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HELLP syndrome is still a serious, life-threatening complication of pregnancy: admission of 34 women to an eastern Turkish intensive care unit

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Summary

Objective: The transfer of the obstetric patient to the intensive care unit is considered as an indicator of maternal morbidity. The most important two indications for admittance of the obstetric patient to the intensive care unit are postpartum hemorrhage and hypertensive disorders. The purpose of this study was to determine maternal morbidity and mortality rates in patients diagnosed with hemolysis, elevated liver enzyme levels, and low platelet count (HELLP) syndrome who required intensive care. *Materials and Methods:* The charts of 34 patients who were diagnosed with HELLP syndrome and treated in intensive care unit between the years 2005 - 2013 were evaluated retrospectively. *Results:* During the study period, a total of 151 patients were diagnosed with HELLP syndrome and 34 patients were admitted to the intensive care unit. Mean age of the patients was 28.97 ± 7.26 years and there was no significant difference between survivors and non-survivors ($p = 0.442$). There were no significant differences between survivors and non-survivors in terms of gestational age, parity, and multiparity rates ($p > 0.05$). There was 31.2% mortal cases and 77.8% of living cases had received regular antenatal follow-up and the difference was statistically significant ($p = 0.006$). 30 patients (88.2%) required invasive mechanical ventilation. The average Glasgow Coma Score (GCS) of patients was 6.47 ± 4.34. There were significant differences between patients who lived and who died in terms of Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) score, and duration of invasive mechanical ventilation ($p < 0.05$). Twenty-two patients (64.7%) required transfusion of blood and blood products. Maternal mortality occurred in 16 patients (47%). The causes of death were: intracerebral hemorrhage in six cases, acute respiratory distress syndrome (ARDS) in three cases, disseminated intravascular coagulation (DIC) in three cases, sepsis/multiple organ dysfunction syndrome (MODS) in two cases, hepatic rupture in one case, and massive pulmonary embolism in one case. *Conclusion:* HELLP syndrome is still one of the most serious and life-threatening complications of pregnancy. Mortality rate can be reduced by regular antenatal follow-up and transfer of pregnant women who carry risk to the intensive care unit without delay.

Key words: HELLP syndrome; Maternal mortality; Intensive care unit.

Introduction

Despite advances in diagnosis and treatment, hypertension during pregnancy is still an important cause of morbidity and mortality.

HELLP syndrome, characterized by hemolysis, elevated liver enzymes and low platelet count was first described by Weinstein. HELLP syndrome is a multisystemic disorder. Irregular vascular tonus, severe vasospasm, and disorders of the coagulation system are remarkable features of the syndrome [1]. HELLP syndrome is one of the most significant causes of maternal and perinatal mortality and morbidity. Its clinical course includes many life-threatening complications such as acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), cerebral hemorrhage, septic shock, acute renal failure, hepatic rupture, and placental abruption [2]. Maternal mortality related to HELLP syndrome was reported to be between 1.1% and 25% [3, 4]. In recent years, while maternal mortality rates have been significantly declining in developed countries, mortality rate is still high in developing countries and in underdeveloped regions where the perinatal follow-up is poor [5, 6]. The intensive care management of the obstetric patient differs from the other patient groups. Admittance of the obstetric patient to the intensive care unit is rare; it constitutes less than 1% of all intensive care patients and transfer of the obstetric patient to the intensive care unit is considered as an indicator of maternal morbidity [7-9] The purpose of this study was to determine maternal morbidity and mortality rates in patients diagnosed with HELLP syndrome who required intensive care.

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Table 1. — *Clinical characteristics of study patients* [a].

	All patients	Survivor (n=18)	Non-survivor (n=16)	*p* value [b]
Maternal age (years)	28.97 ± 7.26	29.89 ± 7.68	27.94 ± 6,85	0.442
Gestational age (weeks)	33.97 ± 4.97	34.83 ± 4.96	33.00 ± 4.95	0.290
Parity	2.71 ± 2.87	3.33 ± 3.51	2.00 ± 1.75	0.421
Multiparity	15 (44.1%)	8 (44.4%)	7 (43.8%)	NS†
Primiparity	19 (55.9%)	10 (55.6%)	9 (56.2%)	NS†
Antenatal follow-up (n, %)	19 (55%)	14 (77.8%)	5 (1.2%)	0.006 *
Platelets ($\times 10^3$/L)	135080 ± 91391	166666 ± 107354	105923 ± 64973	0.097
AST (U/L)	381.36 ± 552.52	183.58 ± 246.44	563.92 ± 692.58	0.85
ALT (U/L)	212.56 ± 255.27	144.25 ± 215.58	275.62 ± 280.64	0.205
Total bilirubin (mg/dl)	2.13 ± 1.64	2.17 ± 1.75	2.09 ± 1.56	0.825
LDH (U/L)	1377.82 ± 873.77	1467.22 ± 965.43	1277.25 ± 776.48	0.535
Creatinine (mg/dl)	1.02 ± 0.68	0.9 ± 0.62	1.15 ± 0.75	0.237
APACHE-II score	26.38 ± 8.84	20.89 ± 6.30	32.56 ± 7.07	< 0.001 β
GCS score	6.47 ± 4.34	7.89 ± 4.78	4.88 ± 3.24	0.065
SOFA score	968 ± 4.12	7.11 ± 3.07	12.56 ± 3.16	< 0.001β
Mode of delivery				
Vaginal (n, %)	9 (26.5%)	6 (33.3%)	3(18.8%)	NS†
Cesarean (n, %)	25 (73.5%)	12 (66.7%)	13 (81.2%)	NS†
Anesthetic management				
Regional anesthesia (n, %)	3 (12%)	1 (8.3%)	2 (15.4%)	NS†
General anesthesia (n, %)	22 (88%)	11 (91.7%)	11 (84.6%)	NS†

APACHE: Acute Physiology and Chronic Health Evaluation; GCS: Glasgow coma score; SOFA: Sequential Organ Failure Assessment; ICU: intensive care unit; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactic dehydrogenase.
[a] Values are given as number (percentage) or mean ± SD; [b] For the comparison of survivors and non-survivors.
* $p < 0.05$ Chi-square test; † $p > 0.05$ Chi-square test; β $p < 0.05$ Independent sample *t*-test.

Materials and Methods

The charts of 34 obstetric patients admitted to the Atatürk University Medical Faculty, Department of Anesthesiology and Reanimation, Intensive Care Unit between 2005 and 2013 were investigated retrospectively, following the approval of Ethics Committee. The diagnosis of HELLP syndrome was made according to Tennessee classification [3]: hemolysis (the presence of fragmented erythrocytes in peripheral blood smear), serum total bilirubin ≥1.2 mg/dl, elevated liver enzymes (alanine aminotransferase ≥ 70 U/L and/or aspartate aminotransferase ≥ 70 U/L), and low platelet count (< 100,000/ mm³).

The demographic data of diagnosed patients: age, gravidity, parity, gestational week, presence of antenatal follow-up, and delivery mode were identified. Additionally, the laboratory parameters; platelet count, liver function tests (AST, ALT), LDH, total bilirubin, direct bilirubin, renal function tests (BUN, creatinine), and INR values were recorded.

Acute renal failure, DIC, placental abruption, intracranial hemorrhage, subcapsular hematoma, eclampsia, cerebral edema, sepsis, acute respiratory distress syndrome, comorbidities, Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) score, Glasgow Coma Score (GCS), requirement of mechanical ventilation, duration of mechanical ventilation, duration of stay in intensive care unit, transfusion requirement of blood and blood products (packed red cells, fresh frozen plasma, platelets), vasoactive drug usage, dialysis, hemofiltration, requirement of plasmapheresis, and presence of maternal mortality were investigated in patient charts.

Patients diagnosed as HELLP syndrome who were hemodynamically unstable, or have respiratory failure, require mechanical ventilation, dialysis, plasmapheresis or vasoactive drugs were transferred to the intensive care unit.

Statistical analysis

SPSS 20.0 software package was used for statistical analysis. To compare the variables of living and dead patients categorically, the chi-square test was used. The normal distributions of numerical parameters of the patients were evaluated by Kolmogorov Smirnov test. For comparison of parameters showing normal distribution, *t*-test was used. Mann-Whitney U test was used for parameters that did not meet normal distribution. A $p < 0.05$ was considered to be statistically significant.

Results

During the study period, a total of 151 patients were diagnosed with HELLP syndrome and 34 (22.5%) of them were admitted to and treated in intensive care unit. Other patients were treated and followed up in obstetrics clinic.

Demographic characteristics and clinical features of 34 patients managed in intensive care unit are shown in Table 1. The mean age of patients was 28.97±7.26 years and no statistically significant difference was found between groups ($p = 0.442$). There were no statistically significant differences between survivor and non-survivors in terms of gestational week, parity, and multiparity rates ($p > 0.05$). There was 31.2% of dead patients and 77.8% of living patients had received regular antenatal follow-up and the difference was statistically significant ($p = 0.006$). When platelet counts, LDH, AST, ALT, total bilirubin, and creatinine values during their first admittance were taken into consideration, there were no significant differences be-

Table 2. — *Interventions in the intensive care unit.*

	All patients	Survivor (n=18)	Non-survivor (n=16)	*p* value
Mechanical ventilation duration (days)	5.65 ± 5.32	2.61 ± 2.68	9.06 ± 5.53	< 0.001*
Invasive mechanic ventilation (n, %)	30 (88.2%)	14 (77.8%)	16 (100%)	0.045 β
Length of ICU stay (days)	7.26 ± 5.47	5.67 ± 5.64	9.06 ± 5.53	0.07
Inotropic Support (n)	4	-	4	0.024 β
Dialysis Support (n)	6	3	3	0.874
TDP transfusion (units)	4.06 ± 6.45	0.83 ± 1.54	7.69 ± 7.89	< 0.001†
Packed red cells (units)	2.24 ± 3.40	0.67 ± 1.91	4.00 ± 3.88	< 0.001†
Platelet transfusion (units)	0.82 ± 1.85	0.61 ± 1.91	1.06 ± 1.81	0.190

Values are given as number (percentage) or mean ± SD. *$p < 0.001$ Independent sample *t*-test, β $p < 0.05$ Chi-square test, †Mann Whitney U test.

Table 3. — *Causes of maternal deaths and mortality rate.*

Causes of death	n (%)
Intracerebral hemorrhage	6 (37.5%)
ARDS	3 (18%)
DIC	3 (18%)
Sepsis/MODS	2 (12%)
Hepatic rupture	1 (6%)
Massive pulmonary embolism	1 (6%)
Mortality rate (admitted to the intensive care)	16/34 (47%)
Mortality rate (admitted to clinic + intensive care)	16/151 (10.5%)

Values are given as number (percentage).

tween groups ($p > 0.05$). APACHE II, GCS, and SOFA scores of the patients at their admittance to the intensive care unit were analyzed. While no statistically significant difference was found in terms of GCS, there were statistically significant differences between groups in terms of APACHE II and SOFA scores ($p < 0.001$). There were no significant differences in terms of delivery modes and anesthetic management.

Parameters of patients related to intensive care are shown in Table 2. While 77.8% of the living patients required invasive mechanical ventilation, this ratio was 100% for dead patients ($p = 0.045$). The duration of mechanical ventilation was 2.61 ± 2.68 days for living patients and 9.06 ± 5.53 days for dead patients, and the difference between them was found to be statistically significant ($p < 0.001$). Total duration of hospitalization in intensive care unit was 5.67 ± 5.64 days in living patients, whereas it was 9.06 ± 5.53 days in dead patients, and the difference was not statistically significant ($p = 0.07$). When requirements for inotropic drugs, fresh frozen plasma, and packed red cell transfusion were taken into consideration, they were found to be increased in dead patients and the differences were statistically significant (p values were 0.024, <0.001, and <0.001, respectively). There was no statistically significant difference between groups in terms of platelet transfusion ($p = 0.190$). Hemodialysis was required for three patients in each group.

Causes of death for 16 dead patients are shown in Table 3; they were intracerebral hemorrhage (37.5%), ARDS (18%), DIC (18%), sepsis/MODS (12%), hepatic rupture (6%), and massive pulmonary embolism (6%). Mortality rate was 47% in patients admitted to the intensive care unit. Sixteen out of 151 patients who were diagnosed with HELLP syndrome had died throughout the study period; the mortality rate of this group was 10.5%.

Discussion

Maternal death is still a significant problem throughout the world. Reducing maternal mortality is an important international developmental goal [6]. Maternal mortality is described as the death of a woman due to the pregnancy or a cause related to its management during pregnancy or within 42 days following delivery, other than accidents or incidental causes [10]. The most common causes are as follows: hemorrhage, thromboembolism, cardiac disorders, sepsis, hypertensive diseases, and amniotic fluid embolism. Despite studies to reduce maternal mortality in recent years, unfortunately, maternal deaths related to HELLP syndrome have not been reduced significantly. The mortality rates of patients with HELLP syndrome admitted to the intensive care unit differs between developed and developing countries. In reports published recently, mortality rate is between 0% and 3.8% in developed countries [11-15]. While mortality rate is significantly low in developed countries, in developing countries with low socio-economic status, this rate is increased to 10-35% [16-20]. In a study conducted in Turkey, maternal mortality rate related to HELLP syndrome was reported to be 30% [21]. The mortality rate being higher in the present study (47%) when compared to other studies might have been related to the present admission criteria to intensive care unit and since the present hospital is a tertiary center, transport of patients with higher risk to the center from peripheral hospitals. Additionally, due to lack of good antenatal follow-up associated with low socio-economic status of patients in the present region, and general poor systemic conditions of them during admittance to the present clinic, might have increased the mortality rates

HELLP syndrome is known as a significant cause of maternal morbidity throughout the world. The association of HELLP syndrome with renal failure is an important criterion for mortality. The study performed by Sibai and Ra-

madan [22] in 1993, on a series of 32 cases with HELLP syndrome is one of the most remarkable studies. In this series, 31% of the cases required dialysis and mortality rate was reported to be 13%. In the present study, the need of patients for dialysis was six out of 34. While half of these patients died, the other half was discharged and renal functions were not affected in the long term. However, requirement of dialysis was not found to be statistically significant in terms of mortality.

Studies have shown that APACHE and GCS scores were useful in predicting the severity of the disease accurately in critical obstetric patients [23]. In the present study, to evaluate the severity of the disease, the authors used APACHE II, SOFA, and GCS scores; the average APACHE II and SOFA scores were found to be higher in patients who died, when compared to living patients. The present authors consider that this high rate might have been related to the existing respiratory failure of the patients requiring mechanical ventilation and lack of their timely transfer to the intensive care unit from external medical facilities. The difference between dead and living patients in terms of their GCS scores during their admittances to the hospital was not statistically significant. This might have been related to the present clinical conditions of the patients being serious.

While no relations were found between maternal age, gestational age, and parity with maternal mortality and morbidity related to HELLP syndrome in many studies in the literature, vice versa, in some other studies, advanced maternal age and high parity were found to be related to poor clinical outcome [14, 24]. In the present study, maternal age, gestational age, and parity did not have any effects on maternal mortality related to HELLP syndrome.

While there are many reports showing that cases with HELLP syndrome require high amounts of blood and blood products, similar results were obtained in the present study. In the present case series, 22 patients (64.7%) required transfusion of blood and blood products. This shows that preparations should be made for these patients in terms of requirements of blood and blood products, and when necessary, these products should be urgently administered to the patients .

Although the most common cause of death related to HELLP syndrome was reported as cerebral hemorrhage, multiple organ failure, DIC, ARDS, and hepatic rupture are the other significant causes of death. Consistent with the literature, in the present study, maternal deaths occurred due to cerebral hemorrhage in six (37.5%) out of 16 patients [25, 26]. Another important cause of death is hepatic rupture. Hepatic rupture-related deaths occur with rates from 18% to 86%. In the present series, hepatic rupture developed in three cases and one of them died related to hepatic rupture.

Limitations of this study were as follows: firstly, this was a retrospective study, not a randomized clinical trial; secondly, the study population was small. The present study revealed significant results regarding mortality since the study population, although small, included only patients with HELLP syndrome and admitted to the intensive care unit.

As a conclusion, in HELLP syndrome, lack of regular antenatal follow-up is a significant cause of death, especially in developing countries. Despite all improvements in the treatment of HELLP syndrome and intensive care, mortality still cannot be significantly reduced throughout the world. In patients with HELLP syndrome, mortality rates can be reduced by determining the risk factors and transferring patients to the intensive care unit without delay, before requirement for intensive care is manifested.

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