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Neonatal Outcome after Preterm Delivery in HELLP Syndrome

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The present study compares neonatal outcome after preterm delivery of infants in pregnancies complicated by the HELLP syndrome or severe preeclampsia (PS). The maternal and neonatal charts of 71 out of a total of 409 pregnancies that were complicated by hypertensive disorders at Severance hospital between January 1995 and December 2004 were reviewed. Twenty-one pregnancies were complicated by HELLP syndrome and 50 pregnancies were complicated by PS. Fifty normotensive (NT) patients who delivered because of preterm labor comprised the control group. Results were analyzed by the chi-square test and ANOVA. Gestational age and maternal age at delivery were matched among the three groups. The neonatal outcomes of the HELLP syndrome group were compared with the PS and NT groups. There were significant differences between the HELLP syndrome group and the PS group in the incidence of intraventricular hemorrhage (IVH) (61.9% vs. 26%, $p = 0.006$), sepsis (85.7% vs. 44%, $p = 0.003$) and mechanical ventilation (MV) rate (81% vs. 54%, $p = 0.039$). There were significant differences between the HELLP syndrome group and the NT group in the incidence of neonatal death (ND) (19.5% vs. 2.0%, $p = 0.034$), respiratory distress syndrome (RDS) (38.1% vs. 8%, $p = 0.0045$), IVH (61.9% vs. 4%, $p < 0.0001$), sepsis (85.7% vs. 14%, $p < 0.0001$), intensive care (IC) (85.7% vs. 24%, $p < 0.0001$) and MV rate (80.1% vs. 14%, $p < 0.0001$). There were also significant differences between the PS and NT groups in the incidence of ND (20% vs. 2%, $p = 0.0192$), RDS (30% vs. 8%, $p = 0.0085$), IVH (26% vs. 4%, $p = 0.0070$), sepsis (44% vs. 14%, $p = 0.0015$), IC (78% vs. 24%, $p < 0.0001$), MV rate (54% vs. 14%, $p < 0.0001$) and low 5-min APGAR score (50% vs. 16%, $p = 0.0005$). This study shows increased morbidity in newborns of mothers complicated with HELLP syndrome and indicates that early, regular and high quality management of these patients is essential to improve both maternal and neonatal outcome.

Key Words: HELLP syndrome, preeclampsia, neonatal outcome, normotensive preterm delivery

INTRODUCTION

The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) is a variant of severe preeclampsia that is associated with significant maternal and perinatal morbidity and mortality.[1] Maternal mortality is between 0% and 24%, and perinatal mortality is between 6.6% and 60%.[2,3] Perinatal mortality appears to be primarily related to the gestational age at delivery. HELLP syndrome is reported to occur in 20% of women with severe preeclampsia and in 10% of women with eclampsia.[3] Studies involving prenatal management show increased perinatal mortality rates in cases of HELLP, mainly due to stillbirths.[4] However, it does not appear that HELLP syndrome increases neonatal mortality, irrespective of gestational age, and data regarding neonatal outcomes such as respiratory distress syndrome (RDS), intraventricular hemorrhage, necrotizing enterocolitis, and sepsis are conflicting.[5-7] The present study compares neonatal outcome after preterm delivery in pregnancies complicated by the HELLP syndrome with those complicated by severe preeclampsia.

MATERIALS AND METHODS

The maternal and neonatal charts of 71 preg-

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nancies complicated by hypertensive disorders at the perinatal unit in the Severance hospital between January 1995 and December 2004 were reviewed.

Twenty-one pregnancies were complicated by HELLP syndrome and fifty pregnancies were complicated by severe preeclampsia, Fifty normotensive patients who delivered because of preterm labor comprised the control group. A total of 409 pregnancies complicated by hypertensive disorder were enrolled, including 289 pregnancies complicated by severe preeclampsia (PS).

Patients were diagnosed as preeclamptic if they met all of the following criteria: systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg on two occasions 6 hours apart, proteinuria 2+ or greater on two random samples, and serum uric acid concentration ≥ 5.0 mg/dl.

Gestational age was determined by obstetric criteria, including menstrual history, early clinical evaluation, and ultrasonography at < 20 weeks of gestation where available.

Exclusion criteria included multiple pregnancy, fetal anomalies, premature rupture of membranes, and known maternal medical disease. Gestational age and maternal age at delivery were matched among the severe preeclampsia, HELLP syndrome and normotensive groups.

Neonatal medical records were reviewed for several outcome variables. Respiratory distress syndrome (RDS) was defined by the presence of characteristic radiographic findings and an oxygen requirement at 24 h after birth. Intraventricular hemorrhage (IVH) grade 3 was defined as hemorrhage with ventricular dilation, and IVH grade 4 as hemorrhage with parenchymal spread. Necrotizing enterocolitis (NEC) was defined by characteristic clinical symptoms with radiographic findings of pneumatosis cystoides intestinalis (grade 2) or pneumoperitoneum or portal air (grade 3). Fetal growth restriction (FGR) was defined as a birth weight below the 10th percentile for the gestational age. Corticosteroid therapy refers to the use of either betamethasone or dexamethasone for fetal lung maturation and ranged from a single dose (at least 12 h before delivery) to a 48-hour course before delivery. Statistical analyses were performed with the chi-square test and ANOVA and statistical significance was considered at $p < 0.05$.

RESULTS

During the study period, there were 409 pregnancies complicated by hypertensive disorder at perinatal unit in Severance hospital, 289 of which were complicated by severe preeclampsia, with or without HELLP syndrome. 21 cases of HELLP syndrome were compared with 50 cases of PS and 50 normotensive cases. Tables 1 and 2 compare maternal demographic and clinical characteristics for the 3 groups. The incidence of fetal growth restriction (FGR) was 4% in the normotensive (NT) group, 46% in PS (severe preeclampsia) group,

Table 1. Maternal Demographic and Clinical Characteristics

	HELLP (n = 21)	Preeclampsia (n = 50)	Normotensive preterm (n = 50)	Significance (p value)
Age (yr)	32 ± 3.3	31 ± 4.0	30.2 ± 4.5	NS
Nulliparity (%)	57.1	68	42	NS
Male (%)	33.3	44	58	NS
Birth Weight (gm)	1586 ± 478	1390 ± 592	2061 ± 553	NS
Gestational age at delivery (days)	232 ± 19.6	222 ± 23.8	230 ± 16.0	NS
Diagnosis-to-delivery (hours)*	8.5	38	57.4	NS

Values are presented as mean ± SD.
Statistics were analyzed by ANOVA.
NS, not significant.
*median.

Table 2. Comparison of Clinical Characteristics

	HELLP* (n = 21)	Preeclampsia* (n = 50)	Normotensive preterm* (n = 50)	*p* value
Glucocorticoid therapy	14.3	34	18	NS
Cesarean delivery	100	88	22	< 0.0001†
FGR	47.6	46	4	< 0.05†,‡
IUFD	4.8	10	0	NS
Abruptio placentae	33.3	16	2	< 0.05†,‡
Fetal distress	71.4	42	4	< 0.05†,‡,§

*percent.
† Preeclampsia versus Preterm.
‡ HELLP versus Preterm.
§ HELLP versus preeclampsia.
NS, not significant; FGR, fetal growth restriction; IUFD, intrauterine fetal death.

Table 3. Comparison of Neonatal Outcome in Pregnancies with HELLP Syndrome and the Normotensive Preterm Group

	HELLP* (n = 21)	Normotensive preterm* (n = 50)	OR (95% CI)	*p* value
Neonatal death	19.5	2	11.5 (1.2 - 110.4)	0.034
RDS	38.1	8	7.1 (1.8 - 27.3)	0.0045
IVH	61.9	4	39.0 (7.4 - 206.4)	< 0.0001
NEC	14.3	0	> 999.9	NS
Sepsis	85.7	14	36.9 (8.6 - 158.7)	< 0.0001
Mechanical ventilation	81.0	14	26.1 (6.8 - 100.8)	< 0.0001
Intensive care	85.7	24	19.0 (4.8 - 75.8)	< 0.0001
5-min APGAR score < 6	66.7	16	0.4 (0.1 - 1.2)	NS

*percent.
$p < 0.05$, by chi-square test.
NS, not significant; RDS, respiratory distress syndrome; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis

and 47.6% in HELLP syndrome group ($p < 0.05$); these differences were statistically significant. There were significant differences between NT, PS and HELLP syndrome in abruptio placentae (2% vs. 16% vs. 33.3%, $p < 0.05$), fetal distress (4% vs.42% vs. 71.4%, $p < 0.05$), and cesarean delivery rate (22% vs. 88% vs. 100%, $p < 0.0001$) (Table 2).

The neonatal outcomes of the HELLP syndrome group were compared with those of the other groups (Tables 3, 4). There were significant differences between the HELLP syndrome group and the normotensive group in neonatal death (ND) (19.5% vs. 2.0%, $p = 0.034$), respiratory distress syndrome (RDS) (38.1% vs. 8%, $p = 0.0045$), intraventricular hemorrhage (IVH) (61.9 vs. 4%, $p < 0.0001$), sepsis (85.7% vs. 14%, $p < 0.0001$), intensive care (IC) (85.7% vs. 24%, $p < 0.0001$), and mechanical ventilation (MV) rate (81.0% vs. 14%, $p < 0.0001$). There were significant differences between the HELLP syndrome group and the severe preeclampsia group in intraventricular hemorrhage (IVH) (61.9% vs. 26%, $p = 0.006$), sepsis

Table 4. Comparison of Neonatal Outcome in Pregnancies with HELLP Syndrome and Severe Preeclampsia

	HELLP* (n = 21)	Preeclampsia* (n = 50)	OR (95% CI)	*p* value
Neonatal death	19.5	20	0.9 (0.3 - 3.4)	NS
RDS	38.1	30	1.4 (0.5 - 4.1)	NS
IVH	61.9	26	4.4 (1.6 - 13.7)	0.006
NEC	14.3	6	2.6 (0.5 - 14.1)	NS
Sepsis	85.7	44	7.6 (1.9 - 29.3)	0.003
Mechanical ventilation	81.0	54	3.6 (1.1 - 12.3)	0.039
Intensive care	85.7	78	1.7 (0.4 - 6.8)	NS
5-min APGAR score < 6	66.7	50	2.0 (0.7 - 5.8)	NS

*percent.
$p < 0.05$, by chi-square test.
NS, not significant; RDS, respiratory distress syndrome; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis

(85.7% vs. 44%, $p = 0.003$) and mechanical ventilation (MV) rate (81% vs. 54%, $p = 0.039$).

DISCUSSION

The laboratory abnormalities associated with HELLP syndrome were described many years ago and in 1982 Weinstein devised the acronym HELLP (H = hemolysis, EL = elevated liver enzymes, and L = low platelets) to define this specific subset of severe preeclampsia patients.[2]

Maternal mortality is between 0% and 24%, and perinatal mortality is between 6.6% and 60%.[2,3,7,8] Most published evidence indicates a poor outcome in cases of HELLP syndrome.[7,9,10] There is general agreement that both perinatal and infant morbidity and mortality rates are increased in pregnancies complicated by HELLP syndrome.[11-12] The ultimate goal of any protocol for the management of HELLP syndrome is first to reduce maternal mortality and morbidity rates, and second to deliver a healthy and mature baby.

It is important to recognize HELLP syndrome as a unique form of severe preeclampsia since in some cases patients have received a non-obstetric diagnosis, such as cholecystitis or hepatitis, and proper treatment was delayed. Aggressive treatment with maternal stabilization and expeditious delivery have been advocated to prevent maternal and perinatal mortality.[13]

Widespread recognition and early diagnosis of HELLP syndrome as a variant of severe preeclampsia have lead to an improvement in maternal and perinatal outcome. Unfortunately, the only cure for HELLP syndrome is delivery, even at early gestational ages.

Abramovici et al. indicated that neonatal morbidity or death is directly related to gestational age at delivery and showed that prenatal management in HELLP syndrome improved neonatal outcome in cases with advanced gestational age.[15]

The present study compared neonatal outcome of the HELLP syndrome (defined as elevated liver enzymes and low platelet level, combined with pregnancy hypertension), versus preeclampsia without HELLP and a normotensive preterm group. Neonatal morbidity and mortality was higher in infants of women with HELLP syndrome group than in the normotensive group and there was a greater need for mechanical ventilation and neonatal intensive care in the HELLP syndrome group. Neonatal morbidity was also higher in infants of women with HELLP syndrome group than in the severe preeclampsia, group, and there was a greater need for mechanical ventilation and neonatal intensive care. In addition, the rates of cesarean delivery, FGR, fetal distress, IVH, sepsis, lower 5-min APGAR scores and abruptio placentae were increased in the

HELLP syndrome group.

Halil et al. reported that the adverse impact of FGR in infants born to mothers with HELLP syndrome is most prominent beyond 32 weeks.[14] This has recently been supported by evidence that prematurity associated with adverse neonatal outcomes such as RDS, IVH, and NEC is largely unaffected by FGR until the third trimester.[15] After this point, all adverse outcomes were increased in cases of FGR compared with normally grown premature infants. The present study showed that FGR was strongly associated with HELLP syndrome. Therefore, mothers with HELLP syndrome require close and regular monitoring, especially beyond 32 weeks.

The higher incidence of fetal distress as well as the increased blood pressure seen in preeclampsia, severe form and HELLP syndrome.

Abramovici et al. reported that the median time from admission to delivery was 0 days for women with HELLP syndrome and 2 days for women with severe preeclampsia.[15] There are no data concerning the neonatal outcome of HELLP syndrome with a diagnosis-to-delivery time of more than 1 day. Future studies are required to address the neonatal outcome of HELLP syndrome with prenatal management after admission.

The present study showed no statistical differences between the severe preeclampsia group and the HELLP syndrome group in factors affecting neonatal outcome such as age of the mother, gestational age, birth weight, fetal growth restriction, cesarean delivery, abruption placentae, and fetal distress. However, the neonatal outcome of the HELLP syndrome group showed significantly increased morbidities in IVH, sepsis, and mechanical ventilation treatment rate. This result indicates that the morbidity of the neonates in the HELLP syndrome group is higher than that of the severe preeclampsia group.

This study shows that neonatal morbidity is increased in pregnancy complicated by the HELLP syndrome. Thus, management and delivery of HELLP syndrome mothers and infants should be performed at tertiary centers, where highly trained neonatal intensive care unit personnel and facilities are available, and a team approach with obstetricians and specialized pediatricians is essential to improve both the maternal and neonatal outcomes.

REFERENCES

1. van Pampus MG, Wolf H, Westenberg SM, van der Post JA, Bonsel GJ, Treffers PE. Maternal and perinatal outcome after expectant management of the HELLP syndrome compared with pre-eclampsia without HELLP syndrome. Eur J Obstet Gynecol Reprod Biol 1998;76:31-6.
2. Weinstein L. Syndrome of hemolysis, elevated liver enzymes, and low platelet count: a severe consequence of hypertension in pregnancy. Am J Obstet Gynecol 1982;142:159-67.
3. Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). Am J Obstet Gynecol 1993;169:1000-6.
4. Dreyfus M, Tissier I, Baldauf JJ, Ritter J. HELLP syndrome. Review and update. J Gynecol Obstet Biol Reprod 1997;26:9-15.
5. Gilbert WM, Danielsen B. Pregnancy outcomes associated with intrauterine growth restriction. Am J Obstet Gynecol 2003;188:1596-601.
6. Raval DS, Co S, Reid MA, Pildes R. Maternal and neonatal outcome of pregnancies complicated with maternal HELLP syndrome. J Perinatol 1997;17:266-9.
7. Sibai BM, Taslimi MM, el-Nazer A, Amon E, Mabie BC, Ryan GM. Maternal-perinatal outcome associated with the syndrome of hemolysis, elevated liver enzymes, and low platelets in severe preeclampsia-eclampsia. Am J Obstet Gynecol 1986;155:501-9.
8. Eeltink CM, van Lingen RA, Aarnoudse JG, Derks JB, Okken A. Maternal haemolysis, elevated liver enzymes and low platelets syndrome: specific problems in the newborn. Eur J Pediatr 1993;152:160-3.
9. Weinstein L. Preeclampsia/eclampsia with hemolysis, elevated liver enzymes, and thrombocytopenia. Obstet Gynecol 1985;66:657-60.
10. Aarnoudse JG, Houthoff HJ, Weits J, Vallenga E, Huisjes HJ. A syndrome of liver damage and intravascular coagulation in the last trimester of normotensive pregnancy. A clinical and histopathological study. Br J Obstet Gynaecol 1986;93:145-55.
11. Witlin AG, Saade GR, Mattar F, Sibai BM. Predictors of neonatal outcome in women with severe preeclampsia or eclampsia between 24 and 33 weeks' gestation. Am J Obstet Gynecol 2000;182:607-11.
12. Tompkins MJ, Thiagarajah S. HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome: the benefit of corticosteroids. Am J Obstet Gynecol 1999;181:304-9.
13. Curtin WM, Weinstein L. A review of HELLP syndrome. J Perinatol 1999;19:138-43
14. Abramovici D, Friedman SA, Mercer BM, Audibert F,

Kao L, Sibai BM. Neonatal outcome in severe preeclampsia at 24 to 36 weeks' gestation: does the HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome matter? Am J Obstet Gynecol 1999; 180:221-5.
15. Aslan H, Gul A, Cebeci A. Neonatal outcome in pregnancies after preterm delivery for HELLP syndrome. Gynecol Obstet Invest 2004;58:96-9.