platelet activation, altered prostacyclin–thromboxane ratio, and decreased release of endothelium-derived relaxing factor, play a central role in the pathogenesis of each of these conditions (22). A full discussion of how to differentiate amongst these disorders is beyond the scope of this review.

MORTALITY AND MORBIDITY

Mortality rates vary from 0% to 24%. In a review of 54 maternal deaths associated with HELLP syndrome, a delay in diagnosis was noted in 51% with one third the result of patient delay, and the other two thirds resulting from delay in physician diagnosis. The delay in physician diagnosis was secondary to lack of recognition of the severity of the patient's condition. Events associated with maternal death include cerebral hemorrhage (45%), cardiopulmonary arrest (40%), DIC (39%), adult respiratory distress syndrome (28%), renal failure (28%), sepsis (23%), hepatic hemorrhage (20%), and hypoxic ischemic encephalopathy (16%) (23). Persistent hypoglycemia in a patient with possible HELLP syndrome is an indication of severe liver failure. Although it may be related to the differential diagnosis of AFLP, it is an indication for immediate delivery.

In addition, mothers with HELLP syndrome are at increased risk for preterm delivery, DIC, placental abruption, acute renal failure, pulmonary edema, and subcapsular hepatic hematoma (18). Barton and Sibai reported findings of liver hematomas and hemorrhage in women with HELLP syndrome who underwent hepatic imaging. Although liver function test abnormalities did not accurately reflect the presence of abnormal hepatic imaging findings, the severity of the thrombocytopenia did correlate, especially when the platelet count was under 20 K (24). Patients with HELLP syndrome having complaints of right upper quadrant pain along with neck pain, shoulder pain, or relapsing hypotension should undergo imaging of the liver. Ultrasound imaging has the specific advantage of giving a bedside diagnosis without having to mobilize the patient away from the labor and delivery suite. The usual sonographic appearance of an acute subcapsular hepatic hematoma is a crescent-shaped collection of echogenic fluid just beneath the capsule of the liver (25).

Sibai and Ramadan reported acute renal failure in 7.4% of their 435 patients with HELLP syndrome (26). This unusually high rate was usually associated with multiple obstetric complications such as placental abruption, fetal death, DIC, postpartum hemorrhage, and sepsis. Pulmonary edema complicated 6% of the patients' courses in the University of Tennessee series and was correlated with the presence of acute renal failure (15).

EFFECT ON THE NEONATE

Perinatal mortality associated with HELLP syndrome has been reported as high as 37% (27), but more recent figures estimate an 11% perinatal mortality rate (28). Eeltink et al. reported the fetal and neonatal effects in 87 pregnancies with HELLP syndrome. They reported a stillbirth rate of approximately 10%, with another 10% of neonatal deaths occurring within the first week of life. The average gestational age and birthweight was 32 weeks and 1576 g, respectively, with a 44% incidence of small-for-gestational-age infants. Neonatal complications included respiratory disease (43%), hyperbilirubinemia (45%), "perinatal asphyxia" (21.6%), patent ductus arteriosus (16%), neonatal thrombocytopenia (34%), and hypoglycemia (16%). No specific neonatal pathology resulting from maternal HELLP syndrome was found (29). Most of the perinatal complications seemed to be the result of prematurity and placental insufficiency. A review of the neonatal charts of 269 consecutive pregnancies complicated by HELLP syndrome, partial HELLP syndrome, or severe preeclampsia noted no differences in neonatal outcomes among the 3 groups at each gestational age (30). These studies confirm that in severe preeclampsia, neonatal morbidity and mortality are mainly related to gestational age at delivery rather than the presence or absence of the HELLP syndrome.

MANAGEMENT

Delivery

The optimal treatment for maternal safety in confirmed cases of severe preeclampsia or HELLP syndrome is delivery. Unfortunately, at early gestational ages, the neonatal risk of prematurity must be balanced against the maternal and fetal risks of expectant management. No large randomized trials have compared conservative versus aggressive management of women with HELLP syndrome. Expectant management before 32 weeks should only be considered in tertiary care centers or as part of randomized, controlled trials with appropriate safeguards and consent (31). Although expectant management of severe preeclampsia remote from term may be arguable in select instances, the diagnosis of HELLP syndrome is a harbinger that the fetal and maternal risks exceed the benefits to be gained with pregnancy prolongation.

Although many patients with HELLP syndrome do not require antihypertensive therapy, drug management is similar to that used for severe preeclampsia. Antihypertensive agents such as hydralazine, labetolol, nifedipine, or nitroprusside drip may be used to control "stroke range" blood pressures over 180/110 mm Hg (31). Intravenous magnesium sulfate should be administered to lower the risk of seizure, regardless of blood pressure. Intravenous fluid administration and urine output must be meticulously monitored until the patient's complete recovery. Preterm patients should be transferred to a tertiary care center once the mother is stabilized hemodynamically (32).

The route of delivery should be based on obstetric indications. Labor may be induced at any gestational age, and cervical-ripening agents may be helpful in patients with an unfavorable cervix. Labor induction attempts in a nulliparous patient with an unfavorable cervix before 30 weeks gestation often results in a prolonged induction. Many clinicians opt to perform a cesarean delivery outright in these patients because the risk of eventually requiring a cesarean section is high. Intra- and postoperative oozing is common in patients with HELLP syndrome undergoing cesarean section. The surgeon must consider leaving sub- and/or suprafascial closed drains in place to minimize the need for a repeat laparotomy to drain clots or collections. Alternatively, the wound may be left open to the fascia and closed within the first 96 hours, thus allowing ascites, weeping, and oozing to drain. Rarely will patients need a platelet transfusion, even with a platelet count of 25,000. Packed red blood cell transfusion is often necessary postpartum secondary to continued hemolysis.

The choice of anesthesia is dependent on the coagulation status of the patient and the experience of the anesthesiologist. Regional anesthesia, whether for vaginal or cesarean delivery, is contraindicated if a coagulopathy is present. Thrombocytopenia itself does not constitute a coagulopathy, and one can use regional anesthesia even in the face of thrombocytopenia (without DIC), because the incidence of epidural hematoma is exceedingly rare.

The liver should not be biopsied or aggressively palpated at the time of cesarean section. Undiagnosed intraperitoneal blood deserves exploration for a source. If there is evidence of liver rupture, packing should be performed and supportive measures instituted. It is very difficult to resect a ruptured liver. In 24 to 48 hours, the patient can return to the operating room to remove the packs. Subcapsular hematomas should be managed conservatively.

Role of Steroids

Although the diagnosis of preterm HELLP syndrome necessitates delivery, allowing 48 hours after initial steroid administration may improve fetal outcomes with minimal risk to the mother. Any temporizing measure must be weighed against the potential risks to the mother and baby associated with the progression of the HELLP syndrome. Historically, therapies for HELLP syndrome or severe preeclampsia included transfer to a tertiary care center, control of hypertension, and seizure prophylaxis while proceeding toward delivery of the fetus. Case reports have mentioned transient improvements in laboratory values with bedrest and steroid treatment, originally given to improve fetal lung maturity in the premature pregnancy (6,33). Magann et al. simultaneously published the findings of 2 separate nonblinded, randomized, controlled trials demonstrating the effects of dexamethasone on HELLP syndrome given antepartum (34) and postpartum (35). They demonstrated improved blood pressures, urinary output, platelet counts, and liver function tests with 10 mg dexamethasone intravenously every 12 hours. A recent prospective, randomized trial from the University of Mississippi showed that intravenous dexamethasone is more effective than intramuscular betamethasone for improving these same laboratory values (36). Two retrospective analyses of data from the same institution further suggest that antepartum and/or postpartum treatment with high-dose dexamethasone was associated with a lessening of the acuity of illness, leading to a reduction of indicated therapy

interventions and a quicker recovery (37,38). Other retrospective studies using high-dose steroids have suggested a greater likelihood of attaining 24- to 48-hour latency from treatment to delivery, decreased need for blood product transfusion, and improved likelihood of regional anesthesia (39–41). It has been theorized that high-dose steroids act systematically to restore microvascular integrity and prevent platelet–endothelial dysfunction and red cell destruction. They may act as an immunosuppressant, dampening an abnormal immune response associated with the pathophysiology of HELLP syndrome (42). Until randomized, prospective studies demonstrate a difference in outcome or clinical (rather than laboratory) benefit of steroid treatment for HELLP syndrome, we cannot recommend routine use of steroids for maternal benefit.

Postpartum

Eclamptic seizure prophylaxis with magnesium sulfate should be continued for an undefined period postpartum, except in cases complicated by acute renal failure. In contrast to preeclampsia/eclampsia, which is associated with an improvement in symptoms and laboratory values immediately after delivery, the clinical course of HELLP syndrome typically has a nadir of platelets and peak of LDH 24 to 48 hours postpartum (17). Therefore, we recommend continued close monitoring of the postpartum patient with HELLP syndrome in a labor and delivery or intensive-care setting until an improvement in laboratory values is documented. Patients sometimes require repeated, delayed transfusions of packed red blood cells as a result of continued hemolysis. Plasmapheresis is indicated in cases with persistent hemolysis or platelets continuing to decrease more than 72 hours postpartum (17).

COUNSELING FOR THE FUTURE

Recurrence Risk

Sullivan and colleagues at the University of Mississippi studied 81 subsequent pregnancies in women with prior pregnancies complicated by HELLP syndrome. They found that 23% of the subsequent pregnancies were complicated by preeclampsia/eclampsia without HELLP syndrome and 19% were complicated by recurrent HELLP syndrome. HELLP syndrome recurred an average of 2 weeks later than in the index pregnancy (43). Sibai et al. reported the complication rates of 212 pregnancies in 152 women subsequent to a prior pregnancy complicated by HELLP syndrome (44). They reported elevated complication rates of preeclampsia, preterm delivery, intrauterine growth restriction, abruption, and perinatal death with significantly worse outcomes in the women with preexisting chronic hypertension. Overall, the risk for preeclampsia in a subsequent pregnancy was 21%, but the recurrence rate of HELLP syndrome was only 4%. Two of the women with prior ruptured liver hematomas associated with HELLP syndrome had 3 subsequent normotensive, term pregnancies without complications. Chames et al. recently reported a descriptive study of 62 pregnancies in 48 women with a history of HELLP syndrome for which delivery occurred at less than or equal to 28 weeks gestation. They reported increased risks for obstetric complications: preeclampsia (55%), severe preeclampsia (44%), preterm delivery (53%), small for gestational age (27%), abruption (5%), and perinatal mortality (11%). The incidence of recurrent HELLP syndrome was only 6% with all 4 of the cases occurring at less than 30 weeks gestation (45). Similarly, van Pampas reported a 2% rate of recurrence for HELLP syndrome among 92 pregnancies in The Netherlands (46). Although the recurrence risk of HELLP syndrome appears low, this may not accurately reflect the natural history of a pregnancy in a woman who previously had HELLP syndrome. Many of these pregnancies are watched closely, monitored for the development of HELLP syndrome, possibly contributing to their delivery before HELLP syndrome is allowed to fully develop. Therefore, these estimates and those from any potential study of recurrent HELLP syndrome may be artificially lower than what would be seen if the true natural history of the entity were allowed to develop without intervention.

EFFECT ON MATERNAL FUTURE

In women without evidence of chronic hypertension before HELLP syndrome, 6% had chronic hypertension after more than 5 years of follow up. There were no complications reported in women who received oral contraceptive pills after HELLP syndrome, suggesting that they are not contraindicated in these patients (44).

Dekker et al. suggested that patients with a history of severe early-onset preeclampsia be screened for protein S deficiency, activated protein C (aPC) resistance, hyperhomocystinemia, and anticardiolipin antibodies (47). A high prevalence of aPC resistance and the factor V Leiden mutation was reported in 21 German women with a history of HELLP syndrome

(48). In contrast, testing of 18 Italian women revealed no association of aPC resistance or factor V Leiden mutation with HELLP syndrome (49). Lee et al. did not find an association between anticardiolipin antibodies and preeclampsia or HELLP syndrome (50). We do not believe that a thrombophilia or antiphospholipid antibody workup is indicated based on a history of HELLP.

Wilken et al. suggested screening babies from mothers with AFLP or HELLP syndrome for fatty acid oxidation disorders, based on their findings of an increased prevalence of babies with long-chain 3-hydroxyacyl coenzyme A dehydrogenase (LCHAD) deficiency in pregnancies complicated by these 2 disorders (51). In a study of 113 Dutch women who had HELLP syndrome, researchers found only 1 with the most common LCHAD mutation, therefore testing of women with HELLP syndrome for LCHAD deficiency is *not* justified (52). Because there is no intervention or treatment to prevent the disorder, we cannot recommend any form of screening for women with a history of HELLP syndrome.

FUTURE DIRECTIONS

Preeclampsia has been dubbed the "disease of theories." Until we elucidate the pathophysiology of preeclampsia, it is doubtful that we will find therapies to prevent it. As an atypical variant of severe preeclampsia, the pathophysiology and prevention of HELLP syndrome will probably remain just as elusive. Recent research focusing on thromboblast dysfunction and endothelial dysfunction has offered promising insights into the pathophysiology of preeclampsia. High serum inhibin A levels in the first trimester of pregnancy have been associated with an almost 5 times higher odds ratio for the subsequent development of severe preeclampsia (53). Increased levels of circulating soluble fms-like tyrosine kinase 1 (SFlt-1) and decreased levels of placental growth factor (PlGF) may precede the clinical diagnosis of preeclampsia by 5 weeks (54). The decrease in serum aldosterone levels and plasma rennin activity associated with severe preeclampsia were not seen in patients with HELLP syndrome (55). Levels of midtrimester human chorionic gonadotropin (hCG) were higher and unconjugated estriol were lower in women with HELLP syndrome when compared with control subjects who had only severe preeclampsia (56). Eventually, these insights into the similarities and differences of preeclampsia and HELLP syndrome may shed light on the pathophysiology and prevention of each.

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