HELLP Syndrome – a Multisystemic Disorder

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Abstract

HELLP syndrome is a multisystemic disorder with an incidence of 0.17-0.85% of all pregnancies. Its etiopathogenesis is not completely 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. Materno-fetal complications cause a 6.7-70% perinatal mortality rate and a 1-24% maternal mortality rate. The recognition of HELLP syndrome and the rapid initiation of therapy are required for the improvement of materno-fetal prognosis.

Key words
HELLP syndrome - preeclampsia- pregnancy - liver hematoma - diagnosis- therapy

Introduction

HELLP syndrome is a multisystemic disorder that complicates pregnancy and has a poor prognosis. It was first described by Weinstein in 1982. The acronym is for hemolysis (H), elevated liver enzymes (EL), thrombocytopenia (low platelet count – LP) (1). The name of the syndrome (hell + help) suggests the severity of maternal and fetal prognosis. It occurs in 0.17-0.85% of all pregnancies, and is more frequent in older multiparous Caucasian women. In 70% of the cases, the disorder is diagnosed antepartum: 10% before 27 weeks of gestation (WG), 70% between 27-37 WG, 20% after 37 WG (2). In 30% of cases it is diagnosed postpartum.

HELLP syndrome is frequently associated with severe preeclampsia or eclampsia, but can also be diagnosed in the absence of these disorders. The risk of recurrence in a subsequent pregnancy is estimated at 19-27% (3).

Pathogenesis

The pathogenesis of HELLP syndrome is not completely understood.

Morphopathological lesions in preeclampsia involve a deficient remodeling of maternal vascularization through the placental trophoblast, occurring early during the course of pregnancy. Because trophoblast invasion invariably brings the fetus in contact with the immunocompetent maternal cells, feto-maternal interactions during the course of pregnancy are crucial for the prognosis (4). In the third trimester of pregnancy, there is a remarkable activation of maternal leukocytes in peripheral blood. Fetally derived soluble HLA antigen (sHLA-DR) levels are linked to the activated immunocompetent cells, and are due to an intense immune maternal response to the fetus. Since sHLA-DR molecules are able to induce cell apoptosis, even low sHLA-DR levels can be important for the regulation of the maternal immune system or for the maintenance of the feto-maternal immune balance during pregnancy (5). In HELLP syndrome, high plasma sHLA-DR levels are found. The syndrome can be considered an acute rejection of the fetal allograft. Moreover, the assessment of sHLA-DR levels can be used for the identification of the patients with preeclampsia at risk of the HELLP syndrome during pregnancy (5).

In preeclampsia, there is an abnormal expression of cell adhesion molecules, as well as of the endothelial cell growth factor and its receptor in the trophoblast, causing a uteroplacental vascular insufficiency that will result in an abnormal release and metabolization of nitric oxide, prostaglandins and endothelin in the placental tissue. These changes induce platelet aggregation, endothelial dysfunction and arterial hypertension (6). Transmembrane Fas proteins, which belong to the tumor necrosis factor receptor family (TNFRSF), expressed by T lymphocytes that regulate the invasion of the trophoblast in the myometrium, also play a role. The substitution of a single nucleotide at position 670 of the maternal (not fetal) TNFRSF6 gene...
results in an increased capacity of maternal lymphocytes to recognize and destroy the trophoblast during invasion of the uterine wall and spiral arteries, leading to an increased risk for HELLP syndrome (7).

Circulating platelets adhere to the damaged or activated endothelium, causing an increase in platelet clearance (8).

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 (9).

The vascular endothelium can be damaged by segmental vasospasm, followed by the formation of a fibrin matrix at the site of the lesion. The break of the platelet membrane and the release of arachidonic acid and other vasoactive mediators produce vasoconstriction, vasospasm and accelerated platelet aggregation (6, 9).

Endothelial cell activation, with the release of von Willebrand factor multimers, cause consumption thrombocytopenia and thrombotic microangiopathy in the HELLP syndrome. The enzyme responsible for the cleavage of von Willebrand factor multimers ADAMTS13 has also a low level in women with HELLP syndrome compared to healthy pregnant women (10).

A reduction in T and B lymphocyte function, as well as in the monocyte function, has been found, preceding the laboratory diagnosis of HELLP syndrome by 1-2 weeks (11).

An inborn error of fatty acid oxidative metabolism may occur in fetuses born in the context of HELLP syndrome. A mutation allows a long chain fatty acid, i.e. a 3-hydroxyacyl metabolite that is produced by the fetus or the placenta, to accumulate at maternal level due to a long chain 3-hydroxyacyl coenzyme A dehydrogenase deficiency (LCHAD), which results in an insufficient mitochondrial oxidation of fatty acids required for ketogenesis, once the liver glycogen source has been exhausted (12).

Hepatic involvement in pregnant women is more frequent when fetuses have a severe enzymatic deficiency (LCHAD). Given the recessive autosomal transmission, molecular diagnosis is recommended for all pregnant women with HELLP syndrome, for those with acute fatty liver of pregnancy (AFLP), as well as their partners and children (13, 14).

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 (15). Hepatic ischemia causes hepatic infarction, subcapsular hematomas and intraparenchymatous hemorrhage, which may result in hepatic rupture, with vital risk (6, 16).

HELP 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, the 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 (1, 2).

The liver pathology is similar to that of the liver in preeclampsia, presenting focal hepatocyte necrosis, periporal hemorrhage and fibrin deposits in the hepatic sinusoids. Macrovesicular fatty loading of the liver is different from that of AFLP. Hematomas are most frequently present in the right hepatic lobe (75%) (17). Liver capsular rupture, a rare but severe complication, is associated with hemoperitoneum.

**Diagnosis**

**Clinical picture**

Onset occurs in the last trimester of pregnancy in 70% of patients, and immediately after delivery in the rest of patients (18). In a study performed on 61 patients with HELLP syndrome, eclampsia was present in 52%, correlated with headache, nausea and vomiting, visual disorders and epigastric pain, with a reserved maternal prognosis (19). Some patients present a pseudoinfluenza syndrome, complaining of headache and visual disorders. Most (90%) present a prodrome several days before seeing a doctor. In certain cases, hemorrhage or gastrointestinal bleeding may occur. Physical examination reveals pain in the right upper abdominal quadrant, a significant weight gain and generalized edema. 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 paraclinical investigations for HELLP syndrome (4).

An association with diabetes insipidus (20) or with antiphospholipid syndrome might be evident (21). In women with an early onset of preeclampsia, less than 34 WG, antiphospholipid antibodies should be searched for (22). In the presence of this association, maternal and fetal mortality increase up to 50% (23).

The main disorders that should be considered in the differential diagnosis are gastrointestinal and liver diseases, renal and hematologic disorders. A difficult differential diagnosis is with AFLP, which also occurs in multiparous women after 30 WG. It has similar manifestations as HELLP syndrome (cytolysis and thrombocytopenia), but hyperglycemia and prolongation of the prothrombin time are present and the evolution is towards acute liver failure. Morphopathological aspect is of microvesicular steatosis, but liver puncture biopsy is rarely performed because of defective coagulation (24).

**Biological investigation**

The early diagnosis of HELLP syndrome is based on the detection of hemolysis, altered liver tests, and renal dysfunction (1, 2, 25, 26).
Hemolysis is evidenced by an increase in lactate dehydrogenase (LDH) levels >600 UI/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 S transferase (GST) and glutathione S transferase (GST) 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. Antithrombin III < 79%, D-dimers > 4 μg/ml and thrombin-antithrombin complexes >26 mg/ml have been proposed as criteria for the induction of delivery in HELLP syndrome (17).

Thrombocytopenia is the major and early cause of alteration of coagulation in the HELLP syndrome. Multiple factors are involved in the pathogenesis of thrombocytopenia: 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 production have also been found. An increase in the response of platelet calcium to arginin-vasopressin, which precedes thrombocytopenia and occurs in the first trimester of pregnancy, has been reported and proposed as a possible predictor of preeclampsia.

When platelet count decreases to less than 50,000/mm³, an association with DIC can be considered, with a worse prognosis (19).

Maternal platelet count decreases immediately after delivery, then rises starting with day 3 postpartum, reaching >100,000/mm³ after day 6 postpartum. The lack of an increase in platelet levels after 96 hours from delivery indicates a severe disorder, with the possible development of multiple organ failure (27).

Acute liver failure is rare due to the double vascularization of the liver and to its capacity to function under low oxygen uptake conditions. However, microangiopathy with sinusoidal obstruction causes hepatocyte necrosis responsible for the increase of aspartate aminotransferase (AST) (mean 250 UI/L) and alanine aminotransferase (ALT) levels (26). In 30% of cases, a moderate increase in gamma GT, alkaline phosphatase and serum bilirubin is found (26). As hepatic necrosis and intraparenchymal hemorrhage are focal lesions, the hepatic syntheses are maintained. The prothrombin time is normal, except for severe cases complicated by DIC.

A few patients present significant renal involvement, independent of blood pressure values and of hemolysis degree. Uric acid > 7.8 mg/dl is an independent risk factor for materno-fetal morbidity and mortality (27).

Hyaluronic acid levels increase in preeclampsia to > 100 μg/L, being a reliable marker for HELLP syndrome. The increased serum fibronectin levels indicates vascular involvement in preeclampsia. Higher α-fetoprotein or human chorionic gonadotropin (HCG) values in the second trimester of pregnancy increase the risk of HELLP syndrome up to 47 times. Markers of HELLP syndrome with a predictive value are searched for, by proteome analysis. Serum amyloid A is so far selected, at values > 3.5 mg/L (28).

**Imaging of the liver**

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 ionizing radiation. CT is the method of election in the postpartum period (29,30). Transabdominal US evidences intrahepatic hematomas as hypoechoic 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 (30). Hepatic arteriography, an invasive procedure, can establish the site of hemorrhage and is only performed before arterial embolization (30).

**Liver biopsy**

Liver biopsy has a risk of hemorrhage and hepatic rupture. Periportal hemorrhage, focal parenchymatous necrosis and macrovesicular steatosis can be observed in 1/3 of patients. Fibrin deposits and hyaline deposits are shown by immunofluorescence at the level of liver sinusoids. Liver specimens show a positive reaction with IL-1β, IL-8, TNFα and neutrophil elastase antibodies. These are negative in patients with AFLP (31).

**Classification**

Two classifications for the HELLP syndrome are commonly used (1,2). The Tennessee System classification is based on the assessment of the following parameters: AST>70 UI/L, LDH>600 UI/L, thrombocytes <100,000/mm³. 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/mm³), class II (50,000-100,000/mm³) and class III (100,000-150,000/mm³).

**Complications and prognosis**

Cerebral hemorrhage is the most severe complication, being fatal in 50-65% 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. Transcranial Doppler US evidences cerebral vascular changes similar to vasospasms. The velocity of the cerebral blood flow is increased (32).

Renal complications occur at the microvascularization level (vascular thrombosis, occlusion of renal arteriole lumens, hypoperfusion). HELLP syndrome might cause both tubular necrosis potentially reversible and cortical necrosis (in most cases with sequelae). Cortical ischemia can generate...
arterial hypertension, and microangiopathic thrombosis causes renal dysfunction. Renal failure in HELLP syndrome can be due to coagulation disorders, hemorrhage and shock. Its incidence is about 8% (27).

Nephrogenic diabetes insipidus is a rare complication. It is characterized by resistance to arginin-vasopressin mediated by high vasopressinase levels. The increased vasopressinase levels may occur as a result of deficient hepatic metabolism (33, 34).

Hepatic complications include infarction, hemorrhage and hematomas. Hepatic rupture occurs in 1/40,000 to 1/250,000 cases. Because of the presence of hepatic hemorrhage and subcapsular hematoma, minor trauma (vomiting, patient transportation, liver palpation, labor, seizures) may induce hepatic rupture. Most frequently, the rupture of Glisson capsule occurs at the lower liver margin, causing sudden epigastric pain, anemia and hypotension. Imaging or paracentesis are diagnostic for intraperitoneal hemorrhage. The maternal mortality rate varies from 18 to 86%, and the perinatal mortality can reach 80% (7).

The prognosis of pregnancies complicated by HELLP syndrome depends on early diagnosis and early therapeutic approach (2). Perinatal infantile mortality varies between 6.7 and 70%. It is caused by the premature detachment of the normally inserted placenta, intrauterine asphyxia, and prematurity. About 60% of fetuses die intrauterinely, 30% show intrauterine growth retardation, and 25% thrombocytopenia.

Maternal mortality varies between 1 and 24% and can be due to coagulation disorders, hemorrhagic complications, cardiopulmonary, central nervous system, hepatic and gastrointestinal disorders (35-37).

The critical state of the patient is improved after the induction of delivery. Patient counselling regarding the risk of recurrence of HELLP syndrome for subsequent pregnancies is mandatory, although the higher risk is for developing preeclampsia (43%) or other complications in a new pregnancy (27).

Patients with atypical forms of preeclampsia or HELLP syndrome should be investigated for antiphospholipid antibodies (38).

The early recognition of HELLP syndrome and the initiation of early therapy are required in order to ensure the favorable evolution of the mother and fetus.

**Therapy**

The management of patients with preeclampsia and HELLP syndrome is controversial. Most therapeutic modalities are similar to those applied for severe preeclampsia. 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 corticoids 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 (40-42). In an analysis performed on 170 patients with HELLP syndrome, comparing the dexamethasone group to a control group, maternal mortality and morbidity due to the premature detachment of the normally inserted placenta, acute pulmonary edema and hepatic rupture occurred at the same rate, and perinatal infantile mortality and morbidity were similar. The maternal advantage of corticotherapy was an extension of the time period between hospital admission and the induction of delivery, and the fetal advantage was an increase in weight at birth. The conclusion was that steroid therapy should only be administered to very well selected cases, since it does not improve prognosis (43, 44).

Plasmapheresis with fresh frozen plasma has been proposed as a therapeutic method in patients who show a progressive increase in bilirubinemia, serum creatinin, 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 (45, 46).

Hypertension in preeclampsia can be treated with i.v. Mg sulfate, hydralazine, calcium channel antagonists, nitroglycerine or sodium nitroprussiate (in hypertensive crisis). Diuretics are not used as a routine because they increase maternal hypovolemia and worsen uteroplacental hypoperfusion (2, 4, 47).

**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 WG, immediate induction of delivery is recommended. Severe maternal complications are more frequent when the induction of pregnancy is delayed for more than 12 hours (48). At a gestational age between 24-34 WG, a consensus of the NIH recommends 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% of cases. In the case of cesarean section, subfascial drainage may be necessary in order to reduce the risk of hematomas. If during the cesarean section, a small liver hematoma with an intact Glisson capsule is detected, its evacuation is not required. When the hematoma is extensive, even if the Glisson capsule is intact, it is recommended to open the capsule and evacuate the hematoma in order to avoid its extension and secondary hepatic rupture (49).

Epidural anesthesia can be recommended when the thrombocyte count is higher than 100,000/ mm³, when there are no coagulation disorders and the bleeding time is normal (50,51).

**Surgical approach**

The rupture of a subcapsular liver hematoma followed by shock represents a surgical emergency (52,53). Massive blood transfusions and the correction of coagulopathy with
fresh frozen plasma and thrombocyte mass are mandatory (7). Immediate laparotomy is recommended. The options are: the surgical ligature 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 (7,17,50). Emergency surgical intervention should be performed if the patient shows hemodynamic instability, massive blood loss, increasing pain or hematoma infection (54).

Recent data also support the conservative approach in patients who are hemodynamically stable, under careful clinical, biological and imaging monitoring. Favorable results have been obtained by arterial embolization during hepatic arteriography (30).

The use of argon coagulation for hemostasis after the rupture of liver hematoma has been reported. If necrotic areas are detected intraoperatively, their resection is not required in the same operative time, and can be subsequently performed (55). Administration of recombinant F VIIa might suppress the hemorrhage and save the patient’s life in cases that do not respond to surgical treatment (56, 57). Liver transplantation is necessary when hemorrhage cannot be arrested during laparotomy or in the context of fulminant liver failure (58).

**Conclusion**

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. Severe thrombocytopenia worsens prognosis. The induction of delivery, materno-fetal treatment and monitoring under ICU conditions are required.

**References**
