

## MANAGEMENT OF HELLP SYNDROME BEFORE DELIVERY: A COMPREHENSIVE SYSTEMATIC REVIEW

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### ABSTRACT

**Background:** HELLP syndrome, a rare and serious complication during pregnancy, poses significant risks to both mother and fetus. Early management of HELLP syndrome before delivery may improve the outcomes for patients. This study aims to systematically review literatures on HELLP syndrome management before delivery in the last 10 years.

**Methods:** This systematic review complied with the PRISMA 2020 standards and focused on full-text English literature published between 2014 and 2024. Articles such as editorials and review papers from the same journal, as well as submissions lacking a DOI, were excluded from consideration. Literature was sourced from online platforms like PubMed and SagePub.

**Result:** We found 1629 articles on PubMed and 560 articles on SagePub. Restricting our search to the past decade (2014-2024), PubMed presented 507 articles, whereas SagePub presented 288 articles. From these, we selected 5 papers meeting our criteria, with 3 from PubMed and 2 from SagePub.

**Conclusion:** The main treatment approach for HELLP syndrome involves stabilizing the mother and ensuring timely delivery. Various strategies, including the use of corticosteroids and glucocorticoids, have been explored to reduce the associated morbidity and mortality.

**Keyword:** HELLP syndrome, prenatal, treatment

## INTRODUCTION

HELLP syndrome is a complication observed in pregnant and postpartum individuals, characterized by hemolysis, elevated liver enzymes, and low platelets. A history of preeclampsia or HELLP syndrome increases the likelihood of recurrence in subsequent pregnancies. Factors such as multiparity, age, and genetic predisposition contribute to the risk. Additionally, there's emerging evidence linking SARS-CoV-2 infection during pregnancy to an increased risk of both preeclampsia and HELLP syndrome.<sup>1</sup>

In 1982, Weinstein introduced the term HELLP syndrome to describe a condition he observed in patients he evaluated. Initially thought to be a variation of severe preeclampsia, it was found in 5-20% of women with severe preeclampsia, but up to 15-20% of HELLP syndrome cases occur without preceding preeclampsia. Moreover, about 30% of HELLP syndrome cases are diagnosed postpartum, unlike preeclampsia, which is predominantly diagnosed before childbirth. Recent evidence challenges the idea that HELLP syndrome is always linked to severe preeclampsia, indicating that they might be separate conditions. Some cases of HELLP syndrome develop without preceding hypertension or proteinuria.<sup>2</sup>

The exact cause of HELLP syndrome remains unclear, but it is believed to stem from a systemic inflammatory process involving the complement cascade. Although there may be shared underlying mechanisms with preeclampsia, HELLP syndrome can trigger an exaggerated activation of the complement system and heightened hepatic inflammation for reasons yet to be determined. A subset of HELLP syndrome cases is associated with complement dysregulation, presenting similarly to pregnancy-related hemolytic uremic syndrome. While fetal long-chain 3-hydroxy acyl CoA dehydrogenase deficiency (LCHAD) could play a role in HELLP syndrome development, testing for these genetic variations is unnecessary as they do not impact clinical management.<sup>3</sup>

HELLP syndrome primarily involves the activation of platelets without impacting clotting factors, resulting in normal levels of PT, PTT, and fibrinogen. However, the presence of disseminated intravascular coagulation (DIC) may arise if PT and PTT are prolonged or fibrinogen levels are low. The diagnosis of microangiopathic hemolytic anemia is confirmed by the presence of schistocytes or helmet cells on a peripheral blood smear. Histological examination of the liver typically reveals features such as fatty infiltration, intravascular fibrin deposition, neutrophilic infiltration, sinusoidal obstruction, intrahepatic vascular congestion, hepatic necrosis, and periportal hemorrhage. These pathological changes may eventually lead to intraparenchymal or subcapsular hemorrhage and capsular rupture in severe cases.<sup>2</sup>

This led to the recognition of HELLP syndrome as a distinct medical condition. Its underlying mechanism mirrors that of preeclampsia, involving endothelial damage, elevated inflammatory markers, imbalanced angiogenesis, increased autoantibodies, fibrin deposition in blood vessels, and heightened platelet activity. It is believed that abnormal placental development in early pregnancy contributes to the release of harmful substances, potentially leading to the onset and progression of HELLP syndrome in later stages of pregnancy.<sup>3</sup> This study aims to systematically review literatures on HELLP syndrome management before delivery in the last 10 years.

## METHODS

### Protocol

The author meticulously followed the guidelines set forth in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 to ensure that the study fully complied with its requirements. This methodological approach was specifically chosen with the aim of guaranteeing the precision and reliability of the conclusions derived from the investigation.

### Criteria for Eligibility

This systematic review examined evidence concerning systematically review the management of HELLP syndrome over the past decade, carefully compiling and analyzing data to offer insights and improve patient treatment strategies. The main aim of this paper is to underscore the significance of the identified key points collectively.

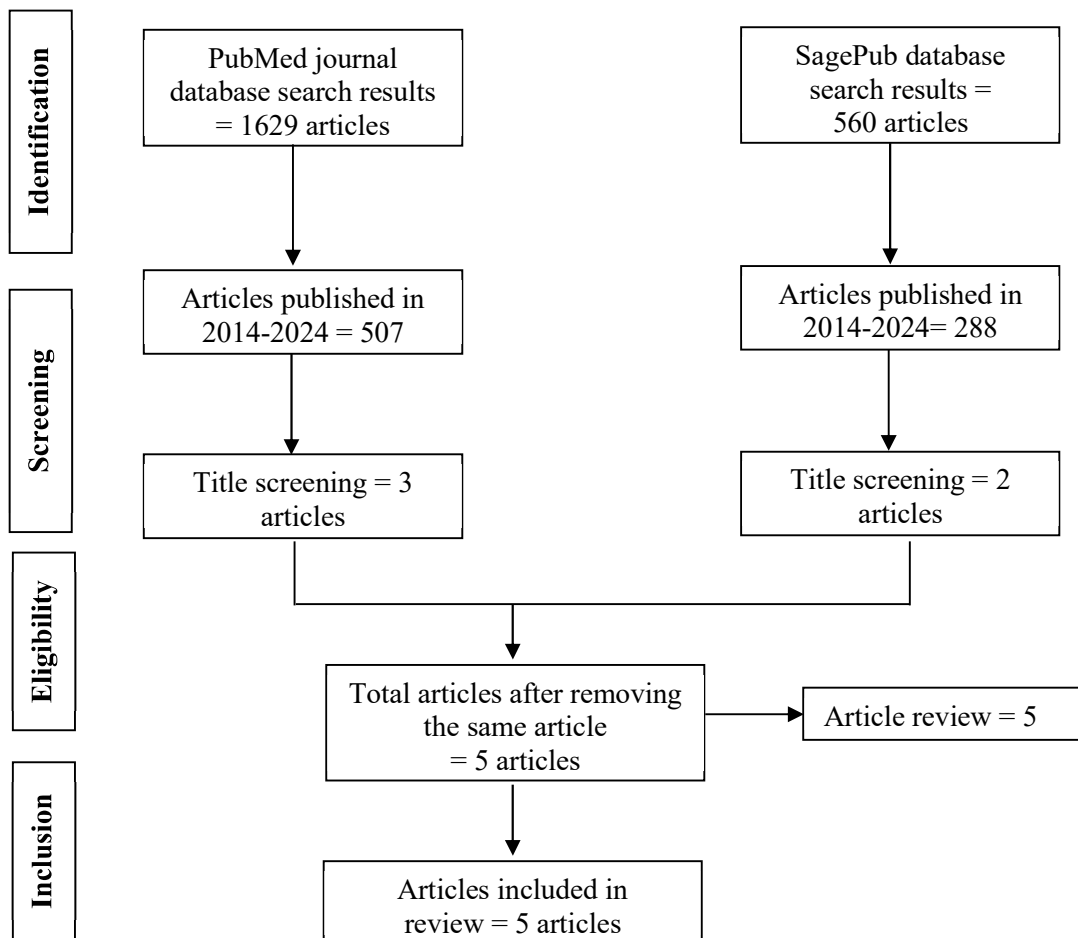
The inclusion criteria for this study are: 1) Papers must be in English, and 2) Papers must be published between 2014 and 2024. The exclusion criteria are: 1) Editorials; 2) Submissions lacking a DOI; 3) Previously published review articles; and 4) Duplicate entries in journals.

### Search Strategy

The keywords used for this research is "HELLP syndrome treatment". The Boolean MeSH keywords inputted on databases for this research are: *((("hella syndrome"[MeSH Terms] OR ("hella"[All Fields] AND "syndrome"[All Fields]) OR "hella syndrome"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment s"[All Fields])) AND (y\_10[Filter] AND (ft[Filter]))*

**Data retrieval**

The authors evaluated studies by examining their abstracts and titles to determine their eligibility. Relevant studies were chosen based on their adherence to the inclusion criteria, aligning with the objectives of the article. A consistent trend observed across multiple studies led to a definitive conclusion. The selected submissions had to meet the eligibility criteria of being in English and previously unpublished.



**Figure 1. Article search flowchart**

This systematic review exclusively incorporated literature that conformed to all predefined inclusion criteria and directly pertained to the topic under investigation. Studies failing to meet these criteria were systematically excluded, and their respective findings were omitted from consideration. The subsequent analysis explored various details revealed during the research process, encompassing elements such as titles, authors, publication dates, locations, study methodologies, and parameters.

**Quality Assessment and Data Synthesis**

Each author independently assessed the research outlined in the publication's title and abstract to determine which publications warranted further exploration. The subsequent stage entails assessing all articles that fulfill the predefined criteria for inclusion in the review. Decisions regarding the inclusion of articles in the review will be based on the findings uncovered during this evaluation process. This criteria serves to streamline the paper selection process for further assessment, providing a comprehensive discussion of previous investigations and the factors that render them suitable for inclusion in the review.

**RESULT**

We identified 1269 articles from the PubMed database and 560 from SagePub. After applying a ten-year filter (2014-2024), PubMed yielded 507 articles, and SagePub produced 288 articles. Ultimately, five papers meeting the criteria were

chosen for the study, with three from PubMed and two from SagePub. Table 1 presents the selected literature included in this analysis.

**Table 1. The literature included in this study**

Author	Origin	Method	Sample	Result
<b>Cadoret, et al.<sup>4</sup> (2021)</b>	Toulouse, France	Retrospective Study	99 patients	Between 2003 and 2016, a retrospective study examined patients diagnosed with HELLP syndrome between 26 and 34 weeks of gestation. Patients were divided based on their obstetric management approach: either active, with delivery initiated within 48 hours of diagnosis, or expectant, where pregnancy continued until maternal or fetal conditions warranted delivery. Out of the 99 patients studied, 61 underwent expectant management. The active management group showed more initial symptoms such as persistent hyperreflexia, headache, and confusion, as well as worse biological and ultrasound findings including decreased prothrombin ratio, elevated creatinine levels, and abnormal umbilical cord and ductus venosus flow. Factors like hyperreflexia, creatinine levels, and abnormal umbilical cord flow were identified as significant predictors. Expectant management allowed for a longer period of gestation post-diagnosis, averaging 7.75 days, without an increase in maternal or fetal mortality.
<b>Kang, et al.<sup>5</sup> (2018)</b>	Suzhou, China	Retrospective case control study	151 patients	A study involving 151 patients with HELLP syndrome categorized them into treatment and control groups based on severity grades. Most outcomes, including maternal and fetal adverse events, showed

				no significant differences between the groups. However, the third-grade control group had a higher primipara rate, and the second-grade treatment group exhibited a higher preterm delivery rate compared to their respective controls. Key biochemical markers did not differ among the groups.
<b>Cui, et al.<sup>6</sup> (2020)</b>	Beijing, China	Retrospective cohort study	106 patients	A retrospective cohort study at Peking University Third Hospital analyzed 106 pregnant women diagnosed with HELLP syndrome from August 2010 to January 2017, alongside a control group of 100 healthy pregnant women. The study collected demographic data, hospital stay duration, postpartum complications, and coagulation marker levels. Results showed a higher incidence of preeclampsia in HELLP syndrome patients with postpartum hemorrhage. Additionally, fibrinogen levels were significantly lower in postpartum hemorrhage cases compared to non-hemorrhage cases and healthy pregnant women. Multivariate analysis indicated that decreased fibrinogen levels independently predicted postpartum hemorrhage in HELLP syndrome patients. The study concluded that fibrinogen levels had good predictive value for postpartum hemorrhage, with a cutoff value of 3.04 g/L showing a sensitivity of 90.90% and specificity of 75.80%.
<b>Poimendi, et al.<sup>7</sup> (2022)</b>	Leicester, UK	Case report	1 patient	HELLP syndrome is associated with a

				spectrum of complications, including placental abruption, fetal loss, acute kidney injury, microangiopathic hemolytic anemia, acute liver failure, and liver capsule rupture. Treatment typically involves delivering the fetus, with ICU admission for multiorgan support required in severe cases.
Sun, et al. <sup>8</sup> (2023)	Multicenter	Randomized controlled trial	485 patients	In a study involving 485 patients from 7 randomized controlled trials, corticosteroid therapy did not show significant improvement in maternal outcomes compared to placebo. This included outcomes such as maternal morbidity, eclampsia, acute renal failure, pulmonary edema, and oliguria. Additionally, there were no significant differences observed in neonatal outcomes between corticosteroid therapy and placebo.

Cadoret, et al.<sup>4</sup> (2021) demonstrated the potential benefits of adopting a conservative strategy for patients with HELLP syndrome before delivery. Identifying monitoring factors was essential for implementing such an approach. Incorporating the monitoring parameters identified in this study along with biomarkers was the most effective method for prolonging pregnancy in HELLP syndrome patients.

Kang, et al.<sup>5</sup> (2018) studied the effectiveness of prenatal glucocorticoid administration in HELLP syndrome. This study found no significant differences between the treatment and control groups in terms of patient characteristics, disease progression, postpartum hemorrhage volume and rate, maternal damage, ICU admission rate, perinatal mortality rate, or overall fetal adverse outcomes. These findings suggest that high-dose glucocorticoids do not notably improve maternal and fetal prognoses. Additionally, the use of high-dose glucocorticoids did not decrease the need for blood products.

Cui, et al.<sup>6</sup> (2020) demonstrated that a low prenatal fibrinogen (FIB) level serves as a dependable biomarker for predicting postpartum hemorrhage in pregnant women with HELLP syndrome. This finding underscores its significance in guiding surveillance therapy and assessing prognosis for pregnant women affected by HELLP syndrome.

Poimendi, et al.<sup>7</sup> (2022) showed that the primary treatment for HELLP syndrome involves delivering the fetus, with ICU admission for multiorgan support required in severe cases. ICU treatment for HELLP syndrome emphasizes supportive measures like blood pressure control and fluid management, alongside interventions such as renal replacement therapy and mechanical ventilation. Managing complications like neuroprotection and liver failure requires a multidisciplinary approach for optimal care.

Sun, et al.<sup>8</sup> (2023) assessed the effectiveness of corticosteroids in HELLP syndrome patients, finding no significant benefits in clinical outcomes for both pregnant women and newborns. This included outcomes such as maternal morbidity, eclampsia, acute renal failure, pulmonary edema, and oliguria.

## DISCUSSION

HELLP syndrome carries the potential for multiple organ failure and mortality, presenting with a range of non-specific symptoms and complications such as disseminated intravascular coagulation, maternal mortality, eclampsia, acute renal failure, hemorrhagic manifestations, pulmonary edema, and oliguria in mothers. It can also result in perinatal death, intrauterine growth restriction, preterm birth, neonatal thrombocytopenia, leukopenia, neutropenia, and respiratory distress syndrome in fetuses. However, neonatal health outcomes are more closely linked to gestational age rather than the presence of HELLP syndrome between weeks 24 to 36 of gestation.<sup>1</sup>

While the exact cause of HELLP syndrome is not fully understood, it might result from fetal trophoblast injury due to immune intolerance in early pregnancy. Risk factors for HELLP syndrome encompass age, pregnancy history, a history of severe preeclampsia, and previous occurrences of HELLP syndrome. Symptoms typically manifest before 36 weeks of gestation, with common complaints including nausea, vomiting, and abdominal pain. Early detection and intervention are crucial given the life-threatening risks HELLP syndrome poses to both mother and fetus.<sup>2</sup>

An active strategy at 34 weeks may result in premature delivery and heightened neonatal morbidity mainly due to prematurity. Studies have noted the absence of specific neonatal complications directly linked to HELLP syndrome. Instead, neonatal outcomes in severe preeclampsia cases are predominantly determined by the gestational age at delivery rather than the presence of HELLP syndrome. Nonetheless, it's crucial to acknowledge the high incidence of intrauterine growth restriction (IUGR) associated with HELLP syndrome. Our cohort revealed that 22% experienced severe IUGR below the 3rd percentile. These findings suggest that adopting a conservative approach could potentially reduce neonatal morbidity stemming from prematurity by prolonging pregnancy and administering full antenatal corticosteroid therapy.<sup>4</sup>

The main treatment for HELLP syndrome involves delivering the fetus and placenta, which requires careful consideration of risks to both mother and baby. ICU care for pregnant patients includes fetal monitoring, planning for labor, and having emergency cesarean delivery equipment readily available. Management strategies focus on controlling blood pressure, correcting abnormal blood clotting, and managing seizures. Safe antihypertensive medications during pregnancy include labetalol, hydralazine, and nifedipine, while magnesium sulfate is essential for preventing seizures. Continuous monitoring is necessary when administering magnesium to prevent toxicity. It's important to be cautious with antihypertensive treatments as they can affect blood flow to the placenta, potentially harming the fetus. Restricting fluid intake is recommended to prevent complications like pulmonary edema, especially in cases involving bleeding or blood clotting issues.<sup>7</sup>

Corticosteroids are commonly used to help the fetal lung maturation, but their impact on the mother's health is uncertain. In severe cases, plasma exchange may be considered as an experimental treatment option, although it carries risks of infection. The proposed mechanisms by which corticosteroids improve laboratory markers in HELLP syndrome include inhibiting endothelial activation, reducing endothelial dysfunction, and decreasing cytokine production. These effects are believed to attenuate the inflammatory and anti-angiogenic responses characteristic of HELLP syndrome. According to previous studies, the administration of intravenous high dose dexamethasone (10 mg every 12 hours until delivery, followed by a postpartum taper) to patients with HELLP syndrome before 34 weeks of gestation increased the likelihood of regional anesthesia and vaginal delivery. Studies also observed that corticosteroid use in women with antepartum HELLP syndrome led to a higher utilization of regional anesthesia.<sup>3</sup>

Glucocorticoids play a crucial role in managing HELLP syndrome by promoting fetal lung maturation, preventing hyaline membrane disease, and improving maternal laboratory indices, particularly blood platelet count (BPC). Glucocorticoids alleviate dropsy, inhibit endothelial activation, reduce vascular endothelial injury, increase hepatic blood flow, prevent thrombotic microvascular hemolysis, and reduce platelet consumption. Some studies suggest significant improvements in BPC, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels, blood pressure, and urinary volume with glucocorticoid treatment, particularly in cases with lower initial BPC.<sup>5</sup>

However, previous study investigated the impact of corticosteroid and high dose glucocorticoids on the various complications associated with HELLP syndrome, for both mothers and fetuses. Despite some observed improvement in certain trials regarding maternal parameters like platelet counts and liver enzymes, there were no consistent benefits found. Some scholars argue that glucocorticoids don't alter maternal and fetal outcomes, and their long-term efficacy remains uncertain. Concerns also include potential fetal growth and adrenal axis inhibition, as well as postpartum depression with high-dose glucocorticoids. Similarly, neonatal outcomes showed no significant differences between corticosteroid-treated and placebo-treated groups. The study underscores the ongoing controversy surrounding the use of corticosteroids and glucocorticoids for HELLP syndrome treatment and emphasizes the need for further research to better understand the condition's underlying mechanisms and optimize treatment strategies.<sup>8</sup>



Patients with HELLP syndrome experience endothelial cell damage, platelet and clotting factor activation, and subsequent changes in the hemostatic system, leading to persistent consumptive alterations. Lower fibrinogen (FIB) levels in these patients independently predict postpartum hemorrhage, with FIB sensitivity at 90.90% and specificity at 75.80% when the cutoff value is 3.04 g/L. FIB levels are more predictive of hemorrhage compared to activated partial thromboplastin time (APTT) and prothrombin time (PT). Maintaining adequate FIB levels during the perinatal period may help mitigate postpartum hemorrhage risk in HELLP syndrome.<sup>6</sup>

## CONCLUSION

Management of HELLP syndrome requires careful consideration. Currently, there is no specific treatment available for HELLP syndrome. However, the primary focus of treatment revolves around stabilizing the mother and ensuring timely delivery. To reduce the morbidity and mortality associated with HELLP syndrome, different treatment approaches have been explored, including the administration of corticosteroids and glucocorticoids to the mother.

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