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# THE DIAGNOSIS AND PERINATAL MANAGEMENT IN HELLP SYNDROME

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## Abstract

***Objective**: HELLP is an obstetric syndromic complication with a challenging diagnosis and multidisciplinary complex management. The purpose of this review is to systematize the recent information from the literature regarding the diagnosis, pathogenesis, complications, management and outcome in HELLP syndrome.*

***Methods**: Specific literature regarding this topic was thoroughly evaluated using Pub Med and Cochrane databases. The keys words used were Hellp syndrome, Hellp syndrome pregnancy, Hellp syndrome management, Hellp syndrome treatment, Hellp syndrome corticosteroids, Hellp syndrome pathogenesis, Hellp syndrome outcome. The data was compiled and systematised and presented in terms of pathogenesis, diagnostic, management and outcome. The novelty of the information was our main target.*

***Results and conclusion**: HELLP syndrome occurs in 0,5-0,9% of all pregnancy. 69% of the cases are diagnosed antepartum and in almost one third (31%) the diagnosis is established postpartum. HELLP syndrome diagnosis is considered highly difficult in some cases, as the features may be nonspecific, subtle and inconclusive. The pathogenesis is still partially elucidated, even if hypotheses have been issued and genetics, nowadays, have a huge involvement. The complications include a high incidence of maternal DIC (disseminated intravascular coagulation), abruptio placentae, acute renal failure and pulmonary edema; a high rate of acute neonatal respiratory distress syndrome, bronchopulmonary dysplasia, intracerebral haemorrhage and necrotizing enterocolitis. The induction of delivery is the only specific therapy in cases of HELLP syndrome, but this does not mean caesarean section necessarily. An important factor remains the age of the gestation, as at or before 34 weeks of pregnancy, administration of corticosteroids and expectant measurements for prolonging pregnancy may be neccessary. The outcome include an increased risk of maternal death (1%), perinatal death ranging from 7.4% to 20,4% and a rate of preterm delivery of approximately 70%. The risk of recurrence in a subsequent pregnancy is estimated at 19-27%.*

## Rezumat: Diagnosticul şi managementul perinatal în sindromul HELLP

***Obiective**: Sindromul HELLP este o complicaţie obstetricală care comportă un diagnostic dificil şi un management complex multidisciplinar. Scopul acestui review este acela de a sistematiza informaţia din literatură cu privire la diagnosticul, patogeneza, complicaţiile, managementul terapeutic şi prognosticul cazurilor complicate cu sindrom HELLP.*

***Metoda**: Am evaluat literatura din ultimii ani cu privire la acest topic folosind bazele de date Pub Med şi Cochrane. Am folosit cuvintele cheie: sindrom Hellp, sarcina sindrom Hellp, management sindrom Hellp, tratament sindrom Hellp, corticosteroizi sindrom Hellp, patogeneza sindrom Hellp, prognostic sindrom Hellp. Datele au fost prelucrate, sistematizate şi prezentate în secţiuni de patogenie, diagnostic, management şi prognostic. Noutatea informaţiei a primat în evaluarea noastră.*

***Rezultate şi concluzii**: Sindromul HELLP apare în 0,5-0,9% sarcini. 69% dintre cazuri sunt diagnosticate antepartum, iar aproape o treime (31%) postpartum. Diagnosticul sindromului HELLP este considerat foarte dificil în unele cazuri, datorită semnelor şi simptomelor nespecifice şi subtile. Patogenia acestui sindrom este încă incomplet elucidată, deşi multiple ipoteze au fost emise; studiile genetice recente au adus informaţii importante referitor la*

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*predispoziţia anumitor grupuri populaţionale. Complicaţiile includ o incidenţă importantă a CID (sindromul de coagulare intravasculară diseminată), dezlipirea prematură a placentei, insuficienţa renală acută, edemul pulmonar acut, precum şi complicaţii fetale: sindromul de detresă respiratorie, displazia bronho-pulmonară, hemoragiile cerebrale şi enterocolita necrozantă. Naşterea reprezintă singura terapie specifică în cazurile de sindrom HELLP, dar asta nu înseamnă neapărat operaţie cezariană. Un important factor în deciderea managementului rămâne vârsta gestaţională, respectiv gradul de prematuritate, care poate necesita administrarea de corticosteroizi şi terapie suportivă de expectativă. Prognosticul este grevat de riscuri severe, precum decesul matern (1%), prematuritate în aproximativ 70% din cazuri şi decesul perinatal al produsului de concepţie, în 7.4% - 20,4% din cazuri. Riscul de recurenţă al sindromului este estimat între 19 şi 27%.*

**Cuvinte cheie:** sindrom HELLP, complicaii perinatale, diagnostic prenatal, management HELLP

## INTRODUCTION

HELLP is an acronym introduced by Weinstein in 1982 to describe the syndrome characterized by hemolysis, elevated liver enzymes and low platelet count. In the past the syndrome was considered a variant of preeclampsia, but in fact it can occur on its own or in association with preeclampsia.[1] Pregnancy-induced hypertension, preeclampsia and HELLP syndrome are related and overlap in their presentations. The diagnosis can be difficult and a high dose of suspicion is needed as preeclampsia occurs in 6-9% of pregnancy and only 4-12% of women with diagnosed preeclampsia will develop HELLP syndrome. As the associated morbidity and mortality are serious, the diagnosis of HELLP syndrome should be considered as early as possible.[2]

This review has the goal to present the main clinical issues of the syndrome regarding the pathogenesis, the diagnosis including the differential diagnosis, the management as time of delivery and method of delivery, the management of complications and the maternal and neonatal outcome for an increased vigilance in the obstetrical practice.

### The pathogenesis

The origin and the development of HELLP syndrome is incompletely elucidated. The syndrome is considered mainly as an acute rejection of the fetal allograft, because trophoblast invasion invariably brings the fetus in contact with the immunocompetent maternal cells.[3] One hypothesis consider an alteration in the immune feto-maternal balance that induces platelet aggregation, endothelial dysfunction and arterial hypertension. Some consider the origin of preeclampsia and HELLP to be attributed to defective trophoblastic invasion, with an abnormal placental cyclooxygenase activity.[4]

Most genetic research investigating pregnancy-associated diseases is performed on the early-onset forms of disease. These forms have the highest morbidity and mortality risk for both mother and child. The consistent observations that the early-onset form shows an abnormal placental morphology indicate that early-onset disease originates in the fetal placenta. Many genes have been proposed as implicated in the pathogenesis of HELLP syndrome, but there is still a long way to go before the genetics of the disease is unravelled. Through the chromosomal linkage associated with the HELLP-syndrome has recently been found to be located on chromosome 12q23.[5]

The liver occupies a central role in the disorder of HELLP syndrome and a major pathogenic mechanism for liver disease is CD95 (APO-1, Fas)-mediated apoptosis of hepatocytes produced by the placenta. Aarnoudse et al. studied needle biopsies of the liver in patients with HELLP syndrome and noted the histologic pattern of injury describing periportal lesions consisting of neutrophilic infiltrates, necrosis

of hepatocytes and fibrin microthrombi, and fibrin deposits in the sinusoids.[6]

Recently, the same complement mutation identified in multiple patients with atypical haemolytic uraemic syndrome was found in a patient with the HELLP syndrome. The pathogenesis of both diseases are reviewed focusing on the role of the complement system and how its dysfunction could result in a thrombotic microangiopathy in the kidney in the case of atypical haemolytic uraemic syndrome and in the liver in the case of the HELLP syndrome.

An inborn error of fatty acid oxidative metabolism may occur in fetuses born in context of HELLP syndrome. In fact women who are carriers for a condition called long chain 3-hydroxyacyl coenzyme A dehydrogenase deficiency (LCHAD), are at risk for pregnancy complications such as HELLP syndrome and acute fatty liver of pregnancy if the unborn child is affected with LCHAD deficiency. Earlier studies have revealed that if a woman has HELLP syndrome during pregnancy, there is a 2% risk of LCHAD deficiency in the baby. In women with AFLP (acute fatty liver in pregnancy) during pregnancy, the risk of a child affected with LCHAD deficiency is 15-20%. [7]

Still it is unclear why certain patients with severe preeclampsia develop HELLP syndrome. It is possible that these patients have more endothelial injury with greater activation of the coagulation system. It was found statistically significant increases in plasma fibronectin and D-dimer levels and decreases in antithrombin- III levels when the patients with HELLP syndrome were compared to the patients with preeclampsia. The HELLP group and the preeclamptic group also showed significant decreases in protein C and S activity as compared to the control normotensive group, but no significant differences in comparison to each other. Other abnormalities identified were anticardiolipin antibodies, protein S deficiency, hyperhomocysteinemia, and activated protein C resistance, maybe a basis for pharmacologic management in subsequent pregnancies. Immunologic factors may be the underlying initiator of preeclampsia and HELLP syndrome.with cytokine-mediated endothelial damage is important in HELLP syndrome. Haeger et al.9 reported increased plasma levels of tumor necrosis factor-a at the time of delivery in patients with HELLP syndrome as compared to normal pregnant controls. Tumor necrosis factor-a, by its effect on endothelial cells and coagulation, may be important in the pathophysiology of preeclampsia and HELLP syndrome. [1]

Some studies have tried to examine placental expression of vimentin and desmin in relation to ultrastructural changes within the placental villi in cases of HELLP syndrome as it was observed an increased expression of vimentin in the intravillous area and increased expression of desmin on blood vessel wall in patients with HELLP syndrome when compared to placentas of healthy pregnant. Research is still in progress.[8]

## MATERNAL AND PERINATAL OUTCOME

Preeclampsia was reported as a pregnancy complication in up to 5-10%, depending on the healthcare levels of the hospitals. 5% of all cases of preeclampsia in turn ultimately progress toward eclampsia and in up to 19% of the cases the condition can manifest as HELLP syndrome, which is associated to increased morbidity-mortality. The adverse maternal consequences in preeclampsia are fundamentally attributable to dysfunction of the central nervous system, liver or kidneys (hemorrhagic stroke, liver rupture or acute renal failure), and to bleeding associated to thrombocytopenia. Preeclampsia-eclampsia is one of the three most common causes of mortality in pregnant women, together with thromboembolic disease and postpartum hemorrhage. [9]

Studies describes HELLP syndrome maternal complications such as placental abruption (9-20%), pulmonary edema (6%), DIC (5-56%), adult respiratory distress syndrome , ruptured liver hematoma (1-2%), acute renal failure(7-36%). Cerebral haemorrhage is rare, but the most severe complication being fatal in 50-65% of cases. Bilateral permanent visual loss associated with retinopathy (Pursher-like) is a rare ophthalmic complication during pregnancy. Audibert et al. report cerebral bleeding

to occur in 1.5% of the cases. The risk of stroke is not increased during pregnancy itself. However, the risk of cerebral infarction and intracerebral haemorrhage is increased some weeks after delivery. Wound haematoma and infection are frequent phenomena in women with the HELLP syndrome undergoing Caesarean section. [10]

Subcapsular liver hematoma has been reported in 1% of pregnancies complicated by HELLP syndrome and may result in maternal death. The symptoms are sudden-onset severe pain in the epigastric and right upper abdominal quadrant radiating to the back, right shoulder pain, anaemia and hypotension. Computed tomography, magnetic resonance imaging, or ultrasound can be used to detect and monitor this complication. Barton and Sibai have recommended close observation in women with unruptured subcapsular hematoma, provided that maternal condition is stable. Ruptured liver hematoma is a surgical emergency with evacuation and drainage of the hematoma, packing as needed and suturing of lacerations if possible. Hepatic rupture may also occur in the post-partum period. Maternal mortality rate in hepatic rupture ranges from 18 to 86%.[11]

Patients who have had HELLP syndrome should be counseled that they have a 19 to 27 % risk of developing the syndrome in subsequent pregnancies. They also have up to a 43 % risk of developing preeclampsia in another pregnancy and a high risk of recurrence.

Sibai has shown that oral contraceptives are safe in women with a prior HELLP syndrome. In a subsequent pregnancy, women with a history of HELLP syndrome at or before 28 weeks' gestation during the index pregnancy are at increased risk for several obstetric complications (preterm birth, pregnancy-induced hypertension and increased neonatal mortality). In patients with prior severe, early-onset preeclampsia thrombophilia screening has been suggested and should include search for protein S deficiency, activated protein C resistance (APC resistance), hyperhomocysteinemia and anti-phospholipid antibodies (both lupus anticoagulant (LA) and anti-cardiolipin). Much controversy surrounds the use of acetylsalicylic acid (aspirin) or calcium to prevent preeclampsia. To date, neither calcium nor aspirin has been specifically studied in patients with HELLP syndrome. In recently studies, neither aspirin therapy did not reduce the incidence of preeclampsia or improve perinatal outcomes in pregnant women at high risk for this complication of pregnancy, nor calcium supplementation during pregnancy did not prevent preeclampsia or adverse perinatal outcomes. [3]The maternal mortality was reported 1,1%, Isler et al. found cerebral haemorrhage or stroke to be the primary cause of death in 26% and the most contributing factor in another 45% of the deaths.

Perinatal mortality in HELLP syndrome ranges from 5% to nearly 20%. Prematurity (70% and 15% of cases before 28 weeks of gestation), placental insufficiency, with or without intrauterine growth restriction (IUGR) (38-61%) and abruptio placentae, are the leading causes of neonatal death. Neonatal morbidity and mortality was higher in infants of women with HELLP syndrome group than in the normotensive group and there was a greater need for mechanical ventilation and neonatal intensive care. In addition, the rates of cesarean delivery, fetal growth restriction, fetal distress, intraventricular haemorrhage, sepsis, lower 5-min APGAR scores and abruptio placentae were increased in the HELLP syndrome group. [12] Studies that advocate expectant or temporizing management have higher perinatal mortality rates, mainly because of stillbirths. Weinstein reported also hematologic abnormalities (thrombocytopenia in 50% of cases, leukopenia and/ or neutropenia in up to 40% of cases, and abnormal peripheral smears) in the neonates born to mothers with HELLP syndrome. Little data is available on liver enzymes in infants born to mothers with HELLP syndrome.

The neonatal outcome of the HELLP syndrome represents a controversy. Neonatal survival in infants born to mothers with HELLP syndrome is mainly dependent upon gestational age and birth weight at delivery. Some authors inform that infants born to mothers with the HELLP syndrome are not at increased risk of morbidity compared to otherwise healthy infants of the same gestational age. Consequently also typical complications following preterm delivery are reported, like bronchopulmonary

dysplasia (BPD) cerebral haemorrhage and persisting ductus arteriosus in HELLP.[9]

We assume that differences in the outcome of the neonates depend on the study publication and also reflect the level of neonatal care.

## DIAGNOSIS

HELLP syndrome is a multifactorial disorder and if undiagnosed, it can result in life threatening complications. The diagnosis can be frustrating to physicians because of the vague nature of presenting complaints and it can be generally delayed for an average of eight days. Many woman with this syndrome are initially misdiagnosed with other disorders and in one retrospective chart review of patients with HELLP syndrome, only two of 14 patients entered the hospital with the correct diagnosis.[13]

### Clinic manifestations

Symptoms include in 90% of cases a generalized malaise, in 65% with epigastric pain, 30% with nausea and vomiting that continue to get worse and 31% with headache. Sometimes it can be associated right upper quadrant or epigastric pain, visual changes and symptoms related to thrombocytopenia such as bleeding from mucosal surfaces, hematuria, petechial, hemorrahages or ecchymosis.[14]

A woman with HELLP may experience other symptoms that often can be attributed to other things such as normal pregnancy concerns or other pregnancy conditions. These include edema , yet not a useful marker, high blood pressure and proteinuria. Although the majority of patients will have hypertension (82–88%), it may be only mild in 15–50% of the cases, and absent in 12–18%. The majority of the patients (86–100%) will have proteinuria by dipstick examination; however, it was reported to be absent in 13% of cases in the 2 largest series

Most patients will give a history of malaise for the past few days before presentation, and some will have nonspecific viral-syndrome–like symptoms. Pregnant women with these clinical manifestation should undergo laboratory investigations for HELLP syndrome, as early diagnosis is crucial. [15]

### Paraclinic investigations

The three chief abnormalities found in HELLP syndrome are hemolysis, elevated liver enzyme levels and a low platelet count.

Hemolysis is evidenced by an abnormal peripheral smear with schistocytosis, polychromasia (implying reticulocytosis), anisocytosis, and poikilocytosis, lactate dehydrogenase >600 U/L and bilirubin > 1.2 mg/dl. The finding of a decreased serum haptoglobin level may confirm ongoing hemolysis when the hematocrit is normal. The hematocrit may be decreased or normal and is typically the last of the three abnormalities to appear. Even if none of these are specific, Sibai recommended that, in addition to an abnormal blood smear, increased bilirubin and lactate dehydrogenase (LDH) should be required for the diagnosis of hemolysis. Paternoster et al. demonstrated LDH elevations in some patients with preeclampsia and found bilirubin elevations in only 25% of their patients with HELLP syndrome, with reductions in serum haptoglobin in all patients, as in Wilke's study also.

There is no consensus to define the degree of liver enzyme elevation. The serum transaminase levels may be elevated to as high as 4,000 U per L, but milder elevations are typical. Sibai made specific recommendations, he defined elevated liver enzymes by an AST (SGOT) value of 70 U/l. The latter value correlated to three standard deviations above the mean in their hospital laboratory, but at the same time other authors have used two standard deviations above the mean to define the elevated liver enzyme component of HELLP syndrome.

Thrombocytopenia is the major and early cause of alteration of coagulation in HELLP syndrome, with a cut-off value of 100.000/mm3.[16]

Other investigations include a D-dimer testing, recently reported to be predictive of patients who will develop HELLP syndrome, a more sensitive indicator of subclinical coagulopathy and proteinuria and uric acid concentration, useful in diagnosing preeclampsia. Glutathione transferase and glutathione

S transferase can be 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.[17]

HELLP syndrome is occasionally associated with hypoglycemia that leads to coma, severe hyponatremia, and cortical blindness.[10]

The literature offers two important classifications of HELLP syndrome: the Mississippi classification and the Tennessee System classification. The Mississippi classification describes 3 classes : class I with AST e" 70 IU/L, LDH e" 600 IU/L and platelets d" 50,000/uL, class II with AST e" 70 IU/L, LDH e" 600 IU/L and platelets˙50,000 d" 100,000/uL and class III with AST e" 40 IU/L, LDH˙600 IU/L and platelets˙100,000 d" 150,000/uL. The Tennessee System classification describes two forms: the complete form with all three components (H, EL and LP) and an incomplete form that consists of only 1 or 2 of the three elements of HELLP. Women with complete HELLP syndrome are at higher risk for complications, including DIC, than women with the incomplete syndrome and should be considered for delivery within 48 hours, whereas those with the incomplete form may be candidates for more conservative management.[17]

The imaging evaluation remains an important tool in the refined diagnosis of pregnant women' pathology as well as fetal pathology. In HELLP syndrome, liver imaging is essential for evaluation of subcapsular or intraparenchymal hemorrhage and hepatic rupture. While ultrasound and MRI (magnetic resonance imaging) are preferred in pregnancy, due to the absence of risk of ionizing radiation, CT (computer tomography) scan is the method of choice in the postpartum period.[18]

**Differential diagnosis**

Differential diagnosis is crucial as the presenting symptoms, clinical findings, and many of the laboratory findings in women with HELLP syndrome overlap with a number of medical syndromes, surgical conditions, and obstetric complications. The main disorders which should be considered include a pathology associated with pregnancy and a nonspecific pregnancy pathology.

Diseases related to pregnancy for HELLP syndrome differential diagnosis include benign thrombocytopenia and acute fatty liver of pregnancy (AFLP). AFLP typically occurs between the 30th and 38th gestational weeks with a 1 to 2 week history of malaise, anorexia, nausea, vomiting, mild epigastric or right upper abdominal pain, headache and jaundice. Hypertension and proteinuria are usually absent, but hypoglycemia and prolongation of the prothrombin time are present and the evolution is towards acute liver failure.[18]

The differential diagnosis can be made with infectious and inflammatory diseases, not specifically related to pregnancy, such as virus hepatitis, cholangitis, cholecystitis, upper urinary tract infection, gastritis, gastric ulcer and acute pancreatitis. In some women, preeclampsia may be superimposed on one of these disorders, further confounding an already difficult differential diagnosis. Because of the remarkably similar clinical and laboratory findings of these diseases, one should make every effort to achieve an accurate diagnosis, since management and outcomes may differ among these conditions.[18]

Thrombocytopenia can be also present in immunologic thrombocytopenia, folate deficiency, systemic lupus erythematosus and antiphospholipid syndrome. Folate deficiency is common in pregnancy, but its progression to megaloblastosis is rare. Haemolytic anaemia, thrombocytopenia, and coagulopathy due to folate deficiency may mimic the incomplete HELLP syndrome. Systemic lupus erythematosus is an autoimmune disorder frequently associated with thrombocytopenia (40-50%), haemolytic anaemia (14-23%) and antiphospholipid antibodies (30-40%),that can be hard to differentiate from HELLP syndrome.[19]

Rare diseases that may mimic HELLP syndrome include thrombotic thrombocytopenic purpura (TTP) and haemolytic uremic syndrome (HUS). Some pathophysiological characteristics of TTP and HUS are common with HELLP syndrome,

but abnormal blood smear, increased LDH and creatinine levels may be useful in differentiation. In addition HUS develops usually in the post-partum period, with signs and symptoms of renal failure. The differentiation between TTP and HELLP syndrome can be difficult, but critical as treatment differs substantially.[20] Although plasmapheresis is the mainstay of therapy in TTP, delivery of the infant is usually required in HELLP syndrome to reverse the course of the disease. Although reduced ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity and elevated Vwf (von Willebrand factor) levels can be seen in HELLP syndrome, a severe reduction in ADAMTS-13 activity along with an increase in ultralarge vWF multimers is usually suggestive of TTP. [21,22] Severe thrombocytopenia in HELLP syndrome usually responds to steroids within 8 to 12 hours; therefore, lack of this response would also favor a diagnosis of TTP .Given that HELLP syndrome is often associated with preeclampsia, maternal hypertension and proteinuria would favor a diagnosis of HELLP syndrome.

There is a dispute in literature whether disseminated intravascular coagulation should be considered for differential diagnosis or HELLP syndrome is a variant of disseminated intravascular coagulation. Still 38% of pregnant women with HELLP syndrome will develop DIC. 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, prekallicrein, might better differentiate DIC from HELLP syndrome, but difficult to obtain.[10,23]

## MANAGEMENT

The first step is to confirm or exclude the diagnosis of HELLP syndrome. Prompt recognition of HELLP syndrome and timely initiation of therapy are vital to ensure the best outcome for mother and fetus. Once the diagnosis is confirmed, HELLP is a syndrome usually characterized by progressive and sometimes sudden deterioration in the maternal condition and management remains controversial dithering between conservative treatment and the aggressive management with expeditious delivery. The first priority is to assess and stabilize the mother with particular attention to blood pressure and coagulation abnormalities and to evaluate fetal well-being using non-stress testing, biophysical profile or Doppler assessment of fetal vessels. Each case of HELLP syndrome should be hospitalized the same as any pregnant woman with severe preeclampsia and those who are remote from term should be referred to a tertiary care center.[24]

If the pregnancy is beyond 34 weeks of gestation, or earlier but associated with multiorgan dysfunction, DIC, liver infarction or haemorrhage, renal failure, suspected abruption placentae or nonreasuring fetal status, the consensus is prompt delivery as the only specific therapy. [10] Even if delivery by caesarean section is required in 60% of cases, in selected cases it can be detrimental for both mother and fetus and vaginal delivery can be considered if the Bishop score is favourable. Vaginal delivery rates of 32% for gestations less than 30 weeks, 61% at 30 to 31 weeks, and 62% at 32 to 33 weeks can be achieved. Nevertheless, because vaginal delivery rates with HELLP syndrome are below 50% for gestations less than 30 weeks, Sibai advocates elective cesarean delivery for all women diagnosed with HELLP syndrome at a gestation age less than 30 weeks when spontaneous labor is not present and the Bishop score is less than 5. Oxytocin infusions can be used to induce or to control labor in HELLP syndrome patients. In women with an unripe cervix, cervical ripening may be accomplished pharmaceutically with agents such as prostaglandin gel and hygroscopic dilators (eg, Dilapan, Laminaria digitata), mechanically with dilators such as a Foley catheter, or with an extra-alveolar saline infusion. [10]

Maternal pain relief during labor and delivery can be controlled using small doses of systemic opioids If pudendal block is contraindicated due to the risk of bleeding or hematoma formation, local infiltration anesthesia can be used in case of episiotomy or laceration repair. General anesthesia is the method

of choice for caesarean delivery, but epidural anesthesia can be recommended when thrombocyte count is higher than 100.000/m3 with no coagulation disorders and the bleeding time is normal.[10]

In cases of pregnancies at or before 34 weeks of gestation and with a stable maternal condition, there is a disagreement, some consider administration of corticosteroids to accelerate fetal lung maturity followed by delivery after 24 hours and other consider prolonging pregnancy until the development of maternal or fetal indications for deliver or until achievement of fetal lung maturity. [23]

## Corticosteroids in HELLP syndrome

Patients with HELLP syndrome should be routinely treated with corticosteroids. The specialiazed literature proposes three alternatives: standard corticosteroids treatment to promote foetal lung maturity, high-dose dexamethasone treatment of the mother or treatment with repeated doses to reduce maternal morbidity and hastening recovery.[16]

Foetal lung maturation involves a complex interaction of hormonal and intercellular signalling that leads to differentiation of the surfactant lipid-protein pathway and through less well-defined increases in lung compliance. The foetal lung must be biologically ready for a corticosteroid to "trigger" maturation, most often between 26 and 33 weeks' gestation.[24,25]

The standard-dose CS (corticosteroids) treatment is either 2 doses of betamethasone every 12 hours intramuscularly, or 6 mg dexamethasone intravenously every 12 hour and then deliver 24 hours after the last dose of CS. Recently, betamethasone, instead of dexamethasone, has been recommended as a drug of choice because it may be safer and more protective of the immature brain than dexamethasone. [10]

The probability that HELLP syndrome is a SIRS-like (systemic inflammatory response syndrome) inflammatory form of severe preeclampsia leads to consideration of anti-inflammatory/immunosuppressive agents for treatment, specifically corticosteroids.[26] Several observations are offered to favour routine inclusion of aggressive corticosteroids for patients with HELLP syndrome such as liver haemorrhage or rupture rarely encountered, prevention of progression and significant maternal hepatorenal morbidity, less maternal mortality and morbidity and increased platelet count. Potential maternal risks include rebound thrombocytopenia, adrenal suppression, infection, and the masking of potential complications or other disease processes. Aggressive corticosteroid administration is associated with a significant decrease in the required use of blood products and consequently a secondary decrease in infectious morbidity.[26,27]

Even if high-dose dexamethasone treatment has not been yet proven useful in routine treatment of HELLP syndrome patients, through there is strong evidence for a single course of standard CS treatment in preterm delivery, including severe preeclampsia [28].

As it is possible that there is a critical time, in the progression of the disease, beyond which steroid therapy can be less effective, it is considered that this therapy should be administered as early as HELLP syndrome is diagnosed, even before the referral to a tertiary care center. This can be crucially important for the stabilization of those patients at particularly low gestational ages, in the attempt to postpone delivery and achieve better perinatal outcomes. [28,29]

## Conservative management

The benefit of temporizing management of HELLP syndrome is questioned. After immediate hospitalization, patient with HELLP syndrome treated conservative should benefit from the same management as cases of severe preeclampsia.[31,32]

High blood pressure is controlled differently using 5-mg bolus dose of hydralazine, to be repeated as needed every 15–20 minutes for a maximum dose of 20 mg per hour or labetalol 20–40 mg iv every 10–15 minutes for an hourly maximum 220 mg, and nifedipine 10–20 mg orally every 30 minutes for an hourly maximum dose of 50 mg. A hypertensive crisis may be treated with a continuous infusion of nitroglycerin or sodium nitroprusside. Diuretics may compromise placental perfusion and therefore are not used to control blood pressure in patients with HELLP syndrome.[10]

Magnesium sulfate is used to control high blood pressure as well as for prophylaxis against convulsions in a loading dose of 6 g given over 20 minutes, followed by a maintenance dose of 2 g per hour as a continuous intravenous solution. Patients should be observed for signs and symptoms of magnesium toxicity. If toxicity occurs, 10 to 20 mL of 10 percent calcium gluconate should be given intravenously. Because of reported potentiation of effect, care should be taken when nifedipine and magnesium sulfate are given concurrently. In utero exposure of magnesium sulphate may be neuroprotective. [32,33]

Other conservative treatment options include antithrombotic agents, heparin, antithrombin, aspirin in low doses, prostacyclin, immunosuppressive agents, fresh frozen plasma, dialysis.[31,32]

The use of heparin in patients with preeclampsia and HELLP syndrome is still a controversial matter; according to some authors, heparin does not exert any effect, whereas others believe that it can be beneficial. In particular, Brain et al. had suggested that heparin could act by preventing the continuing formation of microthrombi, thus, controlling the cause of the intravascular hemolysis and the thrombocytopenia. At the end of 1980s and in 1990, especially in European countries, some authors were considering the use of heparin for the treatment of HELLP syndrome in the attempt to interrupt the progression of the compensated consumption coagulopathy. Still there are no clear benefits of the heparin treatment in HELLP syndrome. [3,34]

Antithrombin represents a possible therapeutic option for preeclampsia, that may correct hypercoagulability, stimulate prostacyclin production, regulate thrombin-induced vasoconstriction, improve foetal status and promote foetal growth. In contrast to the use of heparin, antithrombin has not been shown to increase the risk of bleeding. Future well designed studies are needed to demonstrate the potential benefit from antithrombin treatment in women with HELLP syndrome.[9]

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.[26,35]

Future promising therapy may involve normalization of glutathione levels in patients with preeclampsia and HELLP syndrome by infusion of S- nitrosoglutathione.[9]

If the HELLP syndrome develops before 24 weeks' gestation, termination of pregnancy should be strongly considered.[16]

**Management of complications**

Cases of diagnosed liver rupture represent an indication for massive transfusions of blood, fresh frozen plasma and platelets as well as immediate laparotomy that may include surgical ligation of the hemorrhaging hepatic segment, embolization of the hepatic artery to the involved liver segment, application of laparotomy sponges as pressure packs and loosely suture omentum or surgical mesh to the liver to improve integrity. Emergency surgical intervention should be performed if the patient shows hemodynamic instability, massive blood loss, increasing pain or hematoma infection. Administration of recombinant factor VIIa might suppress the hemorrhage and save the patient's life in cases that do not respond to surgical treatment.[36]

In cases of severe anemia, the decision to transfuse red blood cells should be based on clinical assessment of the patient's status rather than an arbitrary haemoglobin or hematocrit value. 1]

In the presence of significant bleeding (ecchymosis, bleeding from gums, oozing from puncture sites, wound, intraperitoneal, etc.), platelet transfusions can be indicated, especially if the platelet count is less than 20,000/mm3. Repeated platelet transfusions are not necessary because of the short half-life of the transfused platelets in such patients. Correction of thrombocytopenia is also important before any surgery, some administer 6 units of platelets in all patients with a platelet count less than 40,000/mm3 before intubation if cesarean delivery is needed, others 10 units of platelets for women with a platelet count of less than 50.000/mm3.[4] Generalized oozing from the surgical site is common, with a risk of hematoma formation at these sites of

approximately 20%. Authors indicate the use of a subfascial drain for 24-48 hours and to keep the skin incision open for at least 48 hours in all patients requiring cesarean delivery.

Roberts and colleagues, in a retrospective, descriptive study of intrapartum platelet counts in HELLP syndrome, reported an antepartum platelet count of <40,000/ml to be predictive of postpartum bleeding problems. They found no difference in postpartum bleeding problems between the patients who received prophylactic platelet transfusion and those who did not.[38]

### Postpartum management

After delivery, the majority of patients with HELLP syndrome will show evidence of resolution of the disease process within 48hours. They should be closed monitored regarding vital signs, fluid intake and output, laboratory values and pulse oximetry for at least 48 hours.[39] In cases of complications of HELLP syndrome, the resolution can be delayed or they may even deteriorate in their clinical condition, but finally the patients will recover with supportive therapy only. Some authors recommend the administration of high-dose dexamethasone to accelerate recovery and shorter hospital stay. Others propose exchange plasmapheresis with fresh frozen plasma, but still with no certain results.[40]

HELLP syndrome can also develop for the first time after delivery within 48 hours to 7 days. The diagnosis should be established carefully based on clinical and laboratory findings, as the treatment is the same as for antepartum HELLP syndrome. In women with post-partum HELLP syndrome, risk of renal failure and pulmonary oedema is significantly increased compared to those with an antenatal onset.[41,42,43]

## CONCLUSION

In resource-poor countries eclampsia is liable for maternal death, but in resource-rich countries preeclampsia is the main responsible factor for maternal morbidity and mortality. Prompt recognition of HELLP syndrome and timely initiation of therapy are vital to ensure the best outcome for mother and fetus.[44,45] In the past decades since the original description and management of this dangerous pregnancy complication, research helped to a better understanding of this disorder. The issue of standardization of diagnosis and disease classification is an important goal, so that research findings are comparable and recommended clinical managements can become progressively more evidence based. Yet, there are still a lot to known about this multisystemic disorder with not fully understood pathogenesis.[46,47] In the future, the challenge remains the prompt recognition of HELLP syndrome as well as the delay or the prevention of its' development prior to potential viability so that stillbirths and very preterm losses can be reduced or eliminated. [1,10,16]

## REFERENCES

1.William M. Curtin, Louis Weinstein- A Review of HELLP Syndrome. Journal of Perinatology. March 1999, Volume 19, Number 2, Pages 138-143.
2.J Kelly, DJ Ryan, N O'Brien and WO Kirwan - Second trimester hepatic rupture in a 35 year old nulliparous woman with HELLP syndrome: a case report. World Journal of Emergency Surgery 2009, 4:23.
3.SM Pokharel, SK Chattopadhyay, R Jaiswal and P Shakya- HELLP Syndrome - a pregnancy disorder with poor prognosis. Nepal Med Coll J. 2008 Dec; 10(4): 260-3.
4.Celia J. Fang, Anna Richards, M. Kathryn Liszewski, David Kavanagh and John P. Atkinson- Advances in understanding of pathogenesis of aHUS and HELLP. British Journal of Haematology, November 2008. Volume 143, Issue 3, pages 336–348.
5.Martin Jr JN, Blake PG, Perry Jr KG, McCaul JF, Hess LW, Martin RW.- The natural history of HELLP syndrome: patterns of disease progression and regression. Am J Obstet Gynecol. 1991 Jun;164(6 Pt 1):1500-9; discussion 1509-13.
6.M.E. Sak, E. Devecii1, A. Turgut, S. Sak, M.S. Evsen, T. Gul, S. Kalkanli- Placental expression of vimentin, desmin and ultrastructural changes in the villi in patients with HELLP syndrome. European Review for Medical and Pharmacological Sciences 2013, 17: 874-878.
7.Sibai, B.M., Ramadan, M.K., Chari, R.S. & Friedman, S.A. - Pregnancies complicated by HELLP syndrome: subsequent pregnancy outcome and long-term prognosis. American J Obstet Gynecol. 1995 Jan;172(1 Pt 1):125-9.
8.Wicke C, Pereira PL, Neeser E, Flesch I, Rodegerdts EA, Becker HD- Subcapsular liver hematoma in HELLP syndrome: Evaluation of diagnostic and therapeutic options. Am J Obstet Gynecol. 2004 Jan;190(1):106-12.
9.Hye Yeon Kim, Yong Seok Sohn, Jae Hak Lim, Euy Hyuk Kim, Ja Young Kwon et al.- Neonatal Outcome after Preterm Delivery in HELLP Syndrome. Yonsei Med J. Jun 30, 2006; 47(3): 393–398.
10.Baha M. Sibai- Diagnosis, Controversies, and Management of the Syndrome of Hemolysis, Elevated

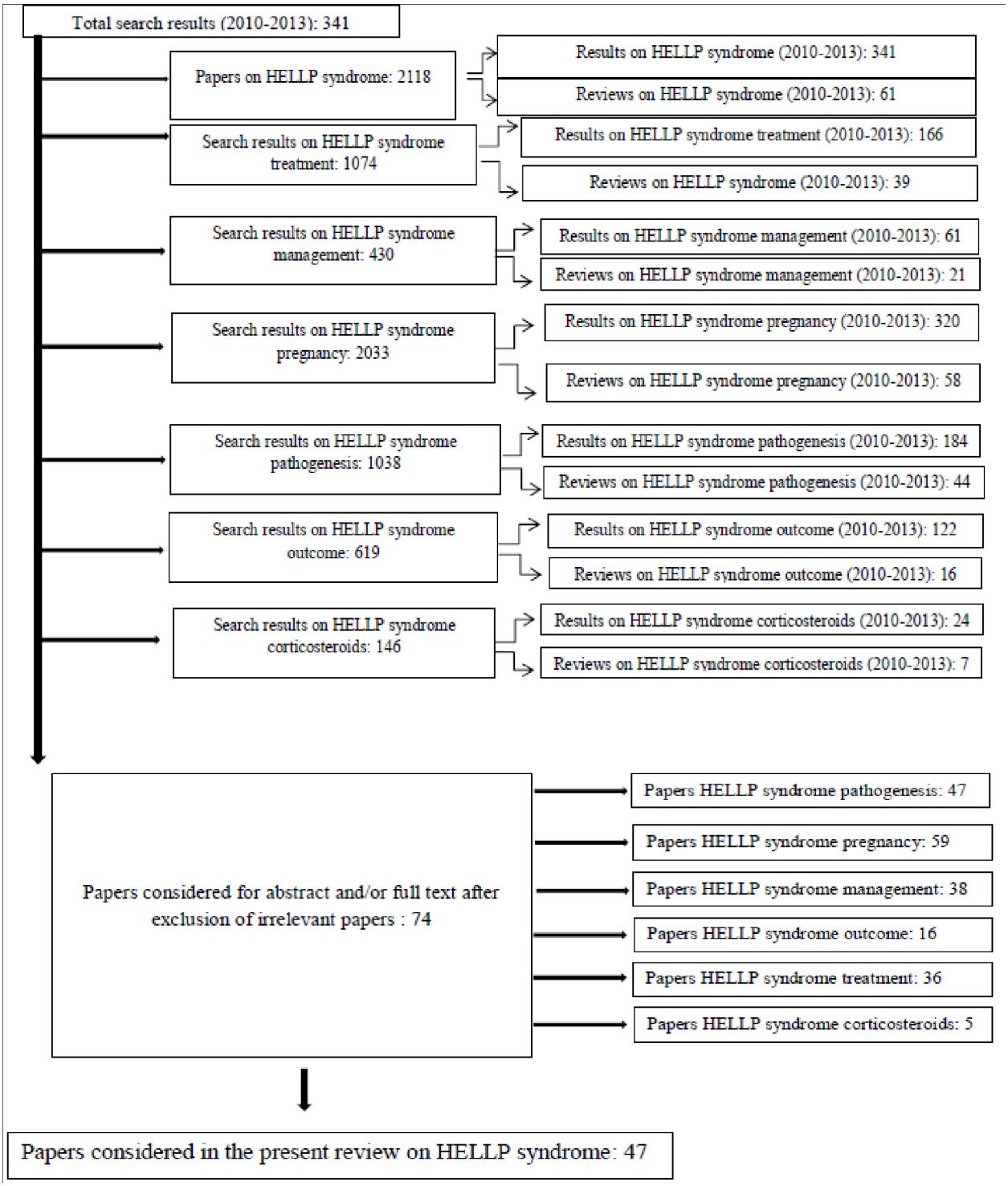


**Figure 1:** Flow diagram showing screened, excluded, and analyzed papers

Liver Enzymes, and Low Platelet Count. Obstet Gynecol. 2004;103(5 pt 1): 981-991.
11.Marie van Dijk, Hari K. Thulluru, Joyce Mulders, Omar J. Michel, Ankie Poutsma et al.- HELLP babies link a novel lincRNA to the trophoblast cell cycle, J Clin Invest. Nov 1, 2012; 122(11): 4003–4011.
12.Baha M. Sibai - A practical plan to detect and manage HELLP syndrome. OBG Management 2005, pages 52-69.
13.Ertan AK, Wagner S, Hendrik HJ, Tanriverdi HA, Schmidt W- Clinical and biophysical aspects of HELLP-syndrome. J Perinat Med. 2002;30(6):483-9.
14.Maureen O'Hara Padden- HELLP Syndrome-Recognition and Perinatal Management. Am Fam Physician. 1999 Sep 1; 60 (3):829-836.
15.Visser W, Wallenburg HC. - Temporising management of severe pre-eclampsia with and without the HELLP syndrome. Br J Obstet Gynaecol. 1995 Feb; 102(2):111-7
16.Kjell Haram, Einar Svendsen and Ulrich Abildgaard- The HELLP syndrome: Clinical issues and management. A Review. BMC Pregnancy and Childbirth 2009, 9:8.
17.Martin JN Jr, Brewer JM, Blake PG, Sunesara IR, Canizaro A, Wallace KW, et al. -HELLP syndrome and composite major maternal morbidity: importance of Mississippi Classification System. J Matern Fetal Neonatal Med. 2013 Aug;26(12):1201-6.
18.Barton JR, Sibai BM. - Hepatic imaging in HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count). Am J Obstet Gynecol. 1996 Jun;174(6):1820-5;

19.Manish Jagia, Salah Taqi, Mahmoud Hanafi, and Fakeir Aisha- Thrombocytopenia-associated multiple organ failure or severe haemolysis, elevated liver enzymes, low platelet count in a postpartum case. Indian J Anaesth. 2013 Jan-Feb; 57(1): 62–65.
20.Ashley Fyfe-Brown, Gwen Clarke, Kara Nerenberg, Sujata Chandra, Venu Jain- Management of Pregnancy-Associated Thrombotic Thrombocytopenia Purpura. AJP Rep. May 2013; 3(1): 45–50.
21.Olivier Pourrat, Remi Coudroy, Fabrice Pierre - ADAMTS13 deficiency in severe postpartum HELLP syndrome. British Journal of Haematology 2013. Volume 163, Issue 3, pages 409–410.
22.Marie van Dijk and Cees Oudejans – Epigenetics of pregnancy-associated diseases. Front Genet. 2013; 4: 180.
23.Federico Mecacci, Lucia Carignan, Riccardo Cioni, Elena Parretti, Marcella Mignosa1 et al.- Time Course of Recovery and Complications of HELLP Syndrome with Two Different Treatments: Heparin or Dexamethasone. Thrombosis Research J. 2001, Volume 102, Issue 2, Pages 99-105.
24.Magann EF, Martin JN Jr:- Twelve steps to optimal management of HELLP syndrome. Clin Obstet Gynecol. 1999 Sep;42(3):532-50.
25.Van Runnard Heimel PJ, Franx A, Schobben AF, Huisjes AJ, Derks JB et all - Corticosteroids, pregnancy, and HELLP syndrome: a review. Obstet Gynecol Surv. 2005 Jan;60(1):57-70.
26.Martin Jr JN, Thigpen BD, Rose CH, Cushman J, Moore A, May WL. - Maternal benefit of high-dose intravenous corticosteroid therapy for HELLP syndrome. Am J Obstet Gynecol. 2003 Sep;189(3):830-4.
27.James N. Martin Jr, MD, Carl H. Rose, MD, Christian M. Briery, MD- Understanding and managing HELLP syndrome: The integral role of aggressive glucocorticoids for mother and child. American Journal of Obstetrics & Gynecology 2006.Volume 195, Issue 4 , Pages 914-934.
28.Magann EF, Graves GR, Roberts WE, Blake PG, Morrison JC et al.- Corticosteroids for enhanced fetal lung maturation in patients with HELLP syndrome: impact on neonates. Aust N Z J Obstet Gynaecol. 1993 May;33(2):131-5.
29.Van Runnard Heimel PJ, Kavelaars A, Heijnen CJ, Peters WH, Huisjes A et al. - HELLP syndrome is associated with an increased inflammatory response, which may be inhibited by administration of prednisolone. Hypertens Pregnancy. 2008;27(3):253–65.
30.E. Curiel-Balsera, M.Á. Prieto-Palomino, J. Mu noz-Bono, M.J. Ruiz de Elvira, J.L. Galeas et al.- Analysis of maternal morbidity and mortality among patients admitted to Obstetric Intensive Care with severe preeclampsia, eclampsia or HELLP syndrome. Med Intensiva.2011; Vol. 35 Num.8, pages 478-83/
31.Sarsam D S, Shamden M, Al Wazan R- Expectant versus aggressive management in severe preeclampsia remote from term. Singapore Med J. 2008 Sep;49(9):698-703.
32.Friedman SA, Schiff E, Lubarsky SL, Sibai BM.- Expectant management of severe preeclampsia remote from term. Am J Obstet Gynecol. 2007 Jun;196(6):514.e1-9.
33.Jeffrey Michael Smith, Richard F Lowe, Judith Fullerton, Sheena M Currie, Laura Harris4 et al.- An integrative review of the side effects related to the use of magnesium sulfate for pre-eclampsia and eclampsia management. BMC Pregnancy and Childbirth 2013, 13:34
34.James Nello Martin Jr.- Milestones in the quest for best management of patients with HELLP syndrome (microangiopathic hemolytic anemia, hepatic dysfunction, thrombocytopenia). International Journal of Gynecology & Obstetrics, June 2013, Volume 121, Issue 3 , Pages 202-207.
35.D Le Thi Thuong, N Tieulié, N Costedoat, et al.- The HELLP syndrome in the antiphospholipid syndrome: retrospective study of 16 cases in 15 women. Ann Rheum Dis. Feb 2005; 64(2): 273–278.
36.Merchant SH, Mathew P, Vanderjagt TJ, Howdieshell TR, Crookston KP- Recombinant factor VIIa in management of spontaneous subcapsular liver hematoma associated with pregnancy. Obstet Gynecol. 2004 May;103(5 Pt 2):1055-8.
37.Dekker GA, de Vries JIP, Doelitsch PM, et al.- Underlying disorders associated with
severe early-onset preeclampsia. Am J Obstet Gynecol 173: 1042-1049.
38.Detti L, Mecacci F, Piccioli A, Ferrarello S, Carignani L et al.- Postpartum heparin therapy for patients with the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP) is associated with significant hemorrhagic complications. J Perinatol. 2005 Apr;25(4):236-40.
39.Sibai BM, Ramadan MK, Chari RS, Friedman SA.- Pregnancies complicated by HELLP syndrome (hemolysis, elevated liver enzymes and low platelets): subsequent pregnancy outcome and long-term prognosis. Am J Obstet Gynecol. 1995 Jan;172(1 Pt 1):125-9
40.Magann EF, Perry KG Jr, Meydrech EF, Harris RL, Chauhan SP et al. - Postpartum corticosteroids: accelerated recovery from the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP), Am J Obstet Gynecol 1994;171:1154-1158.
41.Abraham K, Kenneally M, Dorman AM, Walshe J- Pathogenesis of acute renal failure associated with the HELLP syndrome: a case report and review of the literature. Eur J Obstet Gynecol Reprod Biol. 2003 May 1;108(1):99-102.
42.Celik C, Gezginc K, Altintepe L, Tonbul HZ, Yaman ST et al.- Results of the pregnancies with HELLP syndrome. Ren Fail. 2003 Jul;25(4):613-8.
43.Ebert A, Hopp H, Entezami M, Runkel S, Weitzel H- Acute onset of blindness during labour: report of transient cortical blindness in association with HELLP syndrome. Eur J Obstet Gynecol Reprod Biol. 1999 May;84(1):111-3.
44.Abroug F, Boujdaria R, Nouira S, Abroug S, Souissi M et al.- HELLP syndrome: incidence and maternal-fetal outcome. A prospective study. Intensive Care Med. 1992;18(5):274-7
45.Begum M, Akhter S, Begum A, et al. - Conservative management of eclampsia and severe pre-eclampsia—A Bangladesh experience. Medscape Womens Health. 2002 Jan;7(1):1.
46.Audibert F, Friedman SA, Frangieh AY, Sibai BM- Clinical utility of strict diagnostic criteria for the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. Am J Obstet Gynecol. 1996 Aug;175(2):460-4.
47.Ertan AK, Wagner S, Hendrik HJ, Tanriverdi HA, Schmidt W- Clinical and biophysical aspects of HELLP-syndrome. J Perinat Med. 2002;30(6):483-9.