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ORIGINAL ARTICLE

Is HELLP Syndrome that Occurs After the 34th Week of Pregnancy More Risky for Mothers?

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Abstract

Introduction: We compare patients with hemolysis, elevated liver enzyme levels, and low platelet (HELLP) levels syndrome developing before and after 34 weeks of pregnancy in terms of demographic data, laboratory values, treatments, and maternal and fetal complications.

Methods: This retrospective descriptive study included 42 patients admitted to an intensive care unit (ICU) over 3 years. The patients were divided into two groups: Those who developed the syndrome at ≤34 weeks (Group I, n=23) and at >34 weeks (Group II, n=19) of pregnancy.

Results: The HELLP syndrome rate was 7.08% (42/593). The mean ICU stay was 3.83±4.04 days and the mean hospital stay 7.49±5.71 days. The mean hemoglobin level and hematocrit of Group II patients were significantly lower than those of Group I patients (p=0.019; p=0.025); the aspartate aminotransferase (AST) level and prothrombin time (PT) of the former patients were significantly higher (p=0.047; p=0.001), as was the volume of erythrocyte suspension (ES) required (p=0.01). Most patients with hypertension and pre-eclampsia were in Group I; all patients lacking hypertension and pre-eclampsia were in Group II (p=0.03; p=0.03).

Discussion and Conclusion: Patients with HELLP syndrome developing after 34 weeks of pregnancy had a lower hemoglobin level and hematocrit; a higher AST level and PT; and required more ES. HELLP syndrome developing in the absence of hypertension and proteinuria was especially prevalent in women who were more than 34 weeks' pregnant.

Keywords: Fetal mortality; hemolysis elevated liver enzyme levels and low platelet syndrome; maternal mortality; pregnancy complications.

Preeclampsia, a common complication of pregnancy, is associated with a 10–15% rate of maternal morbidity and mortality[1]. One of the most significant complications of preeclampsia is hemolysis, elevated liver enzyme levels, and low platelet (HELLP) levels syndrome; this complicates 0.2–1.0% of all pregnancies and 2–20% of preeclamptic pregnancies[2-4]. The maternal mortality rate ranges from 1.1% to 3.4%, and is associated with severe bleeding, pulmonary edema, acute renal failure (ARF), disseminated intravascular coagulation (DIC), pleural effusion, and cerebral edema[5-7]. Fetal mortality may also be high, depending on the gestational week of syndrome development. The perinatal infant mortality rate ranges from 7% to 20%, but problems such as low birth weight, birth asphyxia, and a need for resuscitation and neonatal intensive care unit (ICU) admission are more common in such infants[8]. Although the pathophysiology of HELLP syndrome is not fully understood, the principal problem is thought to be placental insufficiency and widespread endothelial dysfunction caused by inadequate trophoblast invasion, as is the case for preeclampsia[8,9]. Microangiopa-

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thy and intravascular coagulation (probably triggered by cytokines released after placental insufficiency and endothelial injury develop) explain the laboratory changes observed in HELLP syndrome patients[9]. The three principal syndromic signs are hemolysis, elevated liver enzyme levels, and a low platelet count. Symptoms are more often classified based on the Tennessee or Mississippi systems. In the Tennessee system, patients are divided into those with full-blown and partial HELLP; in the Mississippi classification, patients are divided into one of three groups based on platelet count[9]. HELLP syndrome usually develops in the third trimester but may commence postpartum in up to 30% of patients[4]. Gestational week 34 is an important marker at which the appropriate treatment changes from that preferred earlier. Patients who develop the syndrome earlier may be treated or closely observed[4]. If the syndrome develops after week 34 and any maternal or fetal risk factor is evident, preterm delivery is recommended[7].

Given the importance of gestational week 34, we compared cases developing before and after this time in terms of demographic data, laboratory values, treatments, and maternal and fetal complications. Furthermore, mothers who required ICU admission were followed up for 3 years in terms of demographics, treatments, complications, and mortality.

Materials and Methods

Study Design and Population, and Data

This study was performed in T.R. HSU Diyarbakır Gazi Yaşargil Training and Research Hospital between January 2017 and December 2019 with the approval of our ethics committee (approval no. 399 dated 20/12/2019). This was a retrospective descriptive study adhering to all relevant tenets of the Helsinki Declaration of 2008.

Our gynecology and pediatric hospital is located in a separate localization from the main building and has its own second-level adult ICU. According to the protocol in our hospital, all pregnant patients who may be life-threatened are followed up in the second-stage ICU for close follow-up before and after birth. Patients whose conditions are getting worse (such as intubated, those who need mechanical ventilation, and those who need dialysis) are sent to the third-level ICU in our main building. Patients who were diagnosed with HELLP syndrome during or after pregnancy at the specified dates, who were between the ages of 18 and 45 years, and who followed up in the 2nd stage ICU were included in the study. HELLP syndrome was diagnosed as follows: (1) Hemolysis: The presence of at least two of the following: Schistocytes or Burr cells in peripheral smears; serum bilirubin level ≥1.2 mg/dL; a low serum haptoglobin level; elevated levels of lactate dehydrogenase (LDH); and serious anemia (not associated with blood loss). (2) Elevated liver enzyme levels: An aspartate or Alanine aminotransferase level, or a LDH level, that was normal or above normal. (3) Platelets <150,000/mm^3. Patients were excluded if they had the acute fatty liver of pregnancy (AFL), thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome (HUS) associated with pregnancy, was hospitalized to treat conditions other than HELLP syndrome, or were not aged 18–45 years. Four patients for whom data were lacking, two patients with possible AFL, and one patient with possible HUS were also excluded. The remaining 42 patients were included in analyses. We recorded demographic and etiological data, Acute physiology and chronic health evaluation score (APACHE II) and sequential organ failure assessment (SOFA) scores, laboratory values, treatments, complications, postpartum fetal status, the durations of ICU and hospital stays, mortality and morbidity rates, and requirements for blood and blood products (erythrocyte suspension [ES], fresh frozen plasma [TDP], whole blood, random platelet suspension [rTA], platelet apheresis [TA], tranexamic acid, and fibrinogen). Patients were classified using the Tennessee and Mississippi systems and divided into Groups I and II (HELLP syndrome developing at ≤34 or >34 weeks of gestation) (n=23 and 19) and compared.

Statistical Analyses

SPSS ver. 16.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Continuous data are expressed as means with standard deviations and categorical data as frequencies with percentages. Categorical data were compared using the chi-squared and Fisher's exact tests. The Kolmogorov–Smirnov test was used to determine whether numerical data were normally distributed. Such data were compared employing the Student's t-test; the Mann–Whitney U-test and the Kruskal–Wallis test were used to compare data that were not normally distributed. A $p<0.05$ was considered statistically significant.

Results

Between January 2017 and December 2019, 593 patients were admitted to our second-stage ICU with hypertensive diseases of pregnancy: 75 (12.6%) with gestational hypertension, 495 (83.4%) with preeclampsia or eclampsia, 11 (1.87%) with chronic hypertension, and 12 (2.13%) with both preeclampsia and chronic hypertension. In total, 49 patients were admitted to the ICU with a preliminary diagnosis of HELLP syndrome. As noted above, we excluded patients for whom data were lacking and those who, after examination, did not in fact have HELLP syndrome, and we finally enrolled 42 patients. Five patients in Group I and four patients in

Group II were hospitalized in the ICU during the antepartum period. All the remaining patients were admitted to the ICU in the postpartum process. The HELLP syndrome rate was 7.08% (42/593). The syndrome was detected in four patients lacking any sign of preeclampsia. When classified according to the Mississippi system, 17 patients (40.4%) were considered to be Class I, 20 (47.6%) to be Class II, and 5 (12%) to be Class III. According to the Tennessee system, 11 (26.1%) patients had partial and 31 (73.9%) had complete HELLP syndrome. The mean duration of ICU hospitalization was 3.83±4.04 days and the mean hospital stay was 7.49±5.71 days. Table 1 lists demographic data and clinical features.

Table 2 lists the treatments, complications, sequelae, and maternal and perinatal mortality rates of ICU patients. One patient lost left leg strength and another developed chronic kidney failure. Pleural effusion developed in two patients. One patient died; she was a 21-year-old, primiparous patient who had experienced intrauterine fetal death in week 38. She developed postpartum hemorrhage, DIC, and ARF after being admitted to the ICU. After initial interventions, she was referred to our third-stage ICU but died on the 1st day of her stay there.

The hemoglobin level and hematocrit were both significantly lower in Group II than in Group I (p=0.019; p=0.025). The aspartate aminotransferase (AST) level and prothrombin time (PT) were both significantly higher in Group II than in Group I (p=0.047; p=0.001). The groups did not differ significantly in terms of demographic or clinical features, laboratory findings, APACHE II or SOFA scores, or ICU or hospital residence times (Table 3). Pa-

Table 1. Demographic and clinical characteristics of the patients

	Mean±SD (n=42)	Min-Max
Age	28.71±6.3	19–45
Gravida	3.05±1.59	1–7
Parity	2.45±1.36	1–6
Gestational week	33.45±4.03	22–39
APACHE II*	6.31±4.83	1–29
SOFA**	4.76±2.12	2–11
Days in intensive care unit	3.83±4.04	1–26
Hospitalization days	7.49±5.71	1–34
Mississippi classification	**n (%)**	
Class I	17 (40.4)	
Class II	20 (47.6)	
Class III	5 (12)	
Tennessee classification		
Partial	11 (26.1)	
Complete	31 (73.9)	
Total	42 (100)	

*APACHE II: Acute physiology and chronic health evaluation score; **SOFA: Sequential organ failure assessment.

Table 2. Treatments applied to patients, complications, mortality and sequelae

Treatments	Yes n (%)	No n (%)
Steroids	25 (59.5)	17 (40.5)
Fibrinogen replacement	8 (19)	34 (81)
Tranexamic acid	6 (14.3)	36 (85.7)
İnotropic agents	2 (4.8)	40 (95.2)
Magnesium sulphate	37 (88.1)	5 (11.9)
Antihypertensive medication	38 (90.5)	4 (9.5)
Albumin	12 (28.6)	30 (71.4)
Complications	31 (73.8)	11 (26.2)
Blood and blood products	25 (59.5)	17 (40.5)
Mechanical ventilation	3 (7.1)	39 (92.9)
Sepsis	3 (7.1)	39 (92.9)
Acute renal failure	8 (19)	34 (81)
DIC*	14 (33.3)	28 (66.7)
Hemodialysis	2 (4.8)	40 (95.2)
Plasmapheresis	0 (0)	42 (100)
Sent to step 3 ICU**	8 (19)	34 (81)
Maternal mortality	1 (2.3)	41 (97.7)
Perinatal mortality	3 (7.1)	39 (92.9)
Sequelae	2 (4.8)	40 (95.2)

*DIC: Disseminated intravascular coagulation, **ICU: Intensive care unit.

Table 3. Evaluation of the patients according to gestational week I

	Group 1 mean±SD[1] (n=23)	Group 2 mean±SD (n=19)	p
Age	29.65±6.64	27.57±5.83	0.29
Gravida	3.35±1.61	2.68±1.52	0.18
Parity	2.74±1.38	2.11±1.28	0.13
Hemoglobin	11.43±2.2	9.7±2.38	0.019
Hematocrit	33.79±6.39	28.95±7.02	0.025
Platelet count	64.26±28.03	63.5±49.5	0.95
Urea	29.93±15.33	28.4±10.8	0.71
Creatinin	0.77±0.45	0.85±0.48	0.55
ALT[2]	234.13±292.3	267.63±211.9	0.67
AST[3]	270.34±268.03	439.68±407	0.047
LDH[4]	1020.73±591.67	1293.1±896.94	0.24
Albumin	26.69±4.14	25.52±4.57	0.39
PT[5]	10.15±1.1	13.09±5.36	0.001
APTT[6]	29.82±7.99	35.62±13.35	0.09
Fibrinogen	255.94±155.58	188.25±84.87	0.18
APACHE II[7]	6.17±3.05	6.47±6.45	0.43
SOFA[8]	4.48±2.06	5.11±2.2	0.34
Days in intensive care unit	3.57±2.57	4.16±5.38	0.94
Hospitalization days	7.18±4.85	7.84±6.69	0.39

[1]Mean±SD: Mean±standard deviation; [2]ALT: Alanine aminotransferase; [3]AST: Aspartate aminotransferase; [4]LDH: Lactate dehydrogenase; [5]PT: Prothrombin time; [6]APTT: Activated partial thromboplastin time; [7]APACHE II: Acute physiology and chronic health evaluation score; [8]SOFA: Sequential organ failure assessment.

tients in Group II required significantly more ES than patients in Group I (p=0.01). The two groups did not differ significantly in terms of blood and blood product levels (other than ES) required (Fig. 1). Group I and Group II patients were also compared in terms of blood group; Rh and primiparous-multiparous status; type of delivery; fetal status; and maternal hypertension, proteinuria, pre-eclampsia, and eclampsia status. Most patients with hypertension and pre-eclampsia were in Group 1; all of the patients who developed HELLP syndrome in the absence of hypertension or pre-eclampsia were in Group II (p=0.03; p=0.03). No other features differed significantly between the two groups (Table 4).

Table 4. Evaluation of the patients according to gestational week II

Features	Group 1 n (%)	Group 2 n (%)	p*
Blood group			
A	6 (14.3)	5 (11.9)	0.9
B	6 (14.3)	4 (9.5)	
AB	2 (4.8)	3 (7.1)	
0	9 (21.4)	7 (16.7)	
Rh			
(-)	1 (2.4)	2 (4.8)	0.58
(+)	22 (52.4)	17 (40.5)	
Primipara-multipara			
Primipara	5 (11.9)	8 (19)	0.15
Multipara	18 (42.9)	11 (26.2)	
Type of delivery			
Vaginal	1 (2.4)	5 (11.9)	0.07
Cesareansection	22 (52.4)	14 (33.3)	
Fetus			
Exitus	1 (2.4)	2 (4.8)	0.58
Alive	22 (52.4)	17 (40.5)	
Hypertension			
No	0 (0)	4 (9.5)	0.03
Yes	23 (54.8)	15 (35.7)	
Proteinuria			
No	2 (4.8)	7 (16.7)	0.55
Yes	21 (50.0)	12 (28.6)	
Pre-eclampsia			
No	0 (0)	4 (9.5)	0.03
Yes	23 (54.8)	15 (35.7)	
Eclampsia			
No	22 (52.4)	17 (40.5)	0.58
Yes	1 (2.4)	2 (4.8)	
Total	23 (54.8)	19 (45.2)	42

*p-values of Chi-square and Fisher's exact tests.

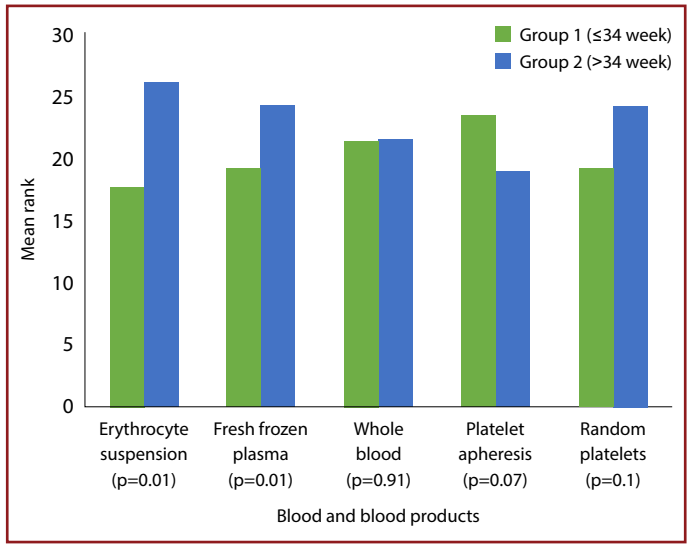

Figure 1. Comparison of the groups according to the blood and blood products given to patients.

Discussion

HELLP syndrome is an important disease during pregnancy; it is a complication of pre-eclampsia/eclampsia and may compromise both the mother and fetus in the absence of an emergency response. The HELLP syndrome rates of women with pre-eclamptic pregnancies differ; 2–20% of pre-eclamptic pregnancies are associated with the syndrome[2,4,10,11]. Our rate was 7.08%, consistent with the literature. However, HELLP syndrome may develop in the absence of pre-eclampsia, thus in 10%–20% of women lacking hypertension, proteinuria, or edema[12-14]. Four of our patients (9.5%) developed HELLP syndrome in the absence of pre-eclampsia; all fetuses were of gestational age >34 weeks. Four patients (9.5%) developed hypertension and nine (21.5%) developed HELLP syndrome in the absence of proteinuria. Of these, all of those who developed HELLP syndrome without hypertension and most of those who developed HELLP syndrome without proteinuria (seven of nine) had fetuses of gestational age >34 weeks. Thus, HELLP syndrome may develop in the absence of hypertension, proteinuria, or pre-eclampsia in women who are more than 34 weeks pregnant. The syndrome usually (70% of cases) develops between weeks 27 and 37 of gestation but can develop earlier or later[12,13]. The risk of preterm delivery is high in women with early-stage pre-eclampsia and HELLP syndrome, increasing the risk of infant complications[15]. The risks of renal failure and pulmonary edema are higher among patients developing postpartum HELLP syndrome[15]. Habli et al.[16] reported that pregnant women with HELLP syndrome developing before 28 weeks of gestation were more likely to develop long-term depression and chronic hypertension. Further-

more, the gestational week during which HELLP syndrome developed can be an indicator of long-term fetal outcomes. We found that HELLP patients with fetuses of gestational age >34 weeks were in poorer clinical condition than HELLP patients with fetuses of gestational age ≤34 weeks. The latter patients had lower hemoglobin levels, reduced hematocrit, and higher AST levels and PT. Such patients required more ES transfusions. However, there was no difference between the two groups in terms of APACHE II and SOFA scores. It was found that these scoring systems did not change the clinical management in this patient group hospitalized in the second-stage ICU. Fetal mortality rates did not differ between the two groups. We did not evaluate other markers of fetal well-being. We suggest that mothers who have HELLP and fetuses of gestational age ≥34 weeks require careful ICU observation.

The complication rate of HELLP syndrome is 34–70%[17,18]. The most common complications are requirements for blood and blood products, DIC, and abruptio placenta, as in our study. Our complication rate was 73.8%; this was high, and we attribute it to our patient population. Our hospital is located in a low socioeconomic region, where pregnant women often do not seek timely attention; this compromises antenatal follow-up and early diagnosis. In other words, many patients visit us only when their problems have become critical, as illustrated by the fact that 73.9% of our patients had complete HELLP syndrome. Therefore, our maternal complication rate may be higher than those cited in previous studies.

The incidence of ARF, a HELLP syndrome complication, ranges from 8% to 48.1%[18,19]. Hemodialysis is the gold standard treatment for ARF[20]. In our study, the rate of ARF was 19%, and 25% of these patients required hemodialysis. Maternal mortality from HELLP syndrome ranges from 1.1 to 3.4% and perinatal mortality from 7 to 20%[3,5,8]. Our maternal and perinatal mortality rates were 2.38% and 7.14%. Hepatic rupture, one of the most serious complications of HELLP syndrome,[20] was not detected in any patient.

Severe cases with HELLP syndrome should be followed up in ICUs[20]. Follow-up of severe cases with HELLP syndrome in ICU will allow patients to be closely monitored, as well as the fast implementation of many necessary treatments. These treatments include dialysis, ventilation support, blood, and blood product replacement. In addition, patients with HELLP syndrome need to be followed up in the ICU to manage possible complications and achieve a multidisciplinary approach. In some hospitals, mild cases are followed up in the clinics, while severe cases are followed in the ICUs. In our hospital, all cases with HELLP syndrome diagnosed are followed up for at least 48 h in the second-level ICU for close follow-up. Patients whose conditions are getting worse (such as those intubated, who need ventilation support, and who need dialysis) are sent to the third-level ICU in our main building. We think that close follow-up of all HELLP syndrome cases in the ICU (mild cases in second-stage ICU, and severe cases in third-level ICU) can be an important practice in reducing maternal mortality and morbidity.

When the patient is first taken to the ICU, the condition of both the mother and the fetus should be examined. For example, does the mother have a condition requiring emergency intervention (hepatic hemorrhage or rupture)? The biophysical profile of the fetus and fetal presentation in the absence of stress should be evaluated, and ultrasonography performed.

For mature fetuses of gestational age ≥34 weeks, the recommended solution is delivery. For fetuses of gestational age <34 weeks, corticosteroids should be prescribed to stimulate surfactant production and release in the lungs, accelerate fetal pulmonary maturation, and reduce perinatal complications[20]. In addition, corticosteroids may aid the maternal clinical course given their anti-inflammatory and immunosuppressive effects[7]. However, a Cochrane systematic review comparing HELLP syndrome patients who did and did not receive corticosteroids found no differences in terms of maternal mortality, serious maternal morbidity, or perinatal infant mortality; the authors concluded that evidence supporting the routine use of corticosteroids was lacking and that the only effect was an increased number of platelets[21]. If the gestational age is <24 or ≥34 weeks, the mother and fetus do not exhibit any complications and are stable, delivery can be performed after steroid treatment. However, in the presence of 24–33 gestational age and any condition such as fetal death, abruptio placentae, pulmonary edema, eclampsia, liver hemorrhage, or stroke, emergency delivery is the recommended method[4]. Of our patients, 59.5% received steroids.

Postpartum follow-up of ICU patients should feature close hemodynamic evaluation with a focus on bleeding, hypertension, and other complications. Vital signs, fluid intake, urine output, and laboratory values should be closely monitored for at least 48 h. Magnesium sulfate infusion prevents seizures; labetalol, hydralazine, or nifedipine stabilizes blood pressure; and hematological, cardiovascular, respiratory, and renal complications are treated as emergencies[20]. In our ICU, patients with pre-eclampsia receive magnesium sulfate for 24 h and usually both labetalol and

amlodipine (antihypertensive agents). Patients whose vital signs have stabilized, who are mobile, and whose laboratory values have normalized are transferred from the ICU to a general ward.

Tranexamic acid and fibrinogen concentrates (anti-fibrinolytic drugs used to reduce obstetric bleeding) are useful in some cases of HELLP syndrome. In the WOMAN trial, 20,060 patients treated from 2010 to 2016 were evaluated in terms of tranexamic acid use; the results revealed that delivery of 1-g amounts of tranexamic acid via slow intravenous infusion reduced maternal mortality caused by postpartum bleeding, without any side effects[22]. The PPH-Consensus Group of Europe recommended that fibrinogen should be given to women exhibiting severe postpartum hemorrhage combined with low fibrinogen levels and/or signs of fibrinogen-related coagulopathy[23]. Our ICU prescribes tranexamic acid and fibrinogen concentrates for selected patients as recommended by the WOMAN trial and the PPH-Consensus Group of Europe. Of all HELLP patients, 14.3% received tranexamic acid and 19% a fibrinogen concentrate.

Conclusion

We found that the HELLP syndrome rate was 7.08%, the complication rate was 73.8%, the maternal mortality rate was 2.38%, and the perinatal infant mortality rate was 7.14%. Patients with HELLP syndrome and fetuses >34 weeks of gestational age had a lower hemoglobin level and hematocrit; a higher AST level and a higher PT; and required more ES. We also found that HELLP syndrome was not associated with hypertension and proteinuria was not uncommon in women with fetuses of gestational age >34 weeks. Pregnant women with HELLP syndrome are critically ill and should be followed up and treated in an ICU. We found that HELLP patients, especially those with fetuses of gestational age >34 weeks, may exhibit without hypertension and proteinuria. Careful attention by clinicians will reduce maternal mortality and morbidity.

Ethics Committee Approval: This study was performed in T.R. HSU Diyarbakır Gazi Yaşargil Training and Research Hospital between January 2017 and December 2019 with the approval of our ethics committee (approval no. 399 dated 20/12/2019).

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