Clinical course and complications of HELLP syndrome according to time of onset

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Summary

Objective: To evaluate the impact of gestational age on clinical laboratory findings and maternal-perinatal outcomes in patients with HELLP syndrome. *Method:* A retrospective review of 74 patients with HELLP syndrome between January 2007 and October 2010 was performed. Data were stratified into two groups by gestational age at the onset of disease: group 1 (< 34 weeks) and group 2 (≥ 34 weeks). Clinical signs and symptoms, laboratory findings, and maternal and perinatal outcomes were evaluated. *Results:* No differences were observed between the two groups in the clinical and laboratory characteristics according to onset of HELLP syndrome except for gravidity, parity, and delivery interval. Maternal complications did not differ between the groups. The perinatal mortality rate was 22.9% in total and it was 43.2% in group 1. *Conclusions:* The time of onset of the HELLP syndrome mainly affects neonatal outcomes. To assess the effect on maternal morbidity more studies are needed.

Key words: HELLP syndrome; Maternal and perinatal outcomes; Temporizing management.

Introduction

Severe preeclampsia, particularly HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome is associated with significant maternal and perinatal morbidity and mortality [1]. Maternal organ systems such as the central nervous system (CNS), lungs, liver, kidneys, and systemic vasculature are susceptible to excessive inflammation and endothelial damage in HELLP syndrome [2]. It is essential to confirm the diagnosis and appropriate clinical management to avoid these multisystemic complications. The debate regarding the definition, diagnosis, etiology, and management of this syndrome is considerable [3]. It has a heterogeneous presentation and a clinical course similar to preeclampsia.

The terminology of early and late onset preeclampsia according to gestational age at the onset of preeclampsia is used largely, as a reflection of the severity of the disease and different etiopathogenesis [2]. Gestational age plays an important role in disease management and also impacts the short-term perinatal morbidity and mortality. Unfortunately, there is insufficient data regarding the impact of gestational age on the clinical course and maternal outcome in HELLP syndrome. It has been demonstrated that some clinical and laboratory parameters predict the severity of HELLP syndrome or disease outcomes, but there remains an ongoing debate and controversy about the potential use in clinical practice [4]. No predictors of adverse maternal and perinatal outcomes were identified in a review by Magee *et al*. [5] for severe preeclampsia. The time of onset of HELLP syndrome is important for perinatal outcome, and the effect on maternal outcome and management should be demonstrated.

The goal of this study was to evaluate the impact of gestational age on clinical laboratory findings and maternal-perinatal outcomes in patients with HELLP syndrome.

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Materials and Methods

A retrospective review of the data of patients with diagnosed HELLP syndrome managed at Cukurova University, School of Medicine, Department of Obstetrics and Gynecology between January 2007 and October 2010 was conducted. This study was exempted from ethical approval by the Local Ethics Committee. The study groups consisted of mostly referred patients because of the tertiary unit. The patients were divided into two groups according to onset of HELLP syndrome. Group 1 (n = 37) consisted of patients with early onset disease (< 34 weeks of gestation) and group 2 (n = 37) consisted of patients with late onset disease (≥ 34 weeks of gestation). Clinical and laboratory findings, and maternal and perinatal outcomes were compared between the groups.

Patients were classified as having hypertension, severe preeclampsia, and eclampsia according to the criteria of the American College of Obstetricians and Gynecologist [6]. HELLP syndrome was defined as the presence of hemolysis which defined lactate dehydrogenase (LDH) ≥ 600 U/l or serum total bilirubin levels > 1.2 mg/dl, elevated liver enzymes, serum aspartate aminotransferase (AST) > 70 U/l) and low platelet counts (< 100,000/mm^3). Typical cases are those that develop before 20 weeks, and beyond 48 hours postpartum, and those that presented with some of the signs and symptoms of preeclampsia without the usual hypertension or proteinuria [7], diabetes mellitus, epilepsy, hepatic, and renal diseases were excluded from this study. At admission hematocrit, hemoglobin, platelet count, liver enzymes, LDH, uric acid, coagulation tests (prothrombin time, partial thromboplastin time, bleeding time), renal function tests (blood urea nitrogen, creatinine), and spot urinary proteinuria were determined. The patients were strictly monitored with blood pressure and urine output measurements and frequent assessment of symptoms. Laboratory assessments of platelet count, liver and renal function tests, LDH, and uric acid values were carried out every six hours. Blood products were administered to patients with existing severe anemia or coagulation abnormalities. Gestational age was determined according to the last menstrual period or first/early second trimester ultrasonography (US). All patients with HELLP syndrome routinely received magnesium sulfate as a 4.5 g IV loading dose before a 2 g maintenance dose per hour. All cases

over 34 weeks of gestation were delivered promptly. Pregnancies before 34 weeks of gestation were terminated following corticosteroid therapy. If the maternal condition was unstable and the fetal well-being tests were non-reassuring, presence of the deterioration of the laboratory values we terminated the pregnancy, without waiting for the period necessary for lung maturity with bethametasone. Ceaserean section was performed in cases of maternal and/or fetal worsening. The latency period between diagnosis and delivery was recorded (delivery interval). After delivery, steroid therapy such as dexamethasone was not administered routinely. Demographics of the patients, such as maternal age, parity, gestational age, history of preeclampsia, complaints at admission, clinical findings including systolic and diastolic blood pressure at admission, presence of a prodromal symptom (such as nausea, vomiting, headache, epigastric pain, visual change), laboratory results, antihypertensive drug administration, corticosteroid therapy, requirement of intensive care unit (ICU), delivery interval, mode of delivery, duration of hospitalization, preoperative betamethazone administration, and postpartum HELLP were evaluated. The Mississippi-Triple Classification System [3, 4] was used for the classification of HELLP syndrome based on the thrombocyte counts: Class I (< 50,000 mm^3), Class II (50,000-100,000 mm^3), Class III (100,000-150,000 mm^3). We recorded adverse maternal outcomes including eclampsia, abruptio placenta, disseminated intravascular coagulation (DIC), acute renal insufficiency (ARI), requirement of transfusion, requirement of ICU, intracranial hemorrhage, and maternal death. Perinatal complications including intrauterine growth restriction (IUGR), oligohydramniosis, stillbirth, requirement of neonatal ICU, and perinatal mortality were also assessed. Low APGAR score was determined as being < 7 of the 5^{th} min.

Statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS version 16.0; SPSS Inc., Chicago, IL, USA) . Data are shown as mean ± SD, median, minimum-maximum value or percent. Student's t-test and Mann-Whitney U tests were used to detemine differences for comparison of groups for parametric and nonparametric data. Statistical significance was set at $p < 0.05$.

Results

A total of 6,622 deliveries occurred during the study period, and 85 of all deliveries were complicated by HELLP syndrome (1.2%). This high prevalance is due to the fact that most patients were referred because of a tertiary unit. Seventy-four of these patients were included in the study because atypic presentation of HELLP syndrome occured in 11 patients. In total 51 patients (68.9%) had severe preeclampsia, 16 patients (21.6%) had superimposed preeclampsia, and seven patients (9.5%) had eclampsia complicated by HELLP syndrome; these associated pathologies were not significantly different between groups ($p = 0.814$). We compared the demographic and clinical characteristics of patients with HELLP syndrome (Table 1). The gravidity and parity of the patients in group 1 were statistically significantly higher than for patients in group 2 (Table 1). Clinical findings of the patients in both groups were similar excluding the delivery interval which was longer in group 1 ($p = 0.044$), as could be expected.

There were no statistically significant differences between the groups in laboratory findings (Table 2). Maternal and neonatal outcomes, and complications are shown in Table 3. There were no statistically significant differences for maternal outcomes between the groups. The main maternal complications were ARI (2.7%), ARDS (2.7%), DIC (21.6%), abruptio placenta (2.7%), eclampsia (9.5%), requirement of intensive care (21.6%), and requirement of blood transfusions (25.7%). ARI occurred in two patients who recovered by hemodialysis. None of these women required long-term dialysis. Nineteen patients required blood transfusions (platelet suspension, erythrocyte suspension, and fresh frozen plasma). No intracerebral hemorrhage, subcapsular liver hematoma or bleeding, or maternal deaths occurred during the study period. The total perinatal mortality rate was 22.9% (n = 17) and the mortality rate in group 1 was 43.2% (n = 16). There were three cases of stillbirth.

Table 1. — *Demographic characteristics and clinical findings of the patients according to the time of onset of HELLP syndrome*.

	HELLP Mean ± SD Median (min-max)		
	Early onset (n = 37)	Late onset (n = 37)	Total (n = 74)
Age (years)	30.5 ± 6.4 30 (17-43)	28.7 ± 6.4 30 (18-45)	29.6 ± 6.4 30 (17-45)
Gravidity	3.1 ± 1.5 3 (1-8)	2.1 ± 1.5* 1 (1-7)	2.6 ± 1.6 3 (1-8)
Parity	1.6 ± 1.3 2 (0-5)	0.9 ± 1.3* 1 (0-6)	1.3 ± 1.3 1 (0-6)
Gestational age (week)	30.5 ± 3.1 31.4 (21-35.6)	36.7 ± 1.8* 36.6 (33-40.4)	33.6 ± 4.0 34.05 (21-40.4)
Sistolic blood pressure (mmHg)	162.2 ± 28.7 160 (110-220)	157.3 ± 28.2 160 (110-230)	159.7 ± 28.3 160 (110-230)
Diastolic blood pressure (mmHg)	107.8 ± 19.3 110 (70-150)	104.3 ± 17.6 100 (70-140)	106.1 ± 18.4 105 (70-150)
Delivery interval (day)	2.1 ± 3.7 1 (1-20)	1.2 ± 1.2* 1 (1-8)	1.7 ± 2.8 1 (1-20)
Birth weight (g)	1374.3 ± 517.4 1380 (550-2360)	2480.4 ± 671.6 2600 (2000-3550)	1927.4 ± 815.2 1875 (550-3550)
Prodromal symptoms[f]	27 (73.0)	29 (78.4)	56 (75.7)
Postpartum HELLP[f]	1 (2.7)*	8 (21.6)	9 (12.2)
Recurrent preeclampsia[f]	4 (10.8)	3 (8.1)	7 (9.5)
IV antihypertensive requirement[f]	31 (83.8)	31 (83.8)	62 (83.8)
Transfusion requirement[f]	9 (24.3)	10 (27.0)	19 (25.7)
Twin pregnancy[f]	3 (8.1)	2 (5.4)	5 (6.8)
Administering of betamethasone[f]	16 (43.2*)	1 (2.7)	17 (23.0)

[f] = n, percent; * = $p \leq 0.005$.

Discussion

Hypertensive disorders of pregnancy have a heterogeneous presentation and might be characterized as a clinical syndrome rather than a single disease entity [8]. Hypertension and proteinuria are not always associated with this syndrome. In this study, 11 patients were excluded due to an atypical presentation. Some studies showed that hypertension may be mild or absent in patients with HELLP syndrome and up to 13% of cases do not have proteinuria [4, 9, 10]. HELLP syndrome may

Table 2. — *Laboratory findings of patients according to time of onset of HELLP syndrome.*

	HELLP Mean ± SD Median (min-max)		
	Early onset (n = 37)	Late onset (n = 37)	Total (n = 74)
Hb (g/dl)	12.6 ± 2.0	12.3 ± 1.4	12.4 ± 1.7
	13 (6.1-15.7)	12.7 (9.4-15)	12.9 (6.1-15.7)
Htc (%)	37.1 ± 5.7	36.8 ± 4.5	37.0 ± 5.1
	38.2 (20-48)	37.1 (27.5-45)	37.65 (20-48)
Plt ($\times 10^9$per l)	91.8 ± 45.5	80.3 ± 38.6	86.1 ± 42.3
	88 (27-243)	75 (29-195)	79.5 (27-243)
White cell count	13.0 ± 5.7	12.8 ± 6.1	12.9 ± 5.9
($\times 10^9$ per l)	13.3 (3.2-28.4)	10.9 (3.2-26.5)	11.55 (3.2-28.4)
AST (U/l)	340.3 ± 450.3	365.8 ± 409.3	353.0 ± 427.6
	172 (63-2559)	289 (72-2298)	202.5 (63-2559)
ALT (U/l)	237.1 ± 282.0	233.6 ± 281.2	235.4 ± 279.7
	167 (74-1578)	156 (63-1624)	158.5 (63-1624)
LDH (U/l)	1051.9 ± 523.7	949.2 ± 416.5	1000.6 ± 472.8
	886 (532-2610)	808 (485-2706)	858.5 (485-2706)
Uric acid (mg/dl)	7.2 ± 2.1	7.4 ± 2.1	7.3 ± 2.1
	6.5 (3.7-12.7)	7.4 (3.7-13)	6.7 (3.7-13)
BUN (mg/dl)	18.0 ± 11.0	14.2 ± 7.5	16.1 ± 9.5
	15 (4-54)	13 (5-49)	14 (4-54)
Creatinine (mg/dl)	0.9 ± 0.6	0.8 ± 0.6	0.8 ± 0.6
	0.8 (0.5-3.5)	0.7 (0.1-4.3)	0.7 (0.1-4.3)
Dipstick proteinuria[f]			
+	3 (8.1)	4 (10.8)	7 (9.5)
++	10 (27.0)	9 (24.3)	19 (25.7)
+++	15 (40.5)	19 (51.4)	34 (45.9)
++++	9 (24.3)	5 (13.5)	14 (18.9)

Table 3. — *Maternal and fetal outcomes according to time of onset of HELLP syndrome.*

	HELLP n (%)		
	Early onset	Late onset	Total
Maternal outcomes			
DIC	9 (24.3)	7 (18.9)	16 (21.6)
Eclampsia	3 (8.1)	4 (10.8)	7 (9.5)
ARDS	1 (2.7)	1 (2.7)	2 (2.7)
Ablatio placenta	0 (0.0)	2 (5.4)	2 (2.7)
ATI	1 (2.7)	1 (2.7)	2 (2.7)
ICU admission			
Classification of HELLP	7 (18.9)	9 (24.3)	16 (21.6)
Class I (< 50 x 10^3)	5 (13.5)	7 (18.9)	12 (16.2) **
Class II (50-100 x 10^3)	21 (56.8)	21 (56.8)	42 (56.8)
Class III (> 100 x 10^3)	11 (29.7)	9 (24.3)	20 (27.0)
Fetal outcomes			
Oligohydramniosis	10 (27.0)	9 (24.3)	19 (25.7)
IUGR	14 (37.8)	16 (43.2)	30 (40.5)
Stillbirth	2 (5.4)	1 (2.7)	3 (4.1)
Low APGAR score	15 (40.5)*	2 (5.4)	17 (23.0)
NICU admission	31 (83.8)*	13 (35.1)	44 (59.5)
Low birth weight	34 (91.9)*	9 (24.3)	43 (58.1)
Perinatal mortality	16 (43.2)*	1 (2.7)	17 (22.9)

*p < 0.05; **p = 0.766.

develop in the antepartum or postpartum period, and postpartum presentation may be as high as 30% [4]. In our series, HELLP syndrome developed in nine postpartum patients (12.2%), and eight of them were in the late onset group. The onset of clinical findings in this group of patients was within 48 hours postpartum. Women with a history of previous preeclampsia are at increased risk of preeclampsia and other adverse pregnancy outcomes in subsequent pregnancies. The magnitude of this risk depends on gestational age at time of disease onset and severity of disease. In our study, seven patients had a history of preeclampsia (9.5%). In a study which evaluated the recurrence risk of delivery before 34 weeks of pregnancy due to early onset of hypertensive disorder, the risk has been determined to be approximately 8% [11]. Prodromal symptoms have been reported with a frequency ranging from 30-90% [2]. The incidence of one or more prodromal symptoms in our study population was 75.7%. These results remind us of the importance of close follow-up of prodromal symptoms in the antenatal and postpartum period.

The purpose of this study was to discuss the impact of gestational age on maternal outcome, clinical findings, and laboratory parameters in patients with HELLP syndrome. We compared clinical and laboratory findings of patients in terms of onset of HELLP syndrome, and observed no differences between the two groups, except for gravidity and parity, and delivery interval. Yıldırım *et al*. [12] evaluated maternal complications according to gestational age and used 28 weeks of gestation for the threshold value; they observed no significant differences between the groups. Approximately 9-16% of HELLP syndrome cases are reported to be associated with eclampsia and it is reported that this association decreased as gestational age increased [13]. The ratio of eclampsia seen with HELLP syndrome was 7.9% in our study population and was not different between the groups. In another study [14] eclampsia did not appear to contribute to a significant adverse impact on the course or outcome of pregnancies complicated by HELLP syndrome.

Identifying patients with increased perinatal or maternal adverse outcomes could facilitate management of these patients. The initial evaluation of laboratory data may not provide predictions of complications. Haddad *et al*. [13] reported that laboratory parameters of HELLP syndrome are not independent risk factors for adverse maternal outcomes and management should be based on clinical endpoints rather than on laboratory parameters alone. According to Cavtaykar *et al*. [15] clinical complaints may help in predicting prognosis better than laboratory findings. However, Martin *et al*. [3] stated that laboratory data are more important to consider; the researchers found higher maternal morbidity rates in class 1 HELLP syndrome (class 1 defined as a platelet count ≤ 50,000 cells/mm^3). In this study we compared the classification of HELLP syndrome by the Mississippi-Triple Classification System with onset of the disease, and did not find significant differences in onset of the disease. Yucesoy *et al*. [16] proposed that low platelet counts might significantly increase the complications of HELLP syndrome. Moreover, some authors have suggested that platelet counts, LDH, AST, and ALT at the time of admission could be useful in predicting the severity of HELLP syndrome [17, 18]. However, Ganzevoolt *et al*. [19] showed that accurate prediction of the clinical

course of disease and patients, development of additional maternal complications with severe hypertensive disorders of pregnancy were not feasible at admission. Another study aimed at determining identification of preeclamptic women at risk of adverse outcomes [20]. An important effect of this study might be identification of preeclamptic women at the lowest risk of adverse outcomes. Gestational age at admission is a strong prognostic indicator for adverse infant outcome for preeclampsia [21]. This study demonstrated that the time of onset of disease was strongly associated with neonatal outcome but did not demostrate an association with maternal outcome, laboratory findings, and clinical course of HELLP syndrome. The most important limitation of this study was that it was retrospective and there were not enough cases for decision-making for maternal outcomes according to time of onset of the disease.

Conclusion

The key clinical issue is to predict the complications of HELLP syndrome. Clinical presentation, symptoms, laboratory tests, and the time of onset of disease should be evaluated carefully to predict maternal and perinatal complications in HELLP syndrome.

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