

## HELLP Syndrome - a pregnancy disorder with poor prognosis

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### ABSTRACT

HELLP syndrome is a pregnancy-specific disorder defined by hemolysis, elevated liver enzymes and low platelet count that is found in parturients, more frequent in older multiparas. It is frequently associated with severe preeclampsia or eclampsia, but can also be diagnosed in the absence of these disorders. The etiology of HELLP syndrome is unknown, and the pathogenesis of this disorder (including the hepatological manifestations) is not fully understood. The most widely accepted hypotheses are: a change in the immune feto-maternal balance, platelet aggregation, endothelial dysfunction, arterial hypertension and an inborn error of the fatty acid oxidative metabolism. Hepatic involvement occurs by intravascular fibrin deposition and hypovolemia. Serum LDH and platelet count are the two most important clinical tools for disease assessment. LDH reflects both the extent of hemolysis and hepatic dysfunction. Maternofetal complications cause a 7.0-70.0% perinatal mortality rate and a 1.0-24.0% maternal mortality rate. The recognition of HELLP syndrome and an aggressive multidisciplinary approach and prompt transfer of these women to obstetric centers with expertise in this field are required for the improvement of materno-fetal prognosis.

**Keywords:** Pre-eclampsia, eclampsia, HELLP syndrome.

### INTRODUCTION

HELLP syndrome is a multisystemic disorder that complicates pregnancy with the laboratory evidence of hemolysis, hepatic dysfunction and thrombocytopenia. It was first described by Weinstein in 1982 and the acronym is for hemolysis (H) elevated liver enzymes (EL) and low platelets (LP).<sup>1</sup>

HELLP syndrome is frequently associated with severe preeclampsia or eclampsia, but can also be diagnosed in the absence of these disorders. It can present both as the primary expression of the preeclampsia process in pregnant patients or as a secondary phenomenon in patients with complicated sepsis, adult respiratory distress syndrome (ARDS), renal failure, and multiple organ disease with disseminated intravascular coagulation (DIC).

In 70.0% of the cases, the disorder is diagnosed antepartum: 10.0% before 27 weeks of gestation, 70.0% between 27-37 weeks and 20.0% after 37 weeks.<sup>2</sup> In 30.0% of cases it is diagnosed postpartum. The risk of recurrence in a subsequent pregnancy is estimated at 19-27.0%.<sup>2</sup>

### PATHOGENESIS

The pathogenesis of HELLP syndrome is not completely understood. It can be considered as an acute rejection of the fetal allograft.

The significantly increased levels of tissue plasminogen activator and plasminogen activator inhibitor-1 (PAI-1) in the context of HELLP syndrome compared to normal pregnancy suggest that platelet activation and the alteration of plasminogen activation are involved in the pathogenesis of this syndrome.<sup>3</sup>

The pathogenesis of liver involvement in HELLP syndrome is unknown. A complex chain of events is initiated in the liver by intravascular fibrin deposition with sinusoidal obstruction, associated with hypovolemia, which is demonstrated by a decrease in the liver blood flow on Doppler examination in patients with preeclampsia, who have subsequently developed HELLP syndrome.<sup>4,5</sup>

Hepatic ischemia causes hepatic infarction, subcapsular hematomas and intraparenchymatous hemorrhage, which may result in hepatic rupture, with vital risk.<sup>6</sup>

Thrombocytopenia is the major and early cause of alteration of coagulation in HELLP syndrome. Multiple factors are involved in the pathogenesis of thrombocytopenia such as vascular endothelial damage, alteration of prostacyclin production and increased fibrin deposits in the vascular wall. Acceleration of platelet destruction, platelet activation, increased platelet volume and megakaryocyte productions have also been found. When platelet count decreases to less than 50,000/mm, disseminated intravascular coagulation (DIC) can occur, with a worse prognosis.

## DIAGNOSIS

### Clinical picture

Onset occurs in the last trimester of pregnancy in 70.0% of patients, and immediately after delivery in rest of the patients. Eclampsia was present in 52.0%, correlated with headache, nausea and vomiting, visual disorders and epigastric pain, with a reserved maternal prognosis.

Some patients present a pseudo influenza syndrome, complaining of headache and visual disorders. Most cases (90.0%) present a prodrome of several days before seeing a doctor. In certain cases, hemorrhage or gastrointestinal bleeding may occur.<sup>7</sup>

Physical examination reveals tenderness in the right upper abdominal quadrant, a significant weight gain and generalized edemas.

Importantly, severe arterial hypertension is not constant and even absent in HELLP syndrome. Because early diagnosis is crucial, pregnant women with these symptoms should undergo laboratory investigations for HELLP syndrome.

An association with diabetes insipidus or with antiphospholipid syndrome might be evident. In women with an early onset of preeclampsia < 34 weeks, antiphospholipid antibodies should be searched for.<sup>8</sup> In the presence of this association, maternal and fetal mortality increase up to 50.0%.

### LABORATORY INVESTIGATION

The early diagnosis of HELLP syndrome is based on the detection of hemolysis, altered liver function tests, and renal dysfunction.

**Hemolysis** is evidenced by an increase in lactate dehydrogenase (LDH) levels >600 IU/L and a decrease in serum haptoglobin values. These early sensitive markers of HELLP syndrome can be detected before the increase of serum unconjugated bilirubin level and decrease of hemoglobin values. Glutathione transferase and glutathione S transferase are early markers of the hemolysis and liver damage. The prothrombin time and the activated partial thromboplastin time (APTT) are normal in early stages, but the levels of fibrin degradation products, D-dimers, and thrombin-antithrombin complexes are increased, being markers of secondary fibrinolysis and platelet aggregation.

**Thrombocytopenia** is the major and early cause of alteration of coagulation in HELLP syndrome.

Two classifications for HELLP syndrome are commonly used. The Tennessee System classification is based on the assessment of the following parameters: AST>70

UI/L, LDH >600 UI/L, thrombocytes <100,000/ mm<sup>3</sup>. Accordingly, there are two forms: **complete** (all elements present) and **partial** HELLP syndrome (one or two elements present). The Mississippi classification relies on the thrombocyte counts: class I (<50,000/mm<sup>3</sup>), class II (50,000- 100,000/mm<sup>3</sup>) and class III (100,000-150,000/mm<sup>3</sup>).

**Liver imaging** is important for the evaluation of subcapsular or intraparenchymal hemorrhage and hepatic rupture. In pregnant women, ultrasound (US) and MRI are preferred due to the absence of risk of ionizing radiation. CT scan is the method of choice in the postpartum period. Transabdominal ultrasonogram evidences intrahepatic hematomas as hypoechogenic structures. CT or MRI can detect hemoperitoneum, intrahepatic hematoma, and an irregular interface between the normal hepatic parenchyma and intrahepatic hematoma corresponding to the capsule rupture site.

### DIFFERENTIAL DIAGNOSIS

The main disorders which should be considered in the differential diagnosis are gastrointestinal and liver diseases, renal and hematologic disorders.

**AFLP:** A difficult differential diagnosis is acute fatty liver of pregnancy (AFLP), which also occurs in multiparous women after 30 weeks of gestation. It has similar manifestations as HELLP syndrome (cytolysis and thrombocytopenia), but hypoglycemia and prolongation of the prothrombin time are present and the evolution is towards acute liver failure.

**DIC:** HELLP syndrome should not be considered as a variant of disseminated intravascular coagulation (DIC), even if microangiopathic hemolytic anemia is characteristic for both disorders. There are significant differences between these two entities. The prothrombin time, partial thromboplastin time and serum fibrinogen levels are normal in HELLP syndrome, but are usually altered in DIC. Evaluation of more sensitive markers of DIC, such as antithrombin III, alpha-2 antiplasmin, plasminogens, fibrin monomer, D-dimers, fibronectin, fibrinopeptide A, prekallikrein, might better differentiate DIC from HELLP syndrome

### COMPLICATIONS AND PROGNOSIS

Cerebral hemorrhage is the most severe complication, being fatal in 50.0-65.0% of cases. The sudden increase in diastolic blood pressure over 120 mmHg raises the risk of lethal complications such as hypertensive encephalopathy, ventricular arrhythmias, DIC. Cerebral complications are rare, but particularly severe.

The maternal mortality rate varies from 18 to 86.0%,

and the perinatal mortality can reach 80.0%. About 60.0% of fetuses die intrauterine, 30.0% show intrauterine growth retardation, and 25.0% thrombocytopenia.

## THERAPY

The management of patients with pre-eclampsia and HELLP syndrome is controversial. Most therapeutic modalities are similar to those applied for severe pre-eclampsia. Treatment should be performed in Intensive Care Units (ICU) with dialysis and ventilatory support in severe cases, and consists of plasma expanders, antithrombotic agents, heparin, antithrombin, aspirin in low doses, prostacyclin, immunosuppressive agents, steroids, fresh frozen plasma, dialysis.

The administration of corticosteroids is followed by a rapid improvement of clinical and laboratory parameters, allowing the delay of delivery. The improvement of thrombocytopenia has been more frequently observed for the low doses compared to the high doses.<sup>9</sup> However steroid therapy should only be administered to very well selected cases, since it does not improve prognosis.<sup>10-13</sup>

Plasmapheresis with fresh frozen plasma has been proposed as a therapeutic method in patients who show a progressive increase in bilirubinemia, serum creatinine, and have severe thrombocytopenia. This is also recommended for patients in whom HELLP syndrome persists for more than 72 hours postpartum, but has no favorable results in patients with fulminant hemolysis.<sup>14</sup>

Hypertension in preeclampsia can be treated with i.v. magnesium sulfate, hydralazine, calcium channel antagonists, and nitroglycerine or sodium nitroprusside (in hypertensive crisis). Diuretics are not used as a routine because they increase maternal hypovolemia and worsen uteroplacental hypoperfusion.<sup>2</sup>

## OBSTETRIC APPROACH

The induction of delivery is the only specific therapy in HELLP syndrome. In pregnant women with a gestational age of more than 34 weeks, immediate induction of delivery is recommended. Severe maternal complications are more frequent when the induction of pregnancy is delayed for more than 12 hours.<sup>15</sup> At a gestational age between 24-34 weeks, the use of corticosteroids to accelerate fetal pulmonary maturity, to reduce the risk of necrotic hemorrhagic rectocolitis and intraventricular hemorrhage of the fetus.

If no obstetric complications are present, vaginal delivery is preferred. Delivery by cesarean section is required in 60.0% of cases. In the case of cesarean section, subfascial drainage may be necessary in order to reduce the risk of hematomas.

Epidural anesthesia can be recommended when the thrombocyte count is higher than 100,000/mm<sup>3</sup>, when there are no coagulation disorders and the bleeding time is normal.<sup>16</sup>

## SURGICAL APPROACH

The rupture of a subcapsular liver hematoma followed by shock represents a surgical emergency. Massive blood transfusions and the correction of coagulopathy with fresh frozen plasma and thrombocyte mass are mandatory.<sup>17</sup> Immediate laparotomy is recommended. The options are: surgical ligation of the hemorrhagic hepatic segment, suture and drainage, suture of the omentum, surgical mesh at the level of the liver in order to improve its integrity.<sup>17</sup> Emergency surgical intervention should be performed if the patient shows hemodynamic instability, massive blood loss, increasing pain or hematoma infection.

The use of argon coagulation for hemostasis after the rupture of liver hematoma has been reported. Administration of recombinant F VIIa might suppress the hemorrhage and save the patient's life in cases that do not respond to surgical treatment.<sup>18</sup>

**Follow up:** Repeated lists of platelet count and LDH serum concentration until platelet count is increased to >100,000/mm<sup>3</sup> and effective diuresis is achieved.

**Counseling for future pregnancy:** The use of low dose aspirin (80mg/day) is recommended from early in pregnancy to 36 wks in patients with previous HELLP syndrome, particularly if it was virulent or complicated.

HELLP syndrome is due to a generalized microangiopathy usually occurring in older multiparous women in the third trimester of pregnancy, which develops with focal liver involvement, hemolysis and thrombocytopenia. Hepatic (rupture), cerebral (hemorrhage) and DIC complications are severe and are associated with a high maternal death rate and important perinatal mortality.

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