CEOG Clinical and Experimental Obstetrics & Gynecology

Maternal-fetal prognosis in HELLP syndrome in a level 3 maternal-fetal care centre

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Summary

Purpose of investigation: The purpose of this study was to evaluate the maternal and perinatal outcome and prognosis in pregnant women with HELLP syndrome. *Materials and Methods:* Medical records of eligible pregnant women with HELLP syndrome were reviewed retrospectively. Patients were evaluated in terms of maternal complication, as well as the types of delivery. Perinatal outcome were evaluated in terms of Apgar score, birth weight, respiratory distress syndrome, and neonatal intensive care unit admission. *Results:* The leading maternal complications associated with HELLP syndrome were the following: severe preeclampsia, eclampsia, placental abruption, acute pulmonary edema, acute kidney failure, disseminated intravascular coagulation syndrome, and immediate maternal death. The most prominent neonatal outcomes associated with HELLP syndrome were: antenatal fetal death, intrauterine growth restriction, prematurity. *Conclusion:* The management and delivery of the patients with HELLP syndrome must take place in a tertiary referral maternal and fetal care centre.

Key words: Pregnancy; HELLP syndrome; Severe preeclampsia; Placental abruption; Prematurity.

Introduction

HELLP syndrome is a pregnancy complication considered to be a variant of preeclampsia, with a reserved maternal-fetal vital prognosis. The global incidence is of approximately 0.5–0.9% of all pregnancies, being present in 10–20% of the patients with severe preeclampsia/eclampsia [1, 2]. Still, in 20–40 % of the cases that develop HELLP syndrome, no history of hypertension/proteinuria was found, the recurrence rate being 2-27% [3-5]. Discussions on the diagnosis difficulties and specifications regarding conduct as well as the gravity of the evolution in most cases draw attention on this syndrome with a heterogenic and sometimes misleading clinical picture. The evolution of the biological picture, which is well defined – hemolysis with schistocytes, elevated serum bilirubin and transaminases, and thrombocytopenia, are an important prognosis factor. The pathological changes identified in HELLP syndrome appear as a consequence of vasospasm, the change in the vascular tonus and coagulation defects, which leads to endothelial lesions, platelet activation, and coagulation cascade [6-8]. Patients are at increased risk of preterm delivery, fetal growth restriction, and placental abruption. Fetal morbidity and mortality usually result from placental abruption, intrauterine asphyxia, or prematurity [7, 9]. A HELLP syndrome case can be solved only in a level 3 centre with maternal-fetal intensive care and the improvement of the prognosis involves an immediate delivery by cesarean section or vaginal delivery if it occurs quickly, and with a minimum risk for the mother and fetus.

The evolution of HELLP syndrome is rapid and life-threatening for the mother and fetus, which is why the treatment must be commenced early, and the therapeutic approach must take into account the gestational age and the state of the mother and fetus. In this context, the purpose of this study was to evaluate the maternal and perinatal outcome and prognosis in pregnant women with HELLP syndrome admitted in a tertiary referral maternal and fetal care centre.

Materials and Methods

This study was performed at the "Cuza Vodă" University Hospital of Iaşi, Romania, a tertiary referral center in obstetrics and gynecology, Department of Obstetrics and Gynecology, from January 2009 to December 2013. The medical records of pregnant women admitted for delivery were reviewed retrospectively. Eligible women were identified by the research coordinator and/or the medical staff involved in the study. The data on the clinical evolution of the patients and their lab tests were taken from the hospital computerized database of all the deliveries, as well as their observation charts. Patients with HELLP syndrome were managed according to existing hospital protocol, being monitored in the intensive care unit. The inclusion criterion was the presence of HELLP syndrome, both in antepartum or postpartum period,

Revised manuscript accepted for publication May 6, 2015

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLIII, n. 3, 2016
doi: 10.12891/ceog3111.2016

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Table 1. — *Demographic data of patients with HELLP syndrome.*

Sr. No.	Demographic data of study group n	Total: Mean ± SD; % (x/n);
1.	Maternal age (years)	29.21 ± 8.97 (19−39)
2.	Age of gestation (weeks)	31.82 ± 1.98 (27−38)
3.	Weight (kg)	82.84 ± 16.98
4.	Height (cm)	168.64 ± 8.12
5.	BMI (kg/m^2)	28.48 ± 5.02
6.	Primipara	44% (11/25)
7.	Multipara	56% (14/25)
8.	Antenatal care	24% (6/25)
9.	HELLP syndrome in 1st trimester	0% (0/25)
10.	HELLP syndrome in 2nd trimester	4% (1/25)
11.	HELLP syndrome in 3rd trimester	96% (24/25)
12.	Class 1 HELLP syndrome	8% (2/25)
13.	Class 2 HELLP syndrome	44% (11/25)
14.	Class 3 HELLP syndrome	48% (12/25)

Table 2. — *Maternal complications of HELLP syndrome in study group.*

Sr. No.	Maternal outcomes n	Total % (x/n)
1.	Severe preeclampsia	40% (10/25)
2.	Eclampsia	16% (4/25)
3.	Uteroplacental apoplexy	16% (4/25)
4.	Acute pulmonary edema	8% (2/25)
5.	Acute kidney failure	36% (9/25)
6.	Disseminated intravascular coagulation syndrome	12% (3/25)
7.	Maternal death	4% (1/25)

Table 3. — *Neonatal complications of HELLP syndrome in study group.*

Sr. No.	Neonatal outcomes n	Total % (x/n)
1.	Intrauterine growth restriction	44% (11/25)
2.	Prematurity (27−34 weeks)	64% (16/25)
3.	Prematurity (34−37 weeks)	20% (5/25)
4.	Neonatal respiratory distress syndrome	24% (6/25)
5.	Fetal death	16% (4/25)

in the patients who gave birth in this period. HELLP syndrome was defined using the Mississippi classification systems for classes 1, 2, and 3 HELLP syndrome [10]. Class 1 HELLP syndrome (platelet count ≤ 50,000/μL, total serum lactic dehydrogenase LDH ≥ 600 IU/L, aspartate aminotransferase AST ≥ 70 IU/L), class 2 HELLP syndrome (platelet count 50,000 of ≤ 100,000/μL, total serum LDH ≥ 600 IU/L, AST ≥ 70 IU/L), and class 3 HELLP syndrome (platelet count 100,000 of ≤ 150,000/μL, total serum LDH ≥ 600 IU/L, AST ≥ 70 IU/L). Partial or incomplete HELLP was defined as the presence of only two of the three major laboratory criteria to establish a diagnosis of complete HELLP syndrome [11]. Patients were evaluated in terms of maternal complication - severe preeclampsia/eclampsia, abruption placenta, pulmonary edema, acute renal disease, disseminated intravascular coagulation, cerebrovascular hemorrhage, and maternal in-hospital mortality. The authors also evaluated the types of delivery. Perinatal outcome were evaluated in terms of Apgar score at one and five minutes, birth weight, respiratory distress syndrome, neonatal intensive care unit admission (in terms of drying, suction, and requirement of oxygenation or bagmask ventilation)/perinatal morbidity and mortality. The exclusion criteria in this study were pregnancies with chromosomal abnormalities /anomalous fetuses, hepatic, renal or preexisting cardiac diseases, diabetes mellitus, autoimmune disease, systemic infection, alcohol consumption, or with incomplete data. The study was approved by the local ethical committee and conducted in accordance with the Helsinki Declaration.

Statistical analysis was performed using SPSS version 17.0 software. Data were expressed as mean ± SD. Mean, standard error of the mean, and standard deviation were determined for quantitative variables. Categorical variables were expressed as number and percentage (%) of patients. Continuous variables were compared by the Student's *t*-test.

Results

Between January 2009 and December 2013 in "Cuza Vodă" University Hospital of Iaşi, 29,352 births were assisted, of which 55 (0.18%) were diagnosed with HELLP syndrome. Of all these patient, only 25 cases were the authors able to recover the full data for a complete statistical processing. Relevant characteristics and demographic data of women included in the study are shown in Table 1. The average biometrical age according to the preoperative ultrasound was of 30.3 weeks of amenorrhea (between 24 and 37). According to the Mississippi classification, there were: two cases in class 1 (the most severe form), 11 cases in class 2, and 12 cases in class 3. The delivery was obtained by cesarean section in 22/25 cases (88%) - the most prevalent indication being acute fetal distress and the remaining three cases who gave birth vaginally had been admitted in advanced labour. The extraction of the fetus by cesarean section or by expulsion took place after an average time of 56.2 hours from admission (between 0.5 and 384 hours).

The lab tests revealed the following values: platelets: mean value 80,600 μL (range 10,000−144,000 μL); AST: mean value 404.24 UI/L (range 45−3,461 UI/L); ALT: mean value 266.28 UI/l (range 31−2,129 UI/L); LDH: mean value 2,434.6 UI/L ± 444.54 (range 635− 14,506 UI/L); uric acid: mean value 7.63 mg/dl (range 4.6−13.6 mg/dl); creatinine: mean value 1.04 mg/dl (range 0.51−4.03 mg/dl). The leading maternal complications associated with HELLP syndrome were the following: severe preeclampsia, eclampsia, placental abruption, acute pulmonary edema, acute kidney failure, disseminated intravascular coagulation syndrome (in the clinical context of coagulation disorders, with fibrinogen < 200 mg/dl and elevated value of APTT, FDP, D dimers), immediate maternal death (within 24 hours from admission) (Table 2). Maternal death was caused by complications associated with disseminated intravascular coagulation syndrome. Mean days of hospital stay was 15.32 ± 7.62.

The most prominent neonatal outcomes associated with HELLP syndrome were: antenatal fetal death, intrauterine growth restriction (IUGR), prematurity (Table 3). Mean birth weight was 1632 g ± 824 grams. Neonatal respiratory distress syndrome was manifested in 24 % of cases. The mean APGAR score was 6.3 (between 1 and 9) after one minute and 7.1 (between 1 and 9) after five minutes. The APGAR score after one minute was 0 in four cases, (antenatal fetal death), ≤ 7 in 12 cases, and > 7 in nine cases. The APGAR score after five minutes was 0 in four cases, (antenatal fetal death), ≤ 7 in 11 cases, and > 7 in ten cases.

Discussion

HELLP, a syndrome characterized by hemolysis, elevated liver enzyme levels, and a low platelet count, is a life-threatening condition that can potentially complicate pregnancy, and is frequently misdiagnosed at initial presentation. The exact cause of HELLP is unknown, but certain risk factors, including an older maternal age, with a mean age of 25 years, multiparity, white race or European descent, and history of poor pregnancy outcome, have been described [12, 13]. In the present study, the mean age of the patients with HELLP syndrome was 29.2 years, most of them were multiparous, and came from rural areas. Also, most patients had a lower socio-economic status, and did not receive a proper monitoring of pregnancy. The overall incidence of the syndrome in our study was 0.18 %, slightly lower than the incidence cited, but consistent with literature values. The syndrome generally presents in the third trimester of pregnancy (24 cases), although it occurs also in second trimester (one case). Most cases were classified in class 2 and 3 of HELLP syndrome, and only five cases in class 1, with the highest risk for maternal morbidity and mortality than other patients. Also, most births in this study were obtained by cesarean section. In general, cesarean versus vaginal delivery in the management of HELLP syndrome, should be determined based on the cervical ripening, fetal non-stress test or biophysical profile results, umbilical artery Doppler study, or mother status [4].

Although the idea is controversial, some propose that HELLP is a severe form of preeclampsia, with a general incidence of this association up to 20 % [7]. In the present study, 14 cases with severe preeclampsia/eclampsia were discovered, with a pathogenesis of this association including a primary/secondary endothelial malfunction associated with cardiovascular and inflammatory changes. Placenta anomalies include defective placental vascular remodeling during weeks 16-22 of pregnancy with the second wave of trophoblastic invasion into the decidua results in inadequate placental perfusion [8, 14, 15]. The uteroplacental apoplexy, that the authors found in four cases in the present study, was a severe anatomo-clinical syndrome due to a premature detachment of the normally inserted placenta, with the formation of a hematoma between the placenta and the uterus. The incidence of its association to HELLP syndrome is of 0.5−1%, and the anatomo-pathologic test reveals dissociate muscle fibres, suffusions in interstitial spaces, fibrin deposits in the intervillous space, and thrombosis of small retroplacental veins. The main complication – disseminated intravascular coagulation DIC) – appears due to the release of decidual and placental thromboplastin in the maternal circulation, which is the most common anatomo-pathological maternal finding [4, 5, 13, 16].

Acute kidney failure, that were found in nine cases in the present study, is an unusual complication with special impact on the maternal prognosis, its incidence being of 2−3% of HELLP syndrome cases, and becoming a cause for maternal death in 56−61% of the cases. In the etipathogeny of this association, the following were incriminated: acute/ reversible tubular necrosis (initial/ confirmed uremia/resumption of diuresis, with endothelial lesions, vasospasm, hypovolemia, hemolysis, fibrin deposits), and cortical necrosis with irreversible renal lesions [17-20]. The clinical picture was dominated by oliguria (urinary flow < 400 ml/24 hours) generally accompanied by an increased level of serum creatinine by at least 0.5 mg/dL, and a decreased clearance by at least 50%; three patients requiring dialysis. The global incidence of disseminated intravascular coagulation in HELLP syndrome is 4–38% (three cases/25 in the present study) and the incriminated causes being the systemic activation of the coagulation system, formation of microvascular thrombi, consumption of coagulation proteins, and platelets with severe hemorrhagic complications. The proposed etiopathogenic mechanisms support the endothelial malfunction followed by vasospasm, platelet agglutination, aggravating the endothelial alterations/platelet consumption, pulmonary embolism (acute non-cardiogenic pulmonary edema – two cases in this study), which was the principal cause of maternal death (one case) reported in this study [13, 20-22].

Fetal morbidity and mortality associated with the HELLP syndrome is over 9–24 %, (four cases of fetal death in 25 in this study), with the best known cause being anoxia, due to brutal accidents or chronic uteroplacental vascular lesions. The anatomo-pathological test reveals microthrombosis/vasospasm in the uteroplacental circulation associated with uteroplacental insufficiency. Also, death and the retention of the fetus inside the uterus, can lead to serious complications (thromboses, disseminated intravascular coagulation, infections, cataclysmic hemorrhages), culminating in maternal death [23, 24]. In the present study, in the newborns group with the Apgar index 6 – 7, the adaptation to extrauterine life was more difficult and besides standard care, the patients required oxygen therapy and the correction of biological deficits: acidosis, hypoglycemia, hypocalcemia, etc. The Apgar score was re-evaluated after five minutes. In the newborns group with an Apgar index < 5, the severe general state required resuscitation maneuvers

and intensive care (depending on the clinical status of the newborn): oxygen therapy, intubation, assisted ventilation, external heart massage, the correction of hydro-electrolytic, acido-basic and metabolic disorders, etc. Regarding intrauterine growth restriction in HELLP syndrome (11/25 cases), the global incidence of this association is 12–34 %, incriminating anomalies of the uteroplacental circulation and alterations in maintaining the uteroplacental perfusion. In patients without risk factors, the primum movens responsible for the placental insufficiency is unknown, with this condition causing idiopathic oligohydroamnios, associated with a higher risk of meconium in the amniotic fluid, fetal distress, a low Apgar score at birth, and a higher rate of cesarean section [4, 7, 25, 26].

An important correlation was established between prematurity and HELLP Syndrome (22/25 cases). The incidence of this association was 35–50%, and it represents the main perinatal mortality and morbidity cause. The most frequent maternal indication for the premature end of the pregnancy was preeclampsia/eclampsia, and the most frequent fetal indication was intrauterine growth restriction (IUGR) with fetal distress [4, 7, 27, 28]. Most of the premature babies were born at the gestational age of 27–34 weeks of amenorrhea. Infant mortality is significantly higher in this category, the sudden death syndrome being partly responsible for this increase, which can suggest that the same pathological process can be responsible also for inducing premature labour. Surviving premature babies have an important short-term morbidity risk: respiratory distress syndrome, intraventricular hemorrhage, ulceronecrotic enterocolitis, sepsis, prematurity-related retinopathy, and in the long-run the following can occur: spastic paraparesis, neuromotor deficit, intellectual deficit, retinopathy, and respiratory sequelae.

It is very important to know that are other non-obstetrical pathologies that can be mistaken with HELLP syndrome. In this context, the present authors mention two cases of primary and secondary liver malign tumors associated with pregnancy, whose expression was misdiagnosed as HELLP syndrome. The present authors consider that liver ultrasound or CT/ MRI should be integrated in HELLP syndrome diagnosis management, especially in cases with an important cytolytic hepatic reaction, in order to exclude a potential primary hepatic or secondary metastatic tumoral pathology.

Conclusions

The management and delivery of patients with HELLP syndrome must take place in a level 3 centre with a trained multidisciplinary team (obstetrician, anesthesiologist, neonatologist, laboratory physician, operating room, intensive care nurses, and midwives) and provided with the available technical facilities. A quick and correct diagnosis and prompt intervention can reduce the risk of maternal and fetal mortality and morbidity.

Acknowledgements

The authors would like to thank Professor Stamatin Maria, MD, Director of Neonatal Intensive Care Unit (NICU), and Professor Onofriescu Mircea, MD, Director of Maternal-Fetal Medicine Unit, from "Cuza Vodă" University Hospital of Iaşi, Romania, for their expertise and assistance.

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