

HELLP Syndrome after Caesarean Section: Review Article

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ABSTRACT

Background: HELLP occurs in 0.5%–0.9% of all pregnancies. About 30% of the cases happen within 48 hours after delivery. Women with postpartum HELLP syndrome have significantly higher incidences of complications. Because of the absence of classical signs of preeclampsia, it can confuse physicians and lead to delay in diagnosis. Therefore, it is associated with serious maternal and baby morbidity.

Objective: We aimed in this review to highlight on HELLP syndrome after cesarean delivery due to its extreme risk to the mother and baby after birth.

Methods: These databases were searched for articles published in English in 4 data bases: PubMed – Google scholar-The Egyptian knowledge bank and Science direct. Also, Boolean operators (AND, OR, NOT) had been used such as [HELLP Syndrome AND Caesarean section OR preeclampsia] and in peer-reviewed articles between March 1994 and August 2021. A 27-year date range was selected, no language limitations, and filtered in selected data basis for the last 27 years. Documents in a language apart from English have been excluded as sources for interpretation. Papers apart from main scientific studies had been excluded (documents unavailable as total written text, conversation, conference abstract papers and dissertations).

Conclusion: The HELLP syndrome usually occurs with preeclampsia, so timely and early diagnosis of HELLP is important. Additionally, early treatment is important to prevent potentially fatal complications, especially in patients with poor health status.

Keywords: HELLP syndrome, Caesarean section, Pregnant.

INTRODUCTION

HELLP is an acronym that refers to a syndrome characterized by hemolysis, elevated liver enzymes, and a low platelet count ⁽¹⁾. It occurs in 0.5%–0.9% of all pregnancies. About 70% of the cases happen before delivery and within 48 hours after delivery. Although, there are no differences in laboratory findings between HELLP syndrome before and after delivery, women with postpartum HELLP syndrome have significantly higher incidences of complications, such as pulmonary edema, renal failure, disseminated intravascular coagulation, and subcapsular liver haematoma ⁽²⁾.

The clinical triad of hypertension, proteinuria, and oedema is a well-recognized syndrome of the second half of pregnancy known as preeclampsia, although its etiology remains uncertain ⁽¹⁾. Patients' cases that were variants of severe preeclampsia-eclampsia with atypical signs and symptoms or very complicated courses of this disease process have been reported since the end of the 19th century. Many of these descriptions of pregnancies complicated by an uncharacteristic presentation of preeclampsia are representative of the condition now identified as HELLP syndrome ⁽²⁾.

We aimed in this review to highlight on HELLP syndrome after cesarean delivery due to its extreme risk to the mother and baby after birth.

Epidemiology and inheritance:

Inheritance: Sisters and children of a woman who has sustained HELLP have increased risks of HELLP. A woman who has sustained HELLP has a high risk of developing HELLP (14–24%) and PE (22–28%) in subsequent pregnancies, suggesting related pathogenetic mechanisms. A population study indicated

that 35% of the variance in susceptibility to PE were attributed to maternal inheritance, and 20% to fetal genetic effects with similar contribution of maternal and paternal inheritance ⁽³⁾.

Risk factors:

Elevated body mass index, metabolic disorders, as well as antiphospholipid syndrome, significantly increase the risk of HELLP syndrome in all female patients. Females who had or are related to a female with previous HELLP syndrome complications tend to be at a higher risk in all their subsequent pregnancies ⁽⁴⁾. The risk of HELLP syndrome is not conclusively associated with a specific genetic variation, but likely a combination of genetic variations, such as FAS gene, VEGF gene, glucocorticoid receptor gene and the toll-like receptor gene, increases the risk ⁽¹⁾.

Classification:

A classification system has been developed in Mississippi based on the lowest observed maternal platelet count as a primary, easily measured indicator of disease severity, with class I HELLP syndrome referring to a maternal platelet count of < 50,000/ μ l, class II to a platelet count > 50,000 to < 100,000/ μ l and class III to a platelet count > 100,000 to < 150,000/ μ l, with haemolysis and raised liver enzymes levels ⁽²⁾.

Pregnant patients who develop class I HELLP syndrome have the highest incidence of perinatal morbidity and mortality and the most protracted postpartum recovery periods. Tennessee classification system is based on the partial or complete expression of HELLP syndrome ⁽⁵⁾.

Complete HELLP syndrome would have, in addition to the microangiopathic hemolytic anemia in women with severe preeclampsia ⁽⁶⁾, a serum LDH level ≥ 600 IU/L, platelets counts $< 100,000/\mu\text{l}$, and serum aspartate aminotransferase (AST) levels ≥ 70 IU/L. Partial HELLP would have only one or two of the features of the aqLDH, AST or platelets present. The maternal platelet count in most parturient with HELLP syndrome continues to decrease immediately postpartum, with an increasing trend usually noted by the third postpartum day and achievement of a platelet count of $> 100,000/\mu\text{l}$ by the sixth postpartum day ⁽⁷⁾.

Pathophysiology:

The pathophysiology is still unclear and an exact cause is yet to be found. However, it shares a common mechanism, which is endothelial cell injury, with other conditions, such as acute kidney injury and thrombotic thrombocytopenic purpura ⁽¹⁾. As a result of endothelial cell injury, a cascade of pathological 7 reactions manifests and become increasingly severe and even fatal as signs and symptoms progress. Following endothelial injury, vasospasms and platelet activation occur alongside the decreased release of the endothelium-derived relaxing factor and increased release of von Willebrand factor (vWF) ⁽⁸⁾. This leads to general activation of the coagulation cascade and inflammation. Placental components, such as

inflammatory cytokines and syncytiotrophoblast particles interact with the maternal immune system and endothelial cells, further promoting coagulation and inflammation. These interactions also elevate leukocyte numbers and interleukin concentrations, as well as increase complement activity ⁽⁹⁾.

Pathogenetic cascades:

The pathogenesis of the maternal HELLP and PE syndromes may be perceived as cascades of reactions, as shown in (Figure 1). The suggested mechanisms shown in the figure and briefly described in the text of this review are based on statistically significant data. Some results obtained in single studies may be of limited validity and a need for further studies is evident. Although, the relative importance of the substances inducing the thrombotic microangiopathy are not well known. The central role of the antipathy in the development of the clinical HELLP seems well established. It is not only the main cause of the platelet consumption and the microangiopathic anemia, but also contributes to the liver damage. It is logical to assume that therapeutic inhibition of platelet activation, and of anticoagulation could reduce the extent of thrombotic microangiopathy. Clinical multicenter studies regarding the possible prophylactic effect of anti-platelet or anticoagulation medication in pregnant women with a high risk of HELLP seem warranted ⁽¹⁰⁾.

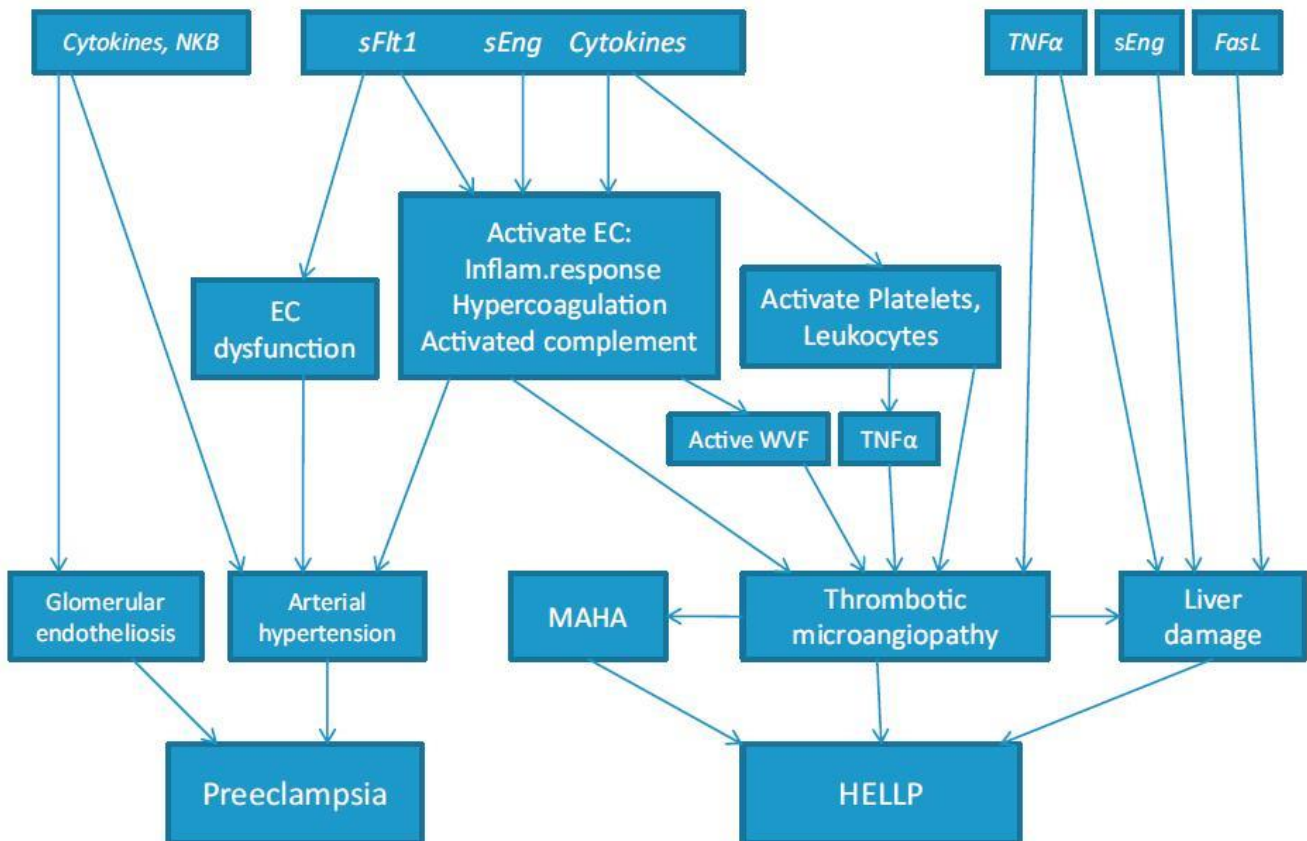


Figure (1): Development of the maternal HELLP and preeclampsia syndromes

(Abbreviations. HELLP, hemolytic anemia, elevated liver enzymes, low platelet count; NKB, neurokinin B; sFlt1, soluble fms-like tyrosine kinase; sEng, soluble endoglin; Fas L, FasLligand, also called CD95 ligand; EC, vascular endothelial cells; WVF, von Willebrand Factor; TNAA, tumor necrosis factor a; MAHA, microangiopathic hemolytic anemia)

Bioactive substances emitted from placenta are shown in the top row of boxes (names of the substances in italics). The substances are emitted from the oxidative stressed placenta to the maternal blood. Their concentrations gradually increase and they in the second half of pregnancy activate cascades of reactions terminating in the maternal signs and symptoms of HELLP syndrome (right side of panel) or preeclampsia (left side of panel). The scheme is focused on pathways in the HELLP syndrome. Reactants shown in the HELLP pathways are also present at lower concentrations in preeclampsia ⁽¹⁰⁾.

Laboratory and clinical diagnosis:

The diagnosis of HELLP syndrome is based on laboratory evidence of microangiopathic haemolytic anemia, hepatic dysfunction, and thrombocytopenia in a patient suspected to have preeclampsia ⁽²⁾.

A peripheral blood smear often will have evidence of schizocytes, burr cells, and helmet cells, which reflect damaged erythrocytes. Increases in lactic dehydrogenase (LDH) levels and decreases in serum haptoglobin levels ($\leq 25\text{mg/dl}$) are sensitive early markers of HELLP syndrome that occur before increases in indirect serum bilirubin concentration and decreases in haemoglobin values ⁽⁷⁾.

Thrombocytopenia is the principal and earliest coagulation abnormality that is present in all women with HELLP syndrome. When the platelets count is less than $50,000/\mu\text{l}$, tests such as fibrin degradation products and antithrombin III activity also can be used to alert the clinician earlier to the presence of an on-going disseminated coagulopathy ⁽¹¹⁾.

Liver dysfunction is reflected by variably elevated serum concentrations of alanine and aspartate transaminases, and LDH. In cases manifesting extreme elevation of aspartate aminotransferase and LDH levels, there is a high risk of maternal mortality ⁽²⁾. Hospital admission laboratory thresholds that indicate a greater than a 75% chance for serious maternal morbidity include a lactic dehydrogenase (LDH) level of $> 1,400\text{ IU/L}$, AST level $> 150\text{ IU/L}$, ALT level $> 100\text{ IU/L}$ and a uric acid concentration of $> 7.8\text{ mg/dl}$. Renal impairment is usually not present early in the disease process, and the levels of the uric acid and serum creatinine concentration are highly variable. The clinical presentation of HELLP is varied. Preeclampsia is typically a disorder of young nulliparous women, whereas HELLP syndrome more often affects older multiparous women ⁽¹²⁾.

Symptoms typically develop in the third trimester, second trimester or postpartum disease is also possible. The most common clinical presentation is abdominal pain and tenderness in the mid epigastrium, right upper quadrant, or below the sternum. Many patients also have nausea, vomiting, and malaise, which may be mistaken for a nonspecific viral illness or viral hepatitis, particularly if the serum aspartate aminotransferase and LDH are markedly elevated ⁽²⁾.

The presence of nausea, vomiting, and/ or epigastric pain is a significant risk factor for maternal morbidity. Hypertension (blood pressure $\geq 140/90\text{ mmHg}$) and proteinuria are present in approximately 85% of cases, but it is important to remember that either or both may be absent in women with otherwise severe HELLP syndrome ⁽¹³⁾.

Serious maternal morbidity may be present at initial presentation or develop shortly thereafter. This includes disseminated intravascular coagulation (DIC), abruptio of placenta, acute renal failure, pulmonary oedema, subcapsular liver hematoma, and retinal detachment. Jaundice and ascites may also be present. Bleeding related to thrombocytopenia is an uncommon presentation. Some patients are asymptomatic ⁽⁸⁾.

Differential Diagnosis:

HELLP syndrome may occasionally be confused with other diseases complicating pregnancy such as acute fatty liver of pregnancy, gastroenteritis, hepatitis, appendicitis, gallbladder disease, idiopathic thrombocytopenic purpura, lupus flare, antiphospholipid syndrome and haemolytic-uremic syndrome ⁽²⁾.

Maternal and perinatal morbidity and mortality:

Maternal morbidity is high (24% in one series of patients). The presenting symptom in 90% of patients who died was nausea-vomiting and right upper quadrant pain, the mean gestational age was 31 weeks, and death occurred by a variety of pathologic processes, including sepsis, shock, haemorrhage, intracerebral bleeding, and cardiopulmonary failure ⁽¹⁴⁾.

Approximately 16% of maternal deaths are attributed to hepatic complications. A large percentage of the maternal deaths associated with HELLP can be attributed to central nervous system catastrophic events including large cerebral and brain stem haemorrhages, extensive thrombosis and infarction, severe cerebral oedema with brain herniation, and carotid artery thrombosis. Serious morbidity is observed in association with advanced cases of HELLP, including disseminated intravascular coagulation (DIC), abruptio placentae, acute renal failure, pulmonary oedema, subcapsular liver hematoma, and retinal detachment. Perinatal morbidity and mortality are increased in women with HELLP primary because of prematurity ⁽⁵⁾.

Treatment:

When the HELLP syndrome is diagnosed, clinically and by laboratory testing, the main priority is to assess and stabilize the woman's condition, especially coagulation dysfunction. Thereafter, fetal wellbeing should be evaluated by ultrasound biophysical profile, umbilical artery Doppler and cardiotocography ⁽⁵⁾. A decision needs to be made as to whether immediate delivery is indicated. The patient with evidence of preeclampsia and right upper quadrant pain and nausea must be seriously evaluated to rule out

HELLP syndrome. The basic laboratory screening for the patient with suspected HELLP syndrome is a complete blood count with platelets levels, urinalysis, serum creatinine, LDH, uric acid, indirect and total bilirubin levels, and transaminases. Tests of PT, PTT, fibrinogen, and fibrin. D-dimer are reserved for these women with a platelet count much below 100,000/ μ l⁽²⁾.

The consensus of opinion for severe cases is that control of hypertension and immediate delivery, usually by caesarean section, is the treatment of choice. A woman with moderate HELLP at a gestational age greater than 34 weeks should also be delivered immediately. Before 34 weeks, the woman should be delivered if her condition cannot be controlled rapidly. Finally, non-reassuring tests of fetal status (e.g. biophysical profile and fetal heart rate testing) indicate also prompt delivery⁽¹⁵⁾. Antihypertensive drugs are used to treat severe hypertension. Hypertension can usually be controlled (blood pressure less than 160/105 mmHg) with labetalol, hydralazine or nifedipine. Magnesium sulphate is given intravenously to prevent convulsions⁽¹⁶⁾.

Platelet transfusion is indicated if there is significant maternal bleeding (spontaneous or from surgical incisions), or if the platelet count is less than 20,000 cells/ μ l. If Caesarean delivery is planned, then some experts recommend platelet transfusion, as necessary, to achieve a preoperative platelet count greater than 40,000 to 50,000 cells/ μ l⁽¹⁷⁾.

Postpartum treatment:

HELLP syndrome can first manifest itself in the postpartum period or worsen following delivery⁽¹⁸⁾. It is thus recommended that all patients with severe preeclampsia-HELLP syndrome be treated intensively until the maternal count exhibits a consistent downward trend in the LDH values. The patient has a diuresis >100 ml/h for 2 consecutive hours, hypertension is well controlled and clinical improvement is obvious to providers and there are no significant complications. Blood pressure must be controlled aggressively and magnesium sulphate is continued during 48 hours. Postpartum corticosteroids can be used to more rapidly resolve the HELLP syndrome, especially in case of severe thrombocytopenia (< 20,000 platelets/ μ l)⁽¹⁾.

Outcome:

Maternal complications are common and potentially life-threatening. Disseminated intravascular coagulation, placental abruption and acute renal failure are common. Other complications include eclampsia, cerebral hemorrhage, adult respiratory distress syndrome (ARDS) and hypovolemic shock. HELLP syndrome is associated with a poor outcome for the mother and her infant, the reported perinatal mortality being 77 to 370 per 1000⁽¹⁹⁾.

Counseling after birth:

Data defining the recurrence risk are sparse because of the rarity of the disease. In the Sullivan's retrospective analysis, the risk of recurrence was approximately 20%, but other groups have projected a much lower recurrent risk for HELLP syndrome⁽²⁰⁾. Women with a history of HELLP syndrome are at high risk for developing preeclampsia in a subsequent pregnancy. The **Beroyz et al.** study has shown that low dose aspirin prophylaxis may be of benefit where severe pre-eclampsia has developed at very early gestational ages, and so it would seem logical to prescribe aspirin to women whose previous HELLP syndrome had occurred early in pregnancy⁽²¹⁾.

Prognosis:

With treatment, maternal mortality is about 1%, although complications such as placental abruption, acute kidney injury, subcapsular liver hematoma, permanent liver damage, and retinal detachment occur in about 25% of women. Perinatal mortality (stillbirths plus death in infancy) is between 73 and 119 per 1000 babies of woman with HELLP, while up to 40% are small for gestational age. In general, however, factors such as gestational age are more important than the severity of HELLP in determining the outcome in the baby⁽¹⁴⁾.

CONCLUSION

The HELLP syndrome usually occurs with preeclampsia, so timely and early diagnosis of HELLP is important and treatment to prevent potentially fatal complications, especially in patients with poor health status.

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