HELLP SYNDROME
(Hemolysis, elevated liver enzymes and low platelets)

Background
1. Definition: A Syndrome, characterized by
   - Hemolysis (H)
   - Elevated liver enzymes (EL)
   - Low platelets (LP)
2. Classification: HELLP syndrome can be classified as Class I, II, or III or full (complete) or partial
   - The Tennessee classification system
     - Complete HELLP syndrome
       - Hemolysis may be indicated by elevated LDH (≥ 600 IU/L), abnormal peripheral smear and elevated serum bilirubin (>1.2 mg/dl),
       - Elevated Liver Transaminases (ALT/AST) (>70 IU/L)
       - Platelet count < 100,000/μL
     - Patient with some, but not all, of these characteristics is considered to have “partial” HELLP syndrome
   - The Mississippi classification system
     - Severe (Class I) HELLP syndrome: LDH levels >600 IU/L, AST and/or ALT levels >70IU/L and platelet count <50,000/uL
     - Moderate (Class II) HELLP syndrome: LDH levels >600 IU/L, AST and/or ALT levels >70IU/L, but platelet count is between 50,000/uL and 100,000/uL
     - Mild (Class III) HELLP syndrome: LDH levels >600 IU/L, AST and/or ALT levels >40 IU/L and platelet count is between 100,000/uL and 150,000/uL
3. General Information
   - Relationship between preeclampsia and HELLP syndrome is controversial. HELLP may be a separate entity, because 15 to 20% of HELLP patients do not have hypertension or proteinuria

Pathophysiology
1. Pathology
   - Liver important to pathogenesis of HELLP syndrome
   - Pathophysiology not completely understood
   - Hypotheses:
     - Placenta-associated liver injury involving CD95 L, a mediator of hepatocytes apoptosis
     - Disordered immunological factors
     - Possible similarity between systemic inflammatory response (SIRS) and HELLP syndrome

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2. Incidence, Prevalence
   - Occurs in 0.2-0.6% of all pregnancies \(^3\)
   - HELLP-type lab abnormalities are present in 2%-20% of pregnancies complicated by preeclampsia \(^1,8,9\)
   - The same abnormal labs are present in 10.8%-32.1% of cases of eclampsia \(^1,8,9\)
   - HELLP normally presents in third trimester of pregnancy \(^1,10\)
   - 69% presents in ante-partum period; 31% in post-partum period \(^2,10\)

3. Risk Factors \(^1,2,10\)
   - Caucasian
   - Maternal age > 25 years
   - Multiparous
   - Previous history of poor pregnancy outcome

4. Morbidity/Mortality
   - Maternal morbidity includes: \(^6\)
     - Hematologic – DIC, hematuria (bleeding rare)
     - Cardiopulmonary – pulmonary edema
     - Central Nervous System/visual – stroke, mental status changes and/or coma
     - Renal – acute tubular necrosis, acute renal failure
     - Hepatic – liver rupture/hemorrhage
     - Infection/sepsis
     - Retinal detachment
     - Obstetric – Cesarean delivery, placental abruption
   - Significant mortality occurs with severe (class I) disease (60%) \(^6\)

Diagnostics

1. History \(^1,4,10\)
   - Right upper quadrant or epigastric pain, nausea or vomiting
   - Prodromic malaise
   - Viral syndrome symptoms
   - Headache
   - Visual changes (17%)
   - Hematuria, ecchymosis, or petechial hemorrhages

2. Physical Exam: may be normal \(^1,4,6,10\)
   - Tenderness in the right upper quadrant, mid-epigastrium
   - Hypertension, (mild in 15% to 50%)
   - Proteinuria
   - Hypertension and Proteinuria present in 85%, but may be absent in patients with severe HELLP syndrome
   - Ascites
   - Signs of Hemolysis
     - Jaundice
Signs of thrombocytopenia
- Petechiae
- Splinter Hemorrhages
- Bleeding gums

3. Other Clinical Features (see also maternal morbidity)
- Severe maternal morbidity may be present at the beginning of HELLP syndrome or can develop later: 1, 4, 6, 10

4. Diagnostic Testing
- Diagnostic Criteria for HELLP syndrome include: 1
  - Hemolysis (LDH >600 IU/L, elevated indirect bilirubin, low serum haptoglobin and abnormal peripheral smear
  - Thrombocytopenia (≤ 100,000 cells/microL)
  - Elevated AST/ALT ≥ 70 IU/L
- CBC: low platelets, hematocrit may be low or normal because of hemoconcentration: 10
- Peripheral smear: schistocytes, burr cells, echinocytes: 4
- Elevated liver transaminases, abnormal creatinine if associated with renal dysfunction, electrolyte abnormalities
- Suggestive signs of hemolysis: 1
  - Elevated serum LDH (>600 IU/L)
  - Elevated indirect bilirubin
  - Low serum haptoglobin (≤25mg/dL)
  - Serum AST ≥ 70 IU/L
- PT, PTT and fibrinogen level can be affected when DIC is present: 10
- Urinalysis: hemoglobinuria, proteinuria
- LDH and Platelet count are best lab markers to guide therapy: 8, 10
- Positive D-dimer test in preeclamptic women is a predictive for developing HELLP syndrome: 11
- Imaging tests – Ultrasound, Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), are helpful in cases where complications are suspected (hepatic infarction, hematoma): 1, 8, 10

Differential Diagnosis
1. Key Differential Diagnosis
- Acute fatty liver of pregnancy: 3
  - May be difficult to distinguish from HELLP
  - Presents between the 30th and 38th weeks of pregnancy
  - Nausea, vomiting, anorexia, epigastric or RUQ pain, malaise, headache and jaundice may present for 1-2 weeks
  - Hypertension and proteinuria are generally absent
  - Differentiating HELLP from acute fatty liver: prolonged PT, aPTT, low glucose and elevated creatinine are MORE common in acute fatty liver compared to HELLP
- TTP – HUS (Thrombotic Thrombocytopenic Purpura – Hemolytic Uremic Syndrome):
  - May be difficult to distinguish from HELLP
  - Share common pathophysiological characteristics
  - TTP can be present in first trimester, whereas HELLP generally presents later in pregnancy
  - In TTP, the percentage of schistocytes on peripheral smear is higher
  - Coagulation abnormalities in TTP affect only platelets. In HELLP syndrome, affects factor V and VIII.
  - HUS – starts in the post partum period and mainly affects kidneys

2. Extensive Differential Diagnosis
   - Antiphospholipid Syndrome
   - Systemic lupus erythematous
   - Pyelonephritis
   - Viral hepatitis
   - Appendicitis
   - Gastroenteritis
   - Cholecystitis/lithiasis
   - Glomerulonephritis
   - Idiopathic thrombocytopenic purpura
   - Hepatic encephalopathy
   - Kidney stones
   - Hyperemesis gravidarum

**Medical treatment**

1. Mainstay of therapy is delivery
   - Initial: assess stability of mother, fetus
   - Fluid management, antihypertensive treatment and magnesium sulfate to prevent seizure
   - Assess for evidence of labor, and cervical readiness: bishop score

2. Immediate delivery is recommended for:
   - Pregnancies ≥ 34 weeks of gestation.
   - Pregnancies before 34 weeks of gestation, if there is nonreassuring fetal status and/or severe maternal complications such as DIC, abruptio placenta, liver infarction or hemorrhage, renal failure
     - The risks related to HELLP syndrome are higher than the possible risks of preterm birth
     - Preferred route of delivery: vaginal, if possible

3. Delayed delivery for pregnancies < 34 weeks of gestations, stable mom and fetus
   - after a short course of steroids when fetal and maternal status is reassuring (SOR:B)
   - No expectant (conservative) management is recommended
Benefits of glucocorticoids to improve maternal outcome is still controversial. (SOR:A)  
- No proven evidence of improvement in severe maternal morbidities, maternal mortality or perinatal deaths

4. Elective Cesarean delivery
  - HELLP syndrome develops before 30 weeks of gestation, patient not in labor, Bishop score <5
  - Gestational age below 32 weeks with unfavorable bishop score plus restricted fetal growth and/or oligohydramnios

5. Prophylaxis with magnesium sulfate should be given to prevent seizure, regardless of the presence of hypertension

6. Bolus of 4-6 g of magnesium sulfate given over 20 minutes, followed by a maintenance infusion of 2 g per hour. Continue for 48 hrs post partum

7. Antihypertensive therapy should be started, if blood pressure remains greater than 160/110 mm Hg.
  - Maintain SBP <155 mm Hg and DBP < 105 mm Hg.

8. Commonly used antihypertensive drugs are hydralazine, labetalol and nifedipine.
9. Diuretics are contraindicated.
10. Plasmapheresis has shown to be effective in patients with severe laboratory abnormalities.

Counseling
1. Subsequent pregnancy: higher risk (between 16% -52%) of having some form of gestational hypertension
  - Recurrence rate varies between 2% to 19%
2. Patients with past history of HELLP syndrome can use oral contraceptive pills.
3. No preventive therapy for recurrence
4. Patients with HELLP: should be screened for anti-phospholipid antibodies

Prognosis
1. Even though relapses can occur, patients with HELLP syndrome tend to recover completely
2. Emotional trauma can be significant
3. Patients with Class I HELLP syndrome prone to be at higher risk for recurrence
4. HELLP syndrome, associated with or without renal failure, does not have effect on long term renal function

Patient Education
References

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