HELLP syndrome
**Introduction**

- HELLP is a syndrome in pregnant and postpartum women characterized by hemolysis with a microangiopathic blood smear, elevated liver enzymes, and a low platelet count.
- It probably represents a severe form of preeclampsia but the relationship between the two disorders remains controversial.
- Some authorities believe that HELLP is a separate disorder from preeclampsia because as many as 15 to 20 percent of patients with HELLP syndrome do not have hypertension or proteinuria.
- Delivery eventually leads to resolution of signs and symptoms.
- Maternal complications are primarily related to bleeding, which can include hepatic hemorrhage.
- Neonatal complications are primarily related to the gestational age at delivery, which is commonly preterm.
Prevalence

HELLP develops in 0.1 to 1.0 percent of pregnant women overall. Among women with severe preeclampsia/eclampsia, 1 to 2 percent have microangiopathic hemolysis and thus can be considered to have HELLP.
Risk factors

- A previous history of preeclampsia or HELLP
- A variety of genetic variants associated with an increased risk for HELLP syndrome has been reported, but they have no role in clinical management.
- In contrast to preeclampsia, nulliparity is not a risk factor for HELLP syndrome. Half or more of affected patients are multiparous.
Pathogenesis

• The pathogenesis of HELLP syndrome is unclear. If it is a severe form of preeclampsia, it likely has the same origin. If it is a separate entity, it can still have a similar origin, but it then diverges along a different pathway for unknown reasons such that there is greater hepatic inflammation and greater activation of the coagulation system than in preeclampsia.

• A subset of HELLP syndrome may be related to thrombotic microangiopathy caused by complement dysregulation, which may be treatable without prompt delivery of the fetus.

• the hypothesis that severe preeclampsia/HELLP is a systemic inflammatory disorder and the complement cascade is a key mediator, and the observation that women with mutations in complement regulatory proteins appear to be at increased risk of severe preeclampsia.
• In less than 2 percent of patients with HELLP, the underlying etiology appears to be related to fetal long-chain 3-hydroxyacyl CoA dehydrogenase (LCHAD) deficiency.

• These complications probably were not due to chance or maternal heterozygosity for LCHAD deficiency alone because three other pregnancies with unaffected fetuses among these mothers were uncomplicated.

• Although these findings inform theories about the pathogenesis of HELLP, evaluation for genetic variants associated with LCHAD deficiency has no role in clinical management of women with HELLP.
**Pathophysiology**

- Microangiopathy and activation of intravascular coagulation can account for all of the laboratory findings in HELLP syndrome.

- Hepatic histology may show microvascular fibrin deposition, neutrophilic infiltrate, fatty infiltration, lobular necrosis, and periportal hemorrhage.

- Although renal dysfunction is not an essential diagnostic criterion, microvascular dysfunction may also occur in the kidney and may increase its vulnerability to an ischemic insult.
Signs and symptoms

- **HELLP** syndrome has a variable presentation. The onset of symptoms is usually rapid onset, and they progressively worsen.
• Abdominal pain, which may be colicky, is the most common symptom and is present in most patients.

• It may be localized to the midepigastrium, right upper quadrant, or below the sternum. The area may be tender on physical examination. Many patients also have nausea, vomiting, and generalized malaise, which may be mistaken for a nonspecific viral illness or viral hepatitis, particularly if the serum aspartate aminotransferase and lactate dehydrogenase levels are markedly elevated.

• Less common symptoms include headache, visual changes, jaundice, and ascites.
On physical examination

- Hypertension (defined as blood pressure $\geq 140/90$ mmHg) and proteinuria are present in approximately 85 percent of cases, but it is important to note that either or both may be absent in women with otherwise severe HELLP syndrome.

- Serious maternal morbidity may be present at initial presentation or develop shortly thereafter.

- This includes disseminated intravascular coagulation, abruptio placentae, acute kidney injury, pulmonary edema, subcapsular or intraparenchymal liver hematoma, and retinal detachment.
• Thrombocytopenia-related bleeding (mucosal, hematuria, petechial hemorrhages, ecchymosis) is an unusual presentation
Gestational age at onset

- Symptoms typically develop between 28 and 36 weeks of gestation, but late second-trimester or postpartum onset is also common.
- In a large series 70 percent occurred before delivery, approximately 80 percent of these cases occurred before <37 weeks, and fewer than 3 percent occurred between 17 and 20 weeks.
- In the 30 percent of cases that occurred postpartum, most were diagnosed within 48 hours of delivery, but occasionally as long as seven days after birth; 80 percent had evidence of preeclampsia before delivery.
Diagnostic Evaluation

- In pregnant women with characteristic symptoms of HELLP (eg, right upper quadrant/midepigastric pain, nausea, vomiting, generalized malaise) and/or new onset hypertension in the second half of pregnancy or first postpartum week, that establish/exclude the diagnosis of HELLP.

- Because pain may precede laboratory abnormalities by several hours, repeating the laboratory tests in four to six hours can be helpful.
Laboratory work-up should include:

✓ Complete blood count
✓ Peripheral smear
✓ Aspartate aminotransferase, alanine aminotransferase, bilirubin
✓ Creatinine

In patients with elevated liver chemistries, we also obtains haptoglobin and lactate dehydrogenase levels and coagulation studies (fibrinogen, prothrombin time, activated partial thromboplastin time).
Diagnosis

• The diagnosis of HELLP syndrome is based upon the presence of all of the laboratory abnormalities comprising its name (hemolysis with a microangiopathic blood smear [fragmented red blood cells; ie, schistocytes, burr cells], elevated liver enzymes, and low platelet count) in a pregnant/postpartum woman.

• Pregnant/postpartum women who have some of the typical laboratory abnormalities but do not meet all of the laboratory criteria described below are considered to have partial HELLP syndrome. These patients may progress and meet all criteria.
Laboratory criteria for diagnosis

**Tennessee classification**

Hemolysis, established by at least two of the following:

- Peripheral smear with schistocytes and burr cells
- Serum bilirubin $\geq 1.2$ mg/dL
- Low serum haptoglobin ($\leq 25$ mg/dL) or lactate dehydrogenase (LDH) $\geq 2$ times the upper level of normal
- Severe anemia, unrelated to blood loss.
Elevated liver enzymes:

• Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq 2$ times the upper level of normal

• Low platelets: $<100,000$ cells/microL
• Severe anemia in pregnancy can be defined as hemoglobin level <8 to 10 g/dL, depending on the trimester.

• The American College of Obstetricians and Gynecologists suggests the following diagnostic criteria and acknowledges the absence of clinical consensus among experts;
  ● LDH ≥600 IU/L
  ● AST and ALT elevated more than twice the upper limit of normal,
  ● Platelet count <100,000 cells/microL
Sub classification

not commonly used, based on severity of thrombocytopenia (Mississippi classification);

- Class 1 – Platelet count ≤50,000 cells/microL plus LDH >600 IU/L and AST or ALT ≥70 IU/L
- Class 2 – Platelet count >50,000 but ≤100,000 cells/microL plus LDH >600 IU/L and AST or ALT ≥70 IU/L
- Class 3 – Platelet count >100,000 but ≤150,000 cells/microL plus LDH >600 IU/L and AST or ALT ≥40 IU/L
DIFFERENTIAL DIAGNOSIS

- The three major disorders in differential diagnosis are
  - acute fatty liver of pregnancy (AFLP),
  - thrombotic thrombocytopenic purpura (TTP),
  - pregnancy-related hemolytic-uremic syndrome (HUS)

- There is also overlap with preeclampsia with severe features, which may not be a separate disease.

- The clinical and histologic features are so similar that establishing the correct diagnosis may not be possible.
Preeclampsia with severe features

• **HELLP** may represent a severe form of preeclampsia.

• In **HELLP**, angiopathy and liver dysfunction are marked, and the magnitude of hypertension is not highly correlated with the level of angiopathy and liver dysfunction.

• By contrast, most cases of severe preeclampsia have severe hypertension; thrombocytopenia and liver dysfunction, although present, are not as markedly abnormal as in **HELLP**.
Acute fatty liver of pregnancy

- Like HELLP, AFLP typically presents in the third trimester, but the diagnosis has been made as early as 22 weeks and as late as four days after delivery.
- The initial symptoms are often nonspecific (e.g., nausea, vomiting, abdominal pain, malaise, headache, and/or anorexia).
- Many patients have hypertension, with or without proteinuria, possibly due to coexistent preeclampsia; however, hypertension is more common in HELLP than in AFLP.
- Although the initial management of both HELLP and AFLP is similar (i.e., supportive care and delivery), it is important to differentiate between the two disorders, if possible, because women with AFLP can rapidly develop liver failure, encephalopathy, and severe hypoglycemia.
• serum fibrinogen levels are the most important test to differentiate this two conditions.
• In the absence of abruption or massive hemorrhage, it is rare to have a fibrinogen level below 300 mg/dL in HELLP, whereas a fibrinogen level below 300 mg/dL is the rule in women with AFLP.
• prolongation of PT and aPTT, severe hypoglycemia, and elevated creatinine are more common in women with AFLP than in those with HELLP.
• AFLP can be confirmed by diagnostic liver biopsy, but this is rarely performed because the information gained would not change management, and the procedure exposes the mother and pregnancy to additional risks. Furthermore, AFLP and HELLP share several common histologic features
• women with AFLP are more likely than women with HELLP to have offspring with an inherited defect in mitochondrial beta-oxidation of fatty acids, such as long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency, short-chain acyl-coenzyme A dehydrogenase deficiency, or carnitine palmitoyltransferase I deficiency. However, this information is not typically available during differential diagnosis and is not highly sensitive or specific.
Thrombotic microangiopathy: TTP and HUS

• TTP is similar to HELLP in that severe thrombocytopenia, severe anemia, and elevated lactate dehydrogenase (LDH) levels occurring late in pregnancy are common to both disorders.

• In contrast to HELLP, aspartate aminotransferase and alanine aminotransferase are minimally elevated in TTP.

• The percentage of schistocytes on peripheral smear is often higher in TTP (2 to 5 percent) than in HELLP (less than 1 percent).

• TTP is always associated with isolated severe platelet consumption, whereas prolongation of the PT and aPTT are typically absent.

• LDH levels are markedly elevated in TTP (often >1000 IU/L and as high as 2000 or 3000 IU/L) whereas they are usually modestly increased in HELLP syndrome, although fulminant cases can have LDH levels that are as high as those seen in TTP.
• The onset of TTP tends to be earlier: approximately 12 percent of TTP in pregnancy occurs in the first trimester, 56 percent in the second trimester, and 33 percent in the third trimester/postpartum, whereas HELLP does not occur before 20 weeks of gestation and most cases are diagnosed in the third trimester.

• Proteinuria and hypertension prior to onset of laboratory abnormalities favors the diagnosis of HELLP.

• The distinction between TTP and HELLP is important for therapeutic and prognostic reasons. Plasma exchange (PEX) is the treatment of choice and life-saving for acquired TTP occurring during pregnancy but not useful for treatment of HELLP.

• The decision to initiate plasmapheresis will depend on the severity of the reduction in platelet count and the trend in change in platelet count in association with change in LDH levels after delivery.

• TTP may relapse years after pregnancy, whereas HELLP is only associated with pregnancy and the postpartum state.
• Although severe \textit{ADAMTS13} deficiency (activity <10 percent) is consistent with a diagnosis of TTP, this testing may take several days, and in patients with a presumptive diagnosis of TTP, urgent therapy with PEX should be initiated.

• Early involvement of the consulting hematologist to assist with diagnosis and presumptive management, including transfer to a facility capable of performing PEX, is advised.
• Pregnancy-related atypical HUS is rare, usually develops postpartum, and may be a complement-mediated disorder triggered by pregnancy. Although both HELLP and HUS are characterized by thrombocytopenia and hemolysis, in contrast to HELLP, kidney injury is prominent in HUS: 71 percent of patients required dialysis at diagnosis in one series and the liver is not severely affected (transaminases may be normal or mildly elevated).
Other disorders

- **Systemic lupus erythematosus (SLE)** – In patients with SLE, it can be difficult to distinguish a flare from HELLP, particularly in patients with lupus hepatitis.

- However, hemolytic anemia is relatively rare in SLE (most patients have anemia of chronic disease). Mild thrombocytopenia (platelet counts between 100,000 and 150,000/microL) has been noted in 25 to 50 percent of patients with SLE; platelet counts <50,000/microL occur in approximately 10 percent of SLE patients.

- Other causes of epigastric or upper abdominal pain in pregnancy include gastroenteritis, hepatitis, appendicitis, cholecystitis, pancreatitis, and pulmonary embolism.
● Acute viral gastroenteritis is associated with fever and diarrhea.
● Hepatitis can be definitively diagnosed based on serologic testing.
● Acute appendicitis is often associated with fever and leukocytosis. Pain is often in the lower right quadrant or midabdomen. The appendix often appears abnormal on imaging.
● Acute cholecystitis is often associated with fever and leukocytosis and typically develops in a patient with a history of symptomatic gall stones. The gall bladder is abnormal on imaging.
● Acute pancreatitis is associated with epigastric pain often radiating to the back, elevation in serum lipase or amylase to three times or greater than the upper limit of normal, and characteristic findings on imaging.
● Pulmonary embolism is characterized by dyspnea and pleuritic chest pain and characteristic findings on imaging.
MANAGEMENT IN PATIENTS PRESENTING BEFORE DELIVERY

• The initial steps in management are to assess the mother as described above, stabilize women who are unstable, and assess fetal status (nonstress test and ultrasound examination for biophysical profile and fetal presentation).

• Because of the potential for severe maternal complications, which can develop rapidly, women with HELLP should be managed at a tertiary care center with appropriate levels of maternal and neonatal intensive care.
Patients requiring urgent assessment or intervention

• **Women with severe hypertension** should receive antihypertensive therapy promptly to reduce the risk of stroke.

• **Women with an abnormal fetal heart rate tracing or low biophysical profile score** should be managed according to usual clinical standards.

• **Women with severe right upper quadrant/epigastric pain** may have hepatic bleeding or hepatic swelling portending liver rupture. The pain may be associated with hypotension and tachycardia; shoulder, back, or neck pain; dyspnea or pain on inspiration; nausea/vomiting; and/or abdominal distention beyond that expected for the pregnant state.
• In a series of 33 HELLP patients complaining of severe right upper quadrant abdominal pain and either shoulder pain, neck pain, or relapsing hypotension, imaging studies revealed an abnormal liver in 45 percent, most commonly subcapsular hematoma and intraparenchymal hemorrhage.

• In the overall population of patients with HELLP, however, the incidence of subcapsular hematoma is much less, estimated to be 0.9 to 1.6 percent.
• The aminotransferases in women with hepatic bleeding are usually modestly elevated, but values of 4000 to 5000 IU/L can occasionally be seen.

• Because the correlation between the magnitude of laboratory abnormalities and hepatic histology is poor, women with severe symptoms should undergo an appropriate imaging study expeditiously to look for hepatic bleeding, even if liver enzymes are not severalfold above the normal range.

• Bedside ultrasound screening is a good initial study, followed by formal ultrasound examination and computed tomography (CT) or magnetic resonance imaging (MRI), when needed for clinical decision making.
• The hematoma may remain contained, or rupture, with resulting hemorrhage into the peritoneal cavity. Rupture is a life-threatening complication for both the mother and fetus, especially if diagnosis and treatment are delayed.

• The management of a hematoma is to support the patient with volume replacement and transfusion of blood and blood products, as needed. Prompt delivery is indicated once she is hemodynamically stable and severe anemia and coagulopathy, if present, have been corrected. We stabilize the mother before delivery, even in cases with nonreassuring fetal heart rate patterns or a low biophysical profile score.

• A team experienced in liver trauma surgery should be consulted.

• A stable contained hematoma may be managed conservatively. Operative management of an expanding or ruptured hematoma includes packing, drainage, hepatic artery ligation, and/or resection of affected areas of the liver.

• For patients with intractable hemorrhage despite these interventions, administration of recombinant factor VIIa and liver transplantation have been successful in case reports.
• Repeat ultrasound evaluation of the liver is performed 48 hours after delivery.
• If stable, repeat testing is performed again in one week and at six weeks postpartum.
• In general, most patients will be discharged by one week postpartum if the images are stable.
• If laboratory abnormalities are resolving after delivery, the patient may be discharged home with outpatient follow-up.
• It may take months for a hematoma to resolve completely.
• Surgical intervention in patients who develop a hematoma after delivery is indicated in those with hemodynamic instability, persistent bleeding, increasing pain, or continued expansion of the hematoma on serial ultrasound examinations.

• Percutaneous embolization of the hepatic arteries is a reasonable first-line therapy in women who are hemodynamically stable.

• There are no ongoing hepatic sequelae following recovery.
• Women with DIC, pulmonary edema, or acute kidney injury should be stabilized and delivered.

• Intravenous fluids are administered as in patients with preeclampsia. **Candidates for prompt delivery** — The cornerstone of therapy for HELLP occurring during pregnancy is delivery, which is the only effective treatment.

• There is consensus among experts that prompt delivery is indicated after maternal stabilization for any of the following;

  • Pregnancies ≥34 weeks of gestation or below the limit of viability
  • Fetal demise
  • Abruptio placentae
• In the absence of any of these three scenarios or the urgent clinical scenarios described above (hepatic bleeding, DIC, pulmonary edema, acute kidney injury, abnormal fetal heart rate pattern), delivery may be delayed until a course of corticosteroids has been administered and completed.

• Magnesium sulfate is given intravenously to patients on the labor and delivery unit to prevent convulsions and for fetal/neonatal neuroprotection in pregnancies between 24 and 32 weeks of gestation with a live fetus.
• We do not manage patients with HELLP syndrome expectantly at any gestational age and consider conservative management for more than 48 hours investigational.

• the aim of expectant management is to improve neonatal morbidity and mortality. There is no evidence demonstrating improvement in overall perinatal outcome with expectant management compared with pregnancies delivered after a course of corticosteroids and no maternal benefits from expectant management. The following studies support our approach:
In a study that treated 128 women with HELLP <34 weeks of gestation with volume expansion and pharmacologic vasodilation under invasive hemodynamic monitoring, delivery was necessitated in 22/128 (17 percent) of patients within 48 hours; the remaining patients had a median prolongation of pregnancy of 15 days.

Although there was no maternal mortality or serious maternal morbidity and more than one-half (55/102) of the women had complete reversal of their laboratory abnormalities with expectant management, 11 fetal and 7 neonatal deaths occurred.

In another series, 41 women with HELLP <35 weeks of gestation were managed expectantly. Delivery was required within 48 hours in 14/41 (34 percent), the remaining patients had a median prolongation of pregnancy of three days, and more than one-half (15/27) had complete reversal of their laboratory abnormalities. However, there were 10 fetal deaths.
• Management of candidates for 48 hour delay before delivery

• Betamethasone administration to promote fetal pulmonary maturity – When both the maternal and fetal status are reassuring and the gestational age is above the lower limit of viability and <34 weeks of gestation, we administer a course of betamethasone before delivering pregnancies complicated by HELLP syndrome

• Although a short delay in delivery for betamethasone administration does not appear to increase maternal or fetal morbidity or mortality, we advise not attempting delaying delivery beyond 48 hours because disease progression usually occurs, sometimes with rapid maternal deterioration.
• We do not give betamethasone for fetal lung maturity in pregnancies with gestational age ≥34 weeks since no patients with HELLP were enrolled in randomized trials of the efficacy of steroids after 34 weeks. During administration of betamethasone, all women are kept in labor and delivery with continuous fetal monitoring.

• ● Magnesium sulfate is initiated at the time of admission and continued through delivery and the postpartum period to prevent maternal seizures and for fetal/neonatal neuroprotection.

• ● Antihypertensive medication is administered to control severe hypertension, if present.
• repeats the complete blood count and platelet count at 24 and 48 hours after administering steroids and more often if clinical deterioration is suspected.

• The ACOG recommends laboratory testing at least at 12 hour intervals until delivery and in the postpartum period.

• This information is useful when considering whether to administer red blood cell transfusions, whether neuraxial anesthesia can be performed safely and whether platelet transfusion is indicated.
• **Indications for red cell transfusion**
  - We transfuse red blood cells if the hemoglobin is <7 g/dL and/or if the patient has ecchymosis, severe hematuria, or suspected abruption.

• **Indications for platelet transfusion**
  - Actively bleeding patients with thrombocytopenia should be transfused with platelets. Platelet transfusion may be indicated to prevent excessive bleeding during delivery if the platelet count is less than 20,000 cells/microL, but the threshold for prophylactic platelet transfusion in this setting is controversial.
• The decision depends on patient-specific factors; consultation with the hematology service may be helpful.

• It is also useful to notify the blood bank that platelet transfusions may be required.

• If cesarean delivery is planned, platelet transfusion may be required. Some experts recommend platelet transfusion to achieve a preoperative platelet count greater than 40,000 to 50,000 cells/microL, but the minimum count before a neuraxial procedure is controversial and depends on factors in addition to platelet concentration.
Route of delivery

• Vaginal delivery is desirable in the absence of standard indications for cesarean delivery. We induce women regardless of gestational age when the cervix is favorable.

• When the cervix is unfavorable, we believe cesarean delivery is probably preferable to induction in pregnancies less than 30 to 32 weeks of gestation, especially if there are signs of fetal compromise (growth restriction, oligohydramnios).

• Induction of these pregnancies, even with use of cervical ripening agents, generally has a high failure rate and is often prolonged, thereby potentially exposing the mother and fetus to a higher risk of complications from severe HELLP syndrome.
Anesthesia/analgesia

- Thrombocytopenia and coagulation abnormalities may preclude use of neuraxial anesthesia for labor and delivery.
- The minimum platelet count necessary to safely perform neuraxial anesthesia is unknown, and practice varies.
- Use of neuraxial and general anesthesia for these patients is reviewed separate.
- Opioids administered intravenously provide some pain relief without risk of maternal bleeding, which may occur with intramuscular administration or with placement of neuraxial anesthesia, removal of a neuraxial catheter, or placement of a pudendal nerve block.
- However, there is no contraindication to perineal infiltration of an anesthetic for performing an episiotomy or repairing the perineum.
Cesarean delivery

• In patients with severe laboratory abnormalities that are suggestive of liver hematoma, we perform a midline skin incision.

• After delivery of the fetus, if preoperative imaging was not performed, the liver may be palpated very gently to assess for the presence of an unruptured hematoma.

• Because of the increased risk of subfascial and wound hematoma in women with thrombocytopenia who undergo cesarean delivery, the author places a subfascial drain and leaves the skin incision open for the first 48 postoperative hours.

• Some surgeons place a subfascial and/or suprafascial drain and close the incision with staples, so it is easy to open partially if a hematoma develops.

• The management of the abdominal wall incision after delivery should be individualized, depending on the surgeon's assessment of risk of hematoma/seroma development.
POSTPARTUM COURSE

• Laboratory values may initially worsen in the 48 hours following delivery (eg, platelet count usually decreases by 40 percent/day, hematocrit falls, and liver enzymes increase) , which is the reason that the ACOG recommends laboratory testing at least at 12 hour intervals in the postpartum period . We stop checking laboratory values once they are clearly beginning to return to normal.

• Although liver enzymes return to normal postpartum, in one report, total bilirubin levels were elevated in 11 (20 percent) of the women who had liver function tests checked 3 to 101 months after delivery.
• An upward trend in platelet count and a downward trend in lactate dehydrogenase (LDH) concentration are usually seen by the fourth postpartum day in the absence of complications.

• In a series of 158 women with HELLP syndrome, platelet counts decreased until 24 to 48 hours after delivery, while serum LDH concentration usually peaked at this time.

• In all patients who recovered, a platelet count greater than 100,000 cells/microL was achieved with supportive care alone by the sixth postpartum day or within 72 hours of the platelet nadir.

• Others have reported similar findings. The platelet count may rebound; one group reported values of 413,000 to 871,000 cells/microL.
• If the platelet count continues to fall and LDH continues to rise after the fourth postpartum day, then diagnoses other than HELLP syndrome (eg, primary thrombotic microangiopathy) should be considered.

• However, recovery can be delayed in women with particularly severe HELLP, such as those with disseminated intravascular coagulation (DIC), platelet count less than 20,000 cells/microL, renal dysfunction, or ascites.

• These women are at risk of developing pulmonary edema and acute kidney injury.

• Magnesium sulfate is usually continued for 24 to 48 hours postpartum.
• Women who are critically ill or at substantial risk for developing serious complications can benefit from transfer to an intensive care setting, rather than a postpartum unit.

• Potential indications for intensive monitoring include threatened or actual liver rupture or fulminant liver failure, DIC, acute kidney injury, massive transfusion with concern about protecting the airway, transfusion-related acute lung injury, and cardiac ischemia or cardiomyopathy. Supportive care may involve oxygenation and ventilation, sedation, pain control, hemodynamic support, monitoring, volume management, nutritional support, stress ulcer prophylaxis, and venous thromboembolism prophylaxis.
OUTCOME AND PROGNOSIS

• Maternal outcome
• Complications — outcome for mothers with HELLP is generally good;
• however, serious complications are relatively common.
• complications were observed
  • ● Bleeding – 55 percent required transfusions with blood or blood products; 2 percent required laparotomies for major intraabdominal bleeding
  • ● Disseminated intravascular coagulation (DIC) – 21 percent
  • ● Abruptio placentae – 16 percent
  • ● Acute renal failure – 8 percent
  • ● Pulmonary edema – 6 percent
  • ● Subcapsular liver hematoma (or hepatic rupture) – 1 percent
  • ● Retinal detachment – 1 percent
  • ● Death – 1 percent
• Many of these complications are interdependent (e.g., abruptio placentae is a common obstetric etiology of DIC, which, in turn, may induce acute kidney injury, which may lead to pulmonary edema).

• Adult respiratory distress syndrome, sepsis, stroke, cerebral hemorrhage and edema, and hepatic infarction (in patients with antiphospholipid syndrome).

• Wound complications secondary to bleeding and hematomas are common in women with thrombocytopenia.

• The risk of serious morbidity correlates with increasing severity of maternal symptoms and laboratory abnormalities.

• In a report of four patients with aspartate aminotransferase levels >2000 IU/L and lactate dehydrogenase levels >3000 IU/L, all had disordered mental status, jaundice, intense hemolysis, and extreme hypertension; one had multiorgan failure; and two died.

• HELLP syndrome with or without acute kidney injury does not affect long-term renal function.
Recurrence in subsequent pregnancies

• In a 2015 meta-analysis of individual patient data from 512 women with HELLP who became pregnant again, 7 percent developed HELLP in a subsequent pregnancy.

• In addition, 18 percent developed preeclampsia and 18 percent gestational hypertension.
Prevention

• There is no evidence that any therapy prevents recurrent HELLP syndrome, but data are limited.
• The author considers HELLP syndrome a form of severe preeclampsia and prescribes low-dose aspirin in future pregnancies to reduce the risk of preeclampsia.
• .
Fetal/neonatal outcome

- Maternal laboratory parameters do not predict risk for fetal demise.
- The neonatal and long-term prognoses are most strongly associated with gestational age at delivery and birth weight.
- The overall perinatal mortality rate is 7 to 20 percent; complications of preterm delivery, intrauterine growth restriction, and abruptio placentae are the leading causes of perinatal death.
- Preterm delivery is common (70 percent; with 15 percent of births before 27 weeks).
- Leukopenia, neutropenia, and thrombocytopenia may be observed in the neonate but appear to be related to intrauterine growth restriction, prematurity, and maternal hypertension rather than HELLP.
- Maternal HELLP does not affect fetal/neonatal liver function.
MANAGEMENT OF PATIENTS PRESENTING AFTER DELIVERY

• All of the signs and symptoms of HELLP, including subcapsular hematoma and liver rupture, can initially appear in the postpartum period.

• Management is similar to that of HELLP diagnosed before delivery, except fetal status no longer needs to be considered.
SUMMARY AND RECOMMENDATIONS

• HELLP syndrome (hemolysis with a microangiopathic blood smear, elevated liver enzymes, and low platelet count) develops in 0.1 to 1 percent of pregnancies.

• The most common clinical presentation is abdominal pain and tenderness in the midepigastrium, right upper quadrant, or below the sternum. Many patients also have nausea, vomiting, and malaise, which may be mistaken for a viral illness. Hypertension and proteinuria are present in approximately 85 percent of cases. Most cases of HELLP are diagnosed between 28 and 36 weeks of gestation, but symptoms may present up to 7 days postpartum.

• The diagnosis of HELLP is based on the presence of all of the following criteria
- Hemolysis, established by at least two of the following:
  - Peripheral smear with schistocytes and burr cells
  - Serum bilirubin ≥1.2 mg/dL (20.52 micromol)
  - Low serum haptoglobin or lactate dehydrogenase (LDH) ≥2 times the upper level of normal
  - Severe anemia, unrelated to blood loss
  - Elevated liver enzymes:
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2 times the upper level of normal
  - Low platelets: <100,000 cells/microL
The three major disorders in differential diagnosis are
- acute fatty liver of pregnancy (AFLP),
- thrombotic thrombocytopenic purpura (TTP),
- pregnancy-related hemolytic-uremic syndrome (HUS).

All of which have overlapping features with HELLP

The outcome for mothers with HELLP syndrome is generally good, but serious complications such as abruptio placentae, acute kidney injury, subcapsular liver hematoma or hepatic rupture, pulmonary edema, and retinal detachment may occur. Future pregnancies are at increased risk of developing HELLP, preeclampsia, and gestational hypertension.

The short-term and long-term prognoses for the infant are primarily related to gestational age at delivery and birth weight: Preterm delivery and low birth weight are common. Maternal HELLP does not affect fetal/neonatal liver function.
Management recommendations

- The initial steps in management are to assess the mother, stabilize women who are unstable, and assess fetal status (nonstress test, ultrasound examination for biophysical profile and fetal presentation). Because of the potential for severe maternal complications, which can develop rapidly, women with HELLP should be managed at a tertiary care center with appropriate levels of maternal and neonatal intensive care.

- Women with severe hypertension should receive antihypertensive therapy promptly to reduce the risk of stroke.
• Although uncommon, severe right upper quadrant/epigastric pain may be due to hepatic bleeding, which may remain contained or rupture the liver capsule.

• The management of a hematoma is to support the patient with volume replacement and transfusion of blood and blood products, as needed. Prompt delivery is indicated once she is hemodynamically stable and severe anemia and coagulopathy, if present, have been corrected.

• A team experienced in liver trauma surgery should be consulted during maternal stabilization and prior to delivery.

• Women with disseminated intravascular coagulation, pulmonary edema, or renal failure should be stabilized and delivered.
• For pregnancies ≥34 weeks of gestation in which maternal and fetal status are reassuring, we recommend delivery rather than expectant management (Grade 1C). In this population, the potential risks of preterm birth are outweighed by the risk of developing serious complication associated with HELLP syndrome. We also deliver pregnancies below the limit of viability because expectant management is associated with a high risk of developing maternal complications without significant improvement in perinatal prognosis.
• For pregnancies above the limit of viability and <34 weeks of gestation in which maternal and fetal status are reassuring, we suggest delivery after a course of betamethasone to accelerate fetal pulmonary maturity rather than expectant management or prompt delivery (Grade 2C). Although the laboratory abnormalities of HELLP syndrome will reverse in a subgroup of patients managed expectantly and serious maternal complications are uncommon with careful maternal monitoring, overall perinatal outcome is not improved with expectant management.
• For pregnancies less than 30 to 32 weeks with an unfavorable cervix, we suggest cesarean delivery (Grade 2C). These patients are likely to have a prolonged induction if vaginal delivery is attempted.

• We recommend not administering dexamethasone for treatment of HELLP syndrome (Grade 1B). Dexamethasone does not accelerate resolution of laboratory abnormalities or reduce the risk of maternal complications.
## Variation in the Features and Management of Thrombotic Microangiopathic Hemolytic Anemia

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<th>Diagnosis</th>
<th>TTP</th>
<th>Postpartum Hemolytic Uremic Syndrome</th>
<th>HELLP Syndrome</th>
<th>Preeclampsia or Eclampsia</th>
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<td>Time of onset</td>
<td>Usually &lt; 24 wk</td>
<td>Postpartum</td>
<td>After 20 wk, most &gt; 34 wk</td>
<td>After 20 wk, most &gt; 34 wk</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>+++</td>
<td>++</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>CNS symptoms</td>
<td>+++</td>
<td>±</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Liver disease</td>
<td>±</td>
<td>±</td>
<td>+++</td>
<td>±</td>
</tr>
<tr>
<td>Renal disease</td>
<td>±</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Rare</td>
<td>±</td>
<td>±</td>
<td>++</td>
</tr>
<tr>
<td>Effect on fetus</td>
<td>Placental infarct can lead to IUGR and mortality</td>
<td>None, if maternal disease is controlled</td>
<td>Placental ischemia/increased neonatal mortality</td>
<td>IUGR; occasional mortality</td>
</tr>
<tr>
<td>Effect of delivery</td>
<td>None</td>
<td>None</td>
<td>Recovery</td>
<td>Recovery</td>
</tr>
<tr>
<td>Management</td>
<td>PEX</td>
<td>Supportive (±PEX)</td>
<td>Supportive/steroids (±PEX)</td>
<td>Supportive</td>
</tr>
</tbody>
</table>

CNS, central nervous system; HELLP, hemolysis, elevated liver enzymes, and low platelets; IUGR, intrauterine growth restriction; PEX, plasma exchange; TTP, thrombotic thrombocytopenic purpura.
Differential Grid for Imitators of Severe Preeclampsia

<table>
<thead>
<tr>
<th></th>
<th>PreEclampsia</th>
<th>AFLP</th>
<th>TTP</th>
<th>HUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytosis</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Anemia</td>
<td>±</td>
<td>-</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Elevated liver</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>transaminases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated bilirubin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Elevated ammonia</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Elevated creatinine</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Elevated uric acid</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

AFLP, acute fatty liver of pregnancy; HUS, hemolytic uremic syndrome; LDH, lactate dehydrogenase; TTP, thrombotic thrombocytopenic purpura.
WITH THANKS