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Incidence, Characteristics, Maternal and Perinatal Outcomes of HELLP Syndrome

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ABSTRACT

Objective: *HELLP syndrome is associated with increased maternal and fetal complications. It was aimed to provide the incidence of HELLP syndrome and related maternal and neonatal mortality and morbidity.*

Patients and Methods: *Patients diagnosed with HELLP Syndrome within the study period were subsequently assessed in this retrospective study of a 5-years period. Primary outcome was to establish the incidence of HELLP syndrome and to investigate the predicting factors for adverse maternal and fetal outcomes. Secondary outcome was to evaluate the factors related with disseminated intravascular coagulation (DIC). The diagnosis of HELLP syndrome was established with using the Sibai criteria.*

Results: *A total of 12.324 women gave birth during the study period. One hundred four pregnant women were diagnosed with HELLP syndrome with an incidence of 0.84%.The rate of maternal mortality was 2.9% (n=3).Out of all, 86.5% (n=90) of the patients had at least one major complication following the birth. Out of all, 60.6% (n=63) of the neonates had at least one major complication following the birth. The rate of prematurity and IUGR was 61.5% (n=64) and 28.2% (n=29), respectively. There were 3 (2.8%) neonatal deaths. The stillbirth rate was 18.3% (n=19).*

Conclusion: *HELLP syndrome is a serious clinical condition with an incidence of 8.4 per 1,000 deliveries and result in high maternal mortality and morbidity. The lack of a sufficient antenatal follow-up and the rural residence of pregnant women were found to be related with major maternal adverse outcomes.*

Keywords

HELLP, Prematurity, Maternal death, Neonatal death.

Introduction

HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome is a disorder belongs to the disease spectrum of preeclampsia and associated with serious maternal morbidity and mortality [1,2]. HELLP syndrome can be seen in 0.5 to 0.9% of all pregnancies and in 10-20% of women with severe preeclampsia [1]. Recent population-based studies showed a rate of perinatal death or severe neonatal morbidity as 20.2% [3].

HELLP syndrome is often associated with increased maternal complications, including placental abruption, blood transfusion, acute renal failure, liver failure, postpartum haemorrhage, pulmonary edema, retinal impairment, sepsis and disseminated

intravascular coagulopathy [4]. Distinguishing diagnosis of HELLP from other obstetric conditions is often challenging and may result in delay of treatment [5]. Although the mainstay of treatment includes maternal stabilization and timely birth, there is no current treatment available for HELLP syndrome [5].

The most common serious complication of preeclampsia spectrum is HELLP syndrome and the main risk factors of those are young age, nulliparity, low level of education, low social status, poor antenatal attendance and previous HELLP syndrome [6,7]. Premature births and poor neonatal services are the main cause of perinatal deaths in developing countries [6].

It was aimed to provide the incidence of HELLP syndrome and related maternal and neonatal mortality and morbidity. In addition, the impact of patients' characteristics on the maternal and perinatal complications of HELLP syndrome was assessed.

Patients and Methods

This retrospective study was conducted in a tertiary referral centre in a 5-years period between January 2004 and August 2009. All pregnant women who have given birth in the study centre were included to the analysis. Patients diagnosed with HELLP Syndromewithin the study period were subsequently assessed. Patients with chronic liver or kidney disease, obstetric cholestasis, Idiopathic thrombocytopenic purpura, gestational thrombocytopenia were excluded from the analysis.

Primary outcome was to establish the incidence of HELLP syndrome and to investigate the predicting factors for adverse maternal and fetal outcomes. Secondary outcome was to evaluate the factors related with disseminated intravascular coagulation (DIC). Patient's health records were analysed with using the local institutional electronical database.

The diagnosis of HELLP syndrome was established with using the Sibai criteria, as defined with laboratory findings indicating haemolysis, elevated liver function tests and low platelet count [8]. DIC was defined based on the International Society on Thrombosis Haemostasis criteria [9]. Patients diagnosed with HELLP Syndrome were actively managed according to local protocols where needed that include antenatal corticosteroids for fetal lung maturity, intravenous magnesium treatment and antihypertensive treatment.

The collected data were analyzed with IBM SPSS Statistics version 22.0 (IBM Corporation, Armonk, NY). Demographic data were summarised as the mean and standard deviation for normally distributed data and frequency for the relevant items. The Chi-square test and Fisher Exact Test were used to compare the means and rates of independent groups as indicated. A P-value of <0.05 was considered to indicate a significant difference.

Results

A total of 12.324 women gave birth during the study period. One hundred four pregnant women were diagnosed with HELLP syndrome that accounts for an incidence of 0.84%. There were no lost to follow-up. The demographic, obstetric characteristics and laboratory findings at admission were shown in Table 1. The mean gestational age at the time of the diagnosis was 32 weeks. 75% (n=78) of the cases gave birth with cesarean section. Out of those, HELLP syndrome was the only indication for cesarean section in 21 (20%) patients. The most common blood type was A Rh(+) with 33 patients (31.7%). 66% (n=69) of the patients were found to be without a proper antenatal follow-up.

Table 1: Demographic, obstetric and clinical characteristics.

	Mean ± SD
Age (years),	29.6 ± 5.9
Gravida (pcs)	3.0 ± 2.3
Parity (pcs)	1.6 ± 2.1
Gestational week	32.2 ± 0.4
	N (%)
Nulliparous	45 (43.3)
Primipara	16 (15.4)
Multipara	43 (41.3)
Number of cases from rural areas	58 (55.7)
Number of cases from urban areas	46 (44.2)
C/S*	78 (75)
History of gestational hypertension	15 (14.4)
History of diabetes	6 (5.8)
History of ART*	5 (4.8)
	Mean ± SD
Systolic blood pressure (mmHg)	161.6 ± 28.3
Diastolic blood pressure (mmHg)	102.2 ± 14.8
Birth weight (g)	2040 ± 86.4
Hemoglobin (g/dl)	11.9 ± 2.2
Hematocrit (%)	35.6 ± 7.0
Leukocytes (l/mm3)	14.1 ± 5.7
Thrombocyte (l/mm3)	69.8 ± 28.2
BUN* (mg/dl)	15.2 ± 5
Creatinine (mg/dl)	0.7 ± 0.2
Protein in spot urine (mg)	750 ± 69
Protein in 24 hour urine (mgr)	5452 ± 1943
CrCl* in 24 hour urine	96.5 ± 4.4
Aspartate aminotransferase (IU/L)	379 ± 109
Alanine aminotransferase (IU/L)	174 ± 16
Lactate dehydrogenase (IU/L)	1497 ± 123
SD: Standard Deviation, BUN*: Blood urea nitrogen CrCl*: Creatinine clearance	

The rate of maternal mortality was 2.9% (n=3). Intracranial haemorrhage following DIC and renal insufficiency were the causes for maternal death in 2 (1.92%) and 1 (0.96%) patient, respectively. The rate of admission to intensive care unit (ICU) was 22.1% (n=23). Patients spent an average of 11 days in the ICU. The mean major and minor complications following birth in patients diagnosed with HELLP syndrome were detailed in Table 2. Out of all, 86.5% (n=90) of the patients had at least one major complication following the birth. The age of gestation was significantly more advanced in cases without a complication when compared to those with at least one complication (34.5 ± 3.7 *vs.* 31.9 ± 4.4 weeks, p= 0.046, Independent Samples T Test).

Table 2: Maternal complications following HELLP Syndrome.

	N (%)
The need for a cesarean section	78 (75.4)
The need for blood and blood product transfusion	55 (52.9)
The need for mechanical ventilation	19 (18.3)
Acute renal failure	17 (16.3)
Opening of the incision site	14 (13.5)
Ablatioplasenta	11 (10.6)
Pulmonary complications	10 (9.6)
Eclampsia	9 (8.7)
DIC*	8 (7.7)
Cerebral edema	6 (5.8)
Retinal detachment	5 (4.8)
Intracranial hemorrhage	5 (4.8)
Maternal mortality	3 (2.9)
Subcapsular hematoma	1 (1.0)
Relaparotomy	1 (1.0)
The number of patients with at least 1 complication	90 (86.5)
The number of patients in need of intensive care	23 (22.1)
	Mean ± SD
Length of stay in intensive care (days)	10.9 ± 6.0
SD: Standard Deviation, DIC*: Disseminated intravascular coagulation	

Adverse fetal outcomes were shown in Table 3. Out of all, 60.6% (n=63) of the neonates had at least one major complication following the birth. The rate of prematurity and intrauterine growth restriction (IUGR) was 61.5% (n=64) and 28.2% (n=29), respectively. There were 3 (2.8%) neonatal deaths. The stillbirth rate was 18.3% (n=19). The rate of admission to NICU was 42.3% (n=44). DIC was developed in 7.7% (n=8) of the patients. The adverse outcomes following development of DIC were detailed in Table 4.

Table 3: Fetal outcomes following birth of women with HELLP Syndrome.

	N (%)
Prematurity	64 (61.5)
Low birth weight	38 (36.5)
Intrauterine growth retardation	29 (28.2)
Respiratory distress syndrome	8 (17.3)
Bronchopulmonary dysplasia	4 (3.8)
Hypoglycemia	10 (9.6)
Intraventricular hemorrhage (n (%))	3 (2.9)
Necrotizing enterocolitis	2 (1.9)
Hyperbiluribinemia	16 (15.4)
Temporary tachypnea	14 (13.5)
IUEF*	19 (18.3)
Neonatal mortality	3 (2.8)
Cord pH<7.16 (arterial)	34 (32.6)
The number of cases with at least 1 complication	63 (60.6)
The number of patients in need of intensive care	44 (42.3)
	Mean ± SD
APGAR* 1st minute	6.1 ± 0.2
APGAR* 5th minute	7.6 ± 0.3
Cord pH (arterial)	6.1 ± 0.2
Length of stay in intensive care (days)	12.1 ± 1.9
SD: Standard Deviation, IUEF*: Intrauterine ex-fetus, APGAR*: Appearance, Pulseness, Grimace, Activity, Respiration	

Table 4: Adverse outcomes following the development of DIC in patients with HELLP syndrome.

	Cases in which DIC was detected	Cases in which DIC was not detected	P-Value
	N (%)	N (%)	
Acute renal failure	5 (62.5)	12 (12.5)	**0.003**
Blood transfusion	8 (100)	47 (49)	**0.006**
Intrauterinexitus	2 (25)	17 (17.7)	0.636
Decollement placenta	5 (62.5)	6 (6.3)	**<0.001**
Opening of the incision	4 (50)	10 (10.4)	**0.011**
Subcapsular hematoma	0 (0)	1 (1)	0.999
Eclampsia	3 (37.5)	6 (6.3)	**0.021**
Cerebral edema	1 (12.5)	5 (5.2)	0.389
Pulmonary complication	2 (25)	8 (8.3)	0.170
The need for a mechanical ventilator	3 (37.5)	16 (16.7)	0.159
Retinal detachment	1 (12.5)	4 (14.2)	0.335
Intracranial hemorrhage	1 (12.5)	4 (4.2)	0.335
Maternal ex	1 (12.5)	2 (2.1)	0.215
Neonatal ex	3 (37.5)	19 (19.8)	0.361

Discussion

This large retrospective study showed that the HELLP syndrome is an uncommon serious clinical condition with anincidence of 8.4 per 1,000 deliveries. When developed, it caused high maternal mortality and overall morbidity rates with 2.9% and 86.5%, respectively. The only preventable factor that predicts the major complications following birth in patients with HELLP Syndrome was found the lack of a sufficient antenatal follow-up.

A recent large population-based study from Canada including over one million mothers found an incidence of 2.5 per 1000 singleton deliveries. The difference in the incidence can be explained with the socioeconomic status and the residential type. The prevention strategies and clinical management of preeclampsia may be affected by geographical and other social and economic barriers to healthcare among women residing in rural areas [3]. In the current study, 55% of the patients had rural residence. On the other hand, the rate of the rural residence among the patients developed HELLP syndrome was 13.2% in the Canada study.

The maternal mortality was found as low in the Canada population-based study with being below 2 per 1000 pregnancies unlike the high maternal mortality rate in our study (2.9%) [3]. A noteworthy feature of pregnant women with HELLP syndrome in the current study was that more than every two thirds of those did not involve in a sufficient antenatal follow-up. We believe that the lack of proper antenatal case and thus, higher obstetric risk of the mothers with HELLP syndrome should be the main related factor with higher maternal mortality and morbidity rate. It has been shown that Regular antenatal follow-up, prompt multidisciplinary treatment, optimum timing of delivery reduces the incidence of maternal mortality and adverse outcomes [10].

The HELLP syndrome is a rapid progressive condition and serious complications can be frequently seen, thus it is crucial to predict its occurrence potential earlier. A prediction model with high

sensitivity and specificity has shown that pregnant women with HELLP syndrome are more likely to be in their first birth and with moderate blood pressure elevation in their first trimester of pregnancy [2]. Although the current study lacked of a cohort to compare with, the 43% of the women with HELLP syndrome was nulliparous and the mean blood pressure of the cohort was 160/100 mmHg. We did not observe advanced maternal age in our cohort. On the other hand, 55.7% of the patients reported to be resided in rural areas that may indicate a lower access to sufficient health care.

Out of all, 86.5% of the patients had at least one major complication following the birth. The age of gestation was significantly more advanced in cases without a complication when compared to those with at least one complication (34.5 ± 3.7 *vs.* 31.9 ± 4.4 weeks, p= 0.046). Erkilinc and Eyi found the rate of at least one maternal complication as 38.5% in their cohort of 171 patients diagnosed with HELLP syndrome according to the Tennessee classification [11]. A review showed that the frequency of reported serious complications was varied up to 56% [12]. Our maternal complication rate was found higher than the literature. The difference in the diagnostic criteria, being a tertiary referral centre and the differences in the maternal demographic features may possibly explain the variety in the maternal complications rate related with the HELLP syndrome.

In the current study, DIC was developed in 7.7% of the patients diagnosed with HELLP syndrome. The large Canadian population-based cohort study found an incidence of 0.26% for DIC in patients with HELLP syndrome [3]. The rate of DIC in pregnant women with HELLP syndrome, when the diagnosis is made with a strict definition is about 15% [12]. The variety in the incidence of DIC among patients with HELLP syndrome may be explained by the difference in population's demographic features. The cause of DIC depends on the development level of the countries. While preeclampsia and the HELLP syndrome are the common causes of DIC in the developing countries, DIC caused by placental abruption and postpartum haemorrhage are seen more in the developed countries.

The fetal outcome was found to be worse when compared with the recent literature. Stillbirth rate was found as 2.7% in a large Thailand cohort and as 1.35% in a large Canadian cohort [3,13]. Our stillbirth rate was much higher with 18.3%. Three of every five neonates had at least one major complication following the birth. Those unfortunate results may be related with our high prematurity and IUGR rates with 61.5% and 28.2%, respectively. We assume that differences in the neonatal outcomes is directly related with the neonatal care and the obstetric profile of the mothers. The prematurity rate was 61.5% in the current study, which is similar with the literature. The preterm birth rate was 67.9% in the study of Kongwattanakul et al. and 52.9% in the study of Lisonkova et al. [3,13]. Although the majority of neonates born from a woman with HELLP syndrome would have a normal long-term development, the prematurity is the main problem rather than HELLP syndrome in itself [1].

One of the limitations of this study was the management of pregnant women diagnosed with HELPP syndrome. All patients were actively managed in the current study and all deliveries were initiated within 48 hours following the diagnosis of HELLP syndrome. The most common approach is the prompt birth when the diagnosis is made over 34 weeks of gestation or even earlier, if a life-threatening maternal condition or fetal compromise occurs [14]. However, this common algorithm may cause an overtreatment when both maternal and fetal conditions are stable. A small two-centred retrospective study found that the expectant management in HELLP syndrome may result with a decreased rate of postpartum haemorrhage and improved neonatal prognosis by reducing prematurity and allowing completion of antenatal corticosteroid treatment [15]. We believe that the impact of this limitation on our study should be minimal, because the difference in prognostic features of the patients with HELLP syndrome should have directly affected the outcomes. Interestingly, Cavaignac-Vitalis et al. had no maternal death in their study that implicate that their cohort may have consisted of low-risk pregnancies [15].

Conclusion

HELLP syndrome is a serious clinical condition with an incidence of 8.4 per 1,000 deliveries and result in high maternal mortality and morbidity. The lack of a sufficient antenatal follow-up and the rural residence of pregnant women were found to be related with major maternal adverse outcomes. Improving antenatal and neonatal care is crucial to improve these outcomes in developing countries.

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