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Review Article

Hellp syndrome

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Introduction

The acronym HELLP was coined by Louis Weinstein in 1982 to describe a syndrome consisting of hemolysis (H), elevated liver enzymes (EL) and low platelets (LP). Some experts consider it a severe form of preeclampsia, while others believe that HELLP syndrome and preeclampsia are separate disorders with overlapping features. As many as 15-20% of the patients with HELLP syndrome do not have antecedent hypertension or proteinuria.

Pathophysiology

This syndrome usually develops suddenly between 28-36 weeks gestation. Its etiology and pathogenesis are not well understood. Generally, the disorder is considered a placenta-instigated, liver-targeted acute inflammatory condition, with elements of disordered immunological processes. Like severe preeclampsia, it results from the aberrant development, function, and ischemia of the placenta. This ischemia in turn triggers the release of factors that injure the endothelium via the loss of normal pregnancy vascular relaxation, release of vasoconstrictors, and activation of platelets. Thus begins a cascade that is terminated only by delivery. The hemolysis which characterizes the syndrome is of microangiopathic origin. Red cells become fragmented as they pass through small vessels with pathological fibrin deposits and damaged endothelium. Obstruction of hepatic blood flow by the same fibrin deposits in hepatic sinusoids results in elevated liver enzymes, and periportal necrosis. In severe cases, intrahepatic hemorrhage, subcapsular hematoma, or even hepatic rupture may occur. Thrombocytopenia, the third aspect of the triad, results from increased consumption and destruction of platelets.

Frequency, Race and Age

HELLP syndrome develops in 1 of 1000 pregnancies overall[1,2], and in 4-12% of the patients already affected by severe preeclampsia or eclampsia. Unfortunately, when preeclampsia is not present, the problem is disguised, and diagnosis of the syndrome is often delayed by as much as 7 days. Onset is antepartum in 70% of the cases, usually in the third trimester, and within 48 hours of delivery in the other 30%. Of the patients affected postpartum, only roughly 20% have any signs or symptoms suggesting preeclampsia prior to delivery. In contrast to preeclampsia, HELLP syndrome is more often associated with Caucasian multiparous women above the age of 25 years.

History and physical

The vague and varied nature of the presenting complaints can make the diagnosis of HELLP syndrome, and its distinction from preeclampsia, frustrating to physicians. Patients with this syndrome may present with various signs and symptoms, none of which are purely diagnostic. In fact, the majority of symptoms may also be seen in

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patients with severe preeclampsia-eclampsia without HELLP syndrome (table-1).

Presentation largely depends on the stage of the disease. Approximately 90% of the patients present with generalized malaise suggestive of a viral illness[3]. Because early diagnosis of HELLP is critical, pregnant women who present with symptoms such as malaise in the second half of their pregnancy should be immediately evaluated with complete blood count and liver function tests to exclude it. Other common symptoms include epigastric or right upper quadrant abdominal pain, nausea, vomiting, headache and visual symptoms. At times, referred pain from the liver can produce atypical neck and shoulder pain. Any pregnant patient with epigastric or right upper quadrant abdominal pain in the second half of pregnancy, particularly if in association with nausea and or vomiting, has HELLP syndrome until proven otherwise[4]. When the upper abdominal pain is writhing in nature and of sudden onset, hepatic bleeding or rupture is the likely cause, constituting an obstetric emergency. A small subset of patients may present with symptoms related to their thrombocytopenia, such as mucosal bleeding, petechial hemorrhages, ecchymosis or hematuria.

Table 1. Signs and symptoms of HELLP syndrome.

Signs and symptoms	Percentage
1. Malaise	90
2. Right upper quadrant tenderness	90
3. Proteinuria	87
4. Hypertension	85
5. Right upper quadrant/epigastric pain	65
6. Headache	60
7. Nausea and vomiting	36
8. Visual changes	17
9. Bleeding	09
10. Ascites	08
11. Jaundice	05
12. Shoulder or neck pain	05
13. Pulmonary edema	6

The physical examination may be deceivingly normal. However, in the majority, blood pressure will be elevated along with proteinuria and right upper quadrant tenderness. Leg swelling, though common in HELLP, may not be a useful marker as it is seen in 30% of healthy pregnant women.

Differential diagnosis

HELLP syndrome can be a great masquerader, and the presenting symptoms, clinical findings and laboratory results of this syndrome may suggest an array of differential diagnoses as shown in Tables 2 and 3. Diagnosis is notoriously difficult in the 15-20% of the patients who have neither hypertension nor proteinuria [5-7]. However, its presence may erringly lead toward preeclampsia. A delay in its diagnosis may be life threatening. As numerous misdiagnoses are possible, and treatment delay could be life-threatening, a pregnant woman with epigastric or right upper quadrant pain, thrombocytopenia and abnormal liver functions in the second half of pregnancy or early postpartum should be considered as having HELLP syndrome until proven otherwise via immediate work up. Lack of response to aggressive steroid treatment, especially with persistence of the disease following delivery or first presentation of the disease more than 7 days postpartum, should instigate testing for other diagnostic possibilities.

Table 2. Differential diagnosis.

1.	Thrombotic thrombocytopenic purpura (TTP)
2.	Hemolytic-uremic syndrome (HUS)
3.	Acute fatty liver of pregnancy (AFLP)
4.	Systemic lupus erythematous (SLE) flare
5.	Antiphospholipid antibody (APA) syndrome
6.	Autoimmune thrombocytopenic purpura
7.	Chronic renal disease
8.	Cholecystitis
9.	Pancreatitis
10.	Gastroenteritis
11.	Hepatitis
12.	Pyelonephritis and glomerulonephritis
13.	Appendicitis
14.	Hyperemesis gravidarum
15.	Kidney stones
16.	Hemorrhagic or septic shock
17.	Disseminated herpes simplex
18.	Acute renal failure with acute tubular necrosis
19.	Acute cocaine intoxication
20.	Pheochromocytoma
21.	Gastric ulcer
22.	Intrahepatic cholestasis

Table 3. Differential diagnosis

Disease	Incidence	Timing	AST/ALT of onset	Renal abnormalities	Other features	Total bilirubin, mg/dl
HELLP Syndrome or severe preeclampsia	1 in 1000	28-36 weeks antepartum and within 48 hour of delivery	<500	May be present	-Hypertension -Proteinuria -Malaise and upper abdominal pain -Thrombocytopenia -Mild microangiopathic hemolytic anemia (mild) -Normal PT and PTT	<2, mostly indirect
AFLP	1 in 7000-16000	Usually third trimester	<1000	May be present	-Hypoglycemia -jaundice -hypertension and proteinuria usually absent -normal hematocrit -Elevated PT and PTT -Associated with LCHAD -Fatty infiltration on liver biopsy	2-10, mostly direct
TTP-HUS	---	Variable	Usually normal or slightly elevated	More severe	More severe anemia and - thrombocytopenia -markedly abnormal peripheral smear -fever and neurological symptoms in case of TTP -HUS patients usually present in 95 % of the time in the postpartum period -renal failure is a common presentation of HUS -ADAMTS 13 is deficient Usually normal	
Viral hepatitis	1 in 1000	Variable	500-3000	None	-Abnormal serology helps with diagnosis	>5
Intrahepatic cholestasis	1 in 1000-10,000	Advanced third trimester	<500	None	-Intense pruritus -No rash -Elevated fasting bile acid -High (60%) recurrence	<5, mostly direct

Acute fatty liver of pregnancy (AFLP) and HELLP syndrome share several clinical features and can occur concurrently, so these are very difficult to distinguish clinically. Prolongation of prothrombin time, activated partial thromboplastin time, hypoglycemia and elevated serum creatinine concentrations are more common with AFLP. Though liver biopsy is the gold standard for diagnosing AFLP, because the procedure may be hazardous during pregnancy, and treatment is often unaltered by results, it is not commonly used in clinical practice.

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) may also cloud the diagnosis of HELLP syndrome. Thrombocytopenia, microangiopathic hemolytic anemia and renal failure are seen with both TTP-HUS and HELLP syndrome. The severity of these three symptoms is typically more serious with TTP-HUS. For therapeutic and prognostic point of view it is important to distinguish TTP-HUS from severe preeclampsia and HELLP syndrome. The time of onset and the association with preceding proteinuria and hypertension help distinguish between these two. TTP-HUS is usually variable in onset, whereas HELLP syndrome typically develops in the third trimester, and is usually associated with hypertension and proteinuria. Coagulation abnormalities are not typically associated with either diagnosis except in severe HELLP syndrome when associated with disseminated intravascular coagulation.

Work up

The diagnosis of HELLP syndrome is most certain in the presence of signs and symptoms of preeclampsia-eclampsia in a pregnant patient along with a triad of laboratory abnormalities indicating microangiopathic hemolysis, liver dysfunction and thrombocytopenia (Table 4). Though considered to be the gold standard, liver biopsy is rarely needed to establish the diagnosis and may be hazardous to perform secondary to the possible underlying coagulopathy. Common histological findings in such biopsies include periportal hemorrhage and fibrin deposits in hepatic sinusoids.

Table 4. Diagnostic criteria for HELLP syndrome.

Hemolysis (at least two of these)
• Abnormal peripheral smear (schistocytes, burr cell, echinocytes, etc)
• Increased total bilirubin (mostly indirect form) >1.2 mg/dl
• Low serum haptoglobin level
• Drop in hemoglobin level unrelated to blood loss
Elevated liver enzymes
• Increased transaminases (AST and ALT) > 70 IU/L (twice the upper limit of normal)
• Increased lactate dehydrogenase > 600 IU/L
• Increased total bilirubin >1.2 mg/dl
Thrombocytopenia
• Platelet count < 100,000-150,000

Looking at its natural progression, it appears that thrombocytopenia occurs first, followed by elevated liver enzymes, and finally hemolysis. The rate of drop of platelets is usually 35-50% per 24 hours (mean daily reduction of 40,000). Requiring a count of less than 100,000 to define thrombocytopenia is ill advised as maternal morbidity doubles when patients with severe preeclampsia have mild thrombocytopenia (platelets = 100,000-150,000) in association with abnormal liver function and increasing lactate dehydrogenase (LDH). In addition, significant pathology such as hepatic rupture or subcapsular hematoma can occur in the patient with HELLP syndrome prior to a drop in platelets to below 100,000 [8].

Depending on the laboratory abnormalities present, HELLP syndrome is grouped into different subtypes per the Mississippi and Tennessee classifications (Table 5). The degree of laboratory abnormality present is difficult to determine with on the history or physical examination. Therefore, laboratory tests should be ordered with minimal clinical indications, and to rule in or out a diagnosis of preeclampsia. Typical laboratory workup includes complete blood count, coagulation studies, serum creatinine, urine protein, blood glucose, peripheral blood smear and liver function tests.

Although some degree of hemolysis is often noted and is the hallmark of the triad for diagnosis, resultant anemia is uncommon or mild. Many physicians use elevated LDH as a better indicator of hemolysis than hemoglobin. There are five different isomers of LDH, and only LDH1 and LDH2 are

Table 5. Classification of HELLP syndrome.

Mississippi classification	Tennessee classification
Class 1 • Platelets <50,000 • AST or ALT > 70 IU/L • LDH >600 IU/L	True or Complete • Platelets < 100,000 • AST > 70 IU/L • LDH >600 IU/L
Class 2 • Platelets = 50,000-100,000 • AST or ALT > 70 IU/L • LDH >600 IU/L	Partial or incomplete · Severe preeclampsia with any one of the following: ELLP, HEL, EL, LP
Class 3 • Platelets = 100,000-150,000 • AST or ALT >40 IU/L • LDH >600 IU/L	

ELLP, Absence of hemolysis; HEL, Absence of low platelets; EL, Elevated liver function; LP, Low platelets.

released from ruptured red cells. However, liver ischemia also causes elevation in total LDH in the majority of patients with severe preeclampsia or HELLP syndrome. Therefore, elevated indirect bilirubin, low haptoglobin and abnormal peripheral smear with schistocytes and or burr cells are used in addition to LDH for diagnosis of hemolysis.

Significant elevation of alkaline phosphatase is often seen in normal pregnancy; however, the elevation of transaminases, lactate dehydrogenase and bilirubin, indicates hepatic pathology. The value of transaminases in early to moderate disease rarely exceeds 1000. Levels in excess of this suggest hepatitis or hepatic rupture from HELLP syndrome.

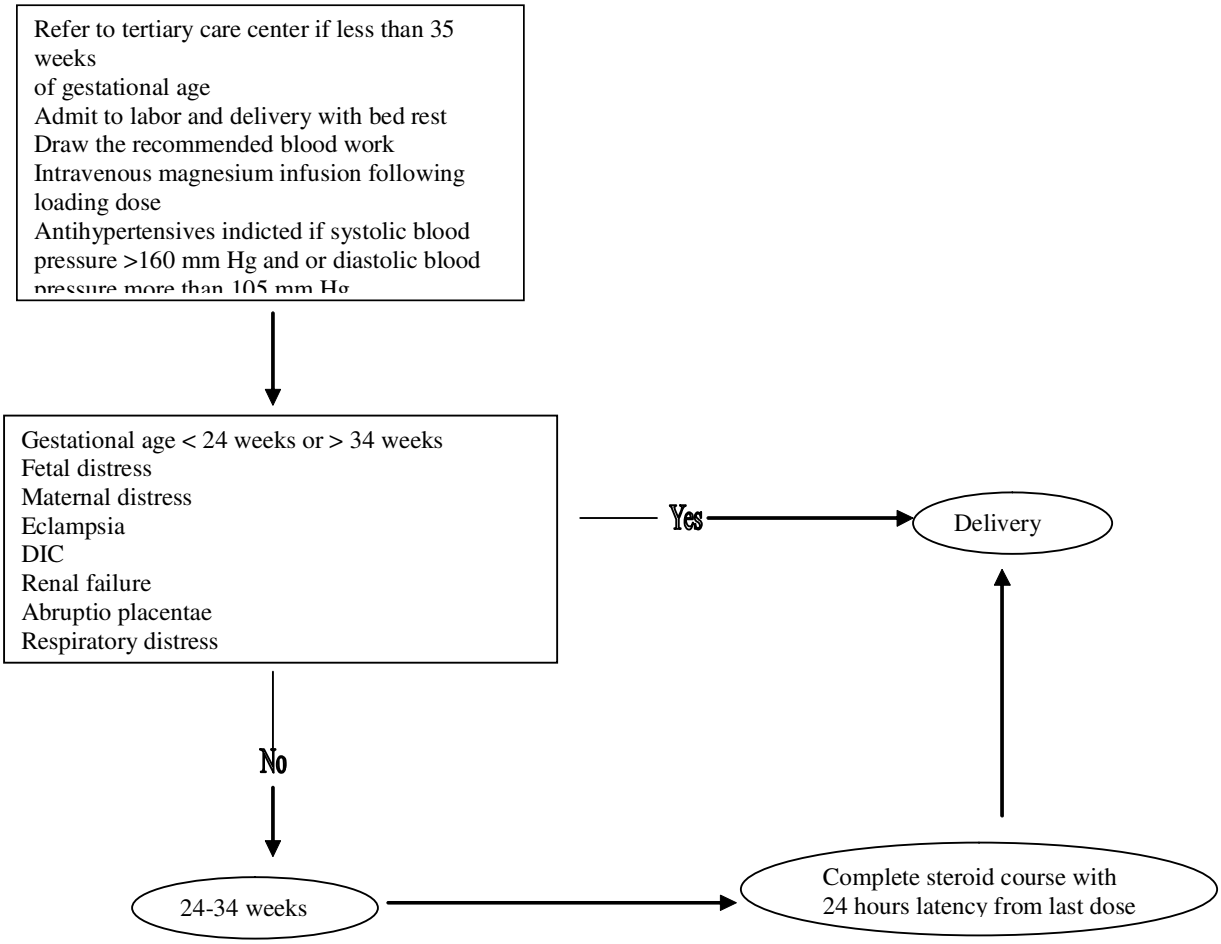
Unfortunately there is no consensus with regard to laboratory parameters for diagnosis of HELLP syndrome. Laboratory abnormalities often return to normal within a short time of delivery with occasional transient worsening within the first 24-48 hour postpartum [9-14]. There should be an upward trend in platelet count and downward trend in lactate dehydrogenase and transaminases by the fourth postpartum day when there are no associated complications from HELLP syndrome [9-11,15]. Liver tests typically normalize earlier than the platelet count. The latter may take as long as 6-11 days depending on the severity of thrombocytopenia.

Further tests such as urine analysis, chest X-ray, liver imaging, etc. are ordered when associated complications such as disseminated intravascular coagulation (DIC), pulmonary edema, subcapsular liver hematoma or liver rupture are suspected. Additional testing may be needed at times to rule out other possible conditions (Table 2) that closely resemble HELLP syndrome.

Treatment

Although management of HELLP syndrome is highly controversial (Table 6), once diagnosed, a decision should be made regarding delivery. Due to the progressive nature of the disease, these patients should always be hospitalized with strict bed rest and care in labor and delivery due to the potential for sudden deterioration of maternal or fetal condition. Patients diagnosed with HELLP prior to 35 weeks should be transferred to a tertiary care center. After assessment and stabilization of maternal status, the fetus is evaluated by fetal heart rate tracing, biophysical profile and or doppler studies. The assessment of maternal and fetal status helps determine when delivery is required or imminent, as delivery is the only true cure for this syndrome.

Table 6. Management of HELLP Syndrome.



When the mother and fetus are both stable and the gestational age is less than 34 weeks, there is considerable disagreement regarding management. For most, delivery is preferably delayed for 24-48 hours for steroid administration. Prompt delivery is indicated when the gestational age is beyond 34 weeks, or earlier in presence of nonreassuring fetal status or if there are associated complications of HELLP syndrome such as multiorgan dysfunction, DIC, abruptio placentae, renal failure, pulmonary edema, liver infarction or hemorrhage etc.[6,17].

Some authors recommend expectant management beyond 48 hours in a select group of stable patients with HELLP syndrome if the fetus is extremely premature (<26 weeks of gestation). This conservative group recommends prolonging pregnancy in the hospital until the development of maternal or fetal indications for delivery, achievement of fetal lung maturity or 34 weeks of gestation. However, it should be noted that there is no improved perinatal outcome associated with this pregnancy prolongation[18]. Some of the measures used in these patients include one or more of the following: bed rest, adequate blood pressure control, chronic intravenous magnesium administration, antithrombotics such as aspirin or dipyridamole, steroids and plasma volume expanders (fresh frozen plasma, crystalloid, colloids, etc).

As HELLP syndrome is considered a systemic inflammatory response syndrome, similar to the inflammatory condition of severe preeclampsia, anti-inflammatory or immunosuppressive agents like corticosteroids are given as consideration for its treatment. There is no consensus regarding the use

of high dose steroids such as dexamethasone (10mg every 12 hours IV) in class 1 and 2 HELLP syndrome or complicated class 3 HELLP syndrome, other than for the indication of aiding fetal lung maturity. The preferred steroid and dosing duration are still not established. Though improvements in laboratory parameters are often seen in HELLP syndrome patients receiving this high dose steroids, maternal morbidity and mortality along with duration of hospital stay and rate of blood product transfusion remain the same. Therefore, the timing of delivery should not be changed in patients showing transient improvement in laboratory values from high dose steroids. Continuation of HELLP syndrome pregnancy beyond 26 weeks and the time necessary for steroid enhancement of fetal lung maturation increases the risk of still birth substantially [19,20].

HELLP syndrome is not an indication for cesarean delivery (Table 7). Vaginal delivery is attempted in patients in gestations beyond 32 weeks, or in the presence of active labor or membrane rupture. Induction or augmentation of labor with pitocin or prostaglandins is acceptable in this group of patients. Alternately, in patients of gestation less than 30 weeks with an unfavorable cervix (Bishop score <5) and in the absence of active labor, cesarean section is the preferred mode of delivery[6]. Elective cesarean section is also recommended for patients with fetal growth retardation or oligohydramnios. When cesarean delivery without a trial of labor is planned, it is recommended that the surgery be scheduled for six hours from the beginning of high dose of steroid administration to stabilize the disease process, improve laboratory parameters, enable institution of regional anesthesia[21,22], and reduce the need for blood product transfusion.

Table 7. Indications for cesarean section.

1.	Nonreassuring fetal status
2.	Abnormal fetal presentation
3.	< 30 weeks gestation with low Bishop score of <5
4.	< 32 weeks of gestation with intrauterine growth restriction or oligohydramnios and low Bishop score of <5
5.	Known subcapsular liver hematoma
6.	Suspected abruptio placentae

Magnesium sulfate should be administered intrapartum and early postpartum for seizure prophylaxis regardless of blood pressure. It is started at the beginning of the observation period, continued through the intrapartum period, and then for 24-48 hours postpartum. The standard regimen includes a 6gm loading dose of magnesium over 20 minutes followed by a maintenance dose of two grams per hour continuous intravenous administration. Serial monitoring of its blood level is indicated in the presence of compromised renal function with serum creatinine more than 1 mg/dl. As in patients with severe preeclampsia, antihypertensives are used for systolic blood pressures above 160, and or diastolic pressures of more than 105 to avoid intracerebral bleeding[6]. The preferred antihypertensives include hydralazine, labetalol and nifedipine (Table 8) [23]. Nitroglycerine and sodium nitroprusside are useful in cases of refractory hypertension if delivery is imminent. The prolonged use of nitroprusside can lead to cyanide poisoning of the fetus, and therefore is used as a last resort. Blood pressure should be recorded every 15 minutes during the implementation of antihypertensive therapy, and once stabilized, recorded every hour.

Table 8. Antihypertensives used in HELLP syndrome for acute treatment of Hypertension.

• Hydralazine
5 mg IV to start with, repeat 5-10 mg every 15-20 minutes when needed, maximum cumulative dose of 20mg or the blood pressure is controlled.
• Labetalol
20 mg IV to start with, followed by 40mg, then 80 mg at 10-15 minutes intervals until the desired response or maximum dose of 220 mg is administered.
• Nifedipine
10-20 mg doses at 30 minutes interval for a maximum of 50 mg (not approved by FDA for hypertension).

For pain control in labor small intermittent doses of narcotics can be given intravenously. When the platelet count is below 75,000, regional anesthesia and pudendal blocks are both contraindicated to avoid the risk of bleeding and hematoma formation. Some physicians use a more conservative 100,000 platelet count to contraindicate regional and

pudendal block. If indicated, patients considered to be at bleeding risk can be delivered by cesarean section under general anesthesia. Some authors noticed greater successful use of epidural anesthesia in patients who had received steroids secondary to the transient improvement in platelet count [22,24]. Once in place, the epidural catheter should not be removed until the count improves. It should be noted that low platelet count is not a contraindication for local infiltration of anesthetics for episiotomy or perineal laceration repair.

Both maternal and fetal conditions are assessed continuously during the intrapartum period. Platelet count should be maintained at more than 20,000 and 40,000 for vaginal and cesarean delivery respectively. In patients with platelet count at less than 40,000, 4-10 units of platelets are transfused at the time of intubation[25]. Platelet transfusion is also indicated in patients with significant bleeding or platelet count less than 20,000 irrespective of the intended mode of delivery. Because of the short half-life of platelets, repeated transfusion is usually not advised. Prophylactic platelet transfusion has been shown to neither reduce the incidence of postpartum hemorrhage nor hasten the normalization of platelet count. In the case of cesarean delivery, intraperitoneal and or subcutaneous closed suction drains through a separate stab incision may reduce wound hematoma formation, which may be seen in up to 20% of the patients with HELLP syndrome. Some even leave the skin incision open for the first 48 hours postoperative, however this delayed skin closure or type of skin incision has been shown to have no effect on wound hematoma incidence [26].

Although hypoglycemia is more commonly seen with AFLP, it can also be seen in patients with HELLP syndrome. As hypoglycemia is a major marker of imminent death in patients with HELLP syndrome, it should be checked frequently during labor. Every attempt should be made to keep blood sugar above 60 mg/dl. The patient might need 10% or 50% dextrose to keep blood sugars in the safe range.

HELLP syndrome may develop de novo most commonly in the first 48 hours postpartum, though it may take up to 7 days to manifest. However, regardless of antepartum or postpartum incidence, management is no different. With good supportive care, a majority of patients recover completely. It is important to continue monitoring fluid balance, laboratory abnormalities, and pulse oximetry closely into the immediate postpartum period. Patients who have developed the severe complications of help warrant monitoring for several days. Seizure prophylaxis with magnesium is continued for 24-48 hours postpartum, and some also continue the high dose intravenous steroids for the first 24-48 hours after delivery. Dexamethasone is the most preferred steroid, and is commonly administered as two 10 milligram doses 12 hours apart, followed by two additional doses of 5 milligrams each at 12-hour interval. Alternatively some physicians continue high dose steroids until liver function improves and platelet count exceeds 100,000. Clinical and laboratory improvements are commonly seen within a few days of the delivery except in patients with severe disease, renal dysfunction, ascites, and DIC. Maternal serum LDH and platelets are the best markers of disease status. If interventions are not successful, and patient condition continues to deteriorate after delivery, it is important to exclude other diagnosis such as TTP, HUS, and AFLP. Plasma exchange and plasma infusion has been used sparingly for recalcitrant and or complicated HELLP syndrome that is unresponsive to standard therapy.

Significant renal injury is infrequently seen in patients with HELLP syndrome in the absence of abruptio placentae or major hemorrhage. Aggressive steroid use has no convincing renal benefits. Most of these patients respond to short repeated cycles of dialysis if needed, and some require only a brief initial dialysis course, to avoid permanent kidney impairment. Short-term dialysis is needed in only a third of the patients with impaired kidney function from HELLP syndrome. However, 40% of the patients with prior chronic hypertension who are affected by HELLP syndrome require chronic dialysis.

The incidence of subcapsular hematoma is less than 2% in HELLP syndrome. It can lead to catastrophic hemorrhage, and rupture may be spontaneous or secondary to labor or convulsions. Typically the right lobe of the liver is involved, and any sudden increase in intraabdominal pressure can result in rupture of a subcapsular hematoma. Therefore, to avoid this most feared complication, exogenous trauma to the liver such as frequent abdominal palpation or emesis should be avoided, and utmost care should taken when transporting patients with

subcapsular hematoma. As the associated maternal and fetal mortality is greater than 50% when rupture occurs, early recognition is the key. Besides pain in the upper abdomen, these patients present with acute abdominal swelling and signs of peritoneal irritation along with hemorrhagic shock and modest elevation of liver enzymes. Profound hypovolemic shock in a previously hypertensive pregnant patient is the hallmark of ruptured liver hematoma. Sudden drop in blood pressure may also be associated with sepsis, severe hemolysis, or excessive vasodilatation from antihypertensives in pregnant women with severe hemoconcentration. Abdominal imaging confirms the diagnosis of rupture, and paracentesis is rarely needed, but can diagnose hemoperitoneum. There are several options for management, including fluid replacement, blood transfusion, correction of coagulopathy, the use of cell saver at the time of laparotomy, surgical packing/drainage, loosely suturing omentum or surgical mesh to the liver's surface, argon beam coagulation, and hepatic artery embolization. In the absence of rupture, subcapsular hematoma patients need surgical intervention only in the presence of hemodynamic instability, persistent bleeding, increasing pain or continued expansion of the hematoma. When they survive, they typically have no hepatic sequelae. Hemodynamically stable patients with subcapsular hematoma can be managed conservatively via close hemodynamic monitoring, coagulation studies and serial surveillance of the hematoma via CT or ultrasound. It should also be kept in mind that there is a risk of recurrence of the syndrome in subsequent pregnancy.

Obstetricians, with the supervision of perinatologists, are able to care for these patients in a majority of cases. Depending on the status of the patient, and the complications associated, additional specialized care may be needed. Other helpful consultants may include hematologists, transfusion medicine specialists, critical care specialists, nephrologists, and surgeons.

Mortality, Morbidity, Complications, Prognosis

Not surprisingly, the presence of HELLP syndrome increases maternal mortality [16] and morbidity. This is particularly high for patients with complete or true HELLP syndrome over those with incomplete HELLP syndrome[27]. Neurologic abnormality due mostly to cerebral hemorrhage/stroke is the most common system involved in autopsy [28]. Understandably, class 1 or class 2 HELLP syndrome patients are more likely to have complications over patients with class 3 HELLP syndrome. However, the outcome of most of the pregnant patients with HELLP syndrome is generally good and they recover completely.

Associated complications may include pulmonary edema, acute renal failure, DIC, abruptio placentae, liver hemorrhage/rupture/failure, adult respiratory distress syndrome, stroke, sepsis, death, wound hematoma, blood product transfusion with its associated risks, and ascites (Table 9). Though not always, the risk of serious morbidity correlates with increasing severity of maternal symptoms and laboratory abnormalities. Marked ascites of a volume of greater than one liter, is associated with a higher incidence of cardiorespiratory complications[29]. While the postpartum onset of HELLP syndrome increases the risk of renal complications and pulmonary edema[30], the presence of abruption increases the incidence of DIC[17,30]. Other comorbid conditions such as lupus, diabetes, fetal demise, eclampsia and peripartum hemorrhage increase the complications associated with HELLP syndrome.

Table 9. Maternal Complications associated with HELLP syndrome.

	Complications	Incidence (%)
1.	DIC	15
2.	Abruptio placentae	10-15
3.	Marked ascitis	10-15
4.	Wound hematoma or infection	14
5.	Pulmonary edema	08
6.	Pleural effusions	6-10
7.	Acute renal failure/acute tubular necrosis	03
8.	Subcapsular hematoma/infarction/failure	<02
9.	Laryngeal edema	1-2
10.	Retinal detachment, vitreous hemorrhage and cortical blindness	01
11.	Death	01
12.	Others-Adult respiratory distress syndrome, sepsis, stroke, pancreatitis, myocardial infarction and diabetes insipidus	01

Liver infarction is another possible complication, which may be manifest by fever, right upper quadrant pain and marked elevation of transaminases. This diagnosis can be confirmed by liver ultrasound, and typically the outcome of these patients is favorable following delivery.

Perinatal mortality ranges from 10-20% in HELLP syndrome[8,19]. This high mortality is associated with early gestational age (<28 weeks) and its complications including growth retardation and abruption of placenta[18,19,31]. Incidence of preterm delivery is up to 70%, with 15% prior to 28 weeks gestation[16,19]. Infants of mothers with HELLP syndrome have high rates of respiratory distress syndrome, bronchopulmonary dysplasia, intracerebral hemorrhage, necrotizing enterocolitis and neonatal thrombocytopenia. Although neonatal thrombocytopenia occurs in a substantial percentage (38%) of newborns, a higher incidence of intraventricular hemorrhage has not resulted when compared with controls matched for same gestational age with no association of HELLP syndrome [32-34].

Patients with HELLP syndrome have a higher incidence of preeclampsia (20%) in subsequent pregnancy, especially those patients who develop HELLP during the second trimester. The overall incidence of recurring HELLP syndrome in subsequent pregnancy is less than 5%. Although aspirin and calcium have been tried, there is no current preventive therapy for recurrent HELLP syndrome. However, because of relatively low incidence of recurrence, subsequent pregnancy is generally not discouraged. Interestingly, the incidence of preterm delivery, fetal growth restriction, abruptio placentae and fetal death is higher in subsequent pregnancies for these mothers, even in the absence of preeclampsia or recurrent HELLP syndrome. Therefore, close follow up is crucial in subsequent pregnancies.

The use of oral contraceptives is not typically contraindicated in these patients outside of pregnancy unless an associated thrombophilia exists. Some recommend a thrombophilia work up, including that for antiphospholipid antibody syndrome, in patients with atypical early presentations of HELLP syndrome.

Despite voluminous literature on this disease entity, its diagnosis and management remains unfortunately controversial. More work needs to be done on this topic.

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