Research Article

Maternal Characteristics, Pregnancy, and Neonatal Outome in Preeclampsia and HELLP Syndrome: a Comparative Study

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Abstract

HELLP syndrome is a complication in pregnancy which may increase maternal morbidity and mortality risk. This study aims to compare maternal characteristics, pregnancy and neonatal outcome between preeclampsia and HELLP syndrome. All preeclampsia without or with severe features and HELLP syndrome using ACOG criteria coming to dr. Cipto Mangunkusumo Hospital from January 2015 to December 2017 were recruited into this cross-sectional study. Demographic, clinical, laboratories parameters, and neonatal outcomes were compared between HELLP and preeclampsia patients. The SPSS 20 for Windows was used for all analyses. There were 676 deliveries which was complicated by preeclampsia without or with severe features and 113 patients with HELLP syndrome. Gestational age, history of hypertension systolic and diastolic blood pressure, hemoglobin, hematocrit, urea, creatinine, uric acid, and albumin are different significantly between HELLP and preeclampsia patients. History of hypertension in previous pregnancy is considered as a significant risk factor for HELLP syndrome (p=0.001); RR 2.33 (95% CI 1.41–3.9). Based on data of gestational age at delivery which lower in HELLP syndrome, it showed lower median birth weight in HELLP syndrome (1442.5 g) compared with preeclampsia (1442.5 g vs 2400 g, p=; 95%CI There is significant difference in gestational age at delivery, nullipara, blood pressure, and laboratory findings (urea, creatinine, uric acid, albumin) between preeclampsia and HELLP syndrome group. History of hypertension in previous pregnancy is a significant risk factor for HELLP syndrome. Regarding neonatal outcome, baby born from HELLP syndrome has lower median birth weight.
Keywords: *HELLP syndrome, preeclampsia, risk factor, neonatal outcome.*

Karakteristik Maternal, Luaran Kehamilan, dan Neonatal pada Preeklamsia dan Sindrom HELLP: Studi Komparatif

Abstrak

Sindrom HELLP merupakan komplikasi kehamilan yang meningkatkan morbiditas dan mortalitas maternal. Studi ini bertujuan untuk mengetahui perbedaan karakteristik antara sindrom HELLP dan preeklamsia serta luaran neonatus. Studi potong lintang ini melibatkan seluruh pasien preeklamsia dengan atau tanpa perburukan dan sindrom HELLP berdasarkan kriteria ACOG yang datang ke RS dr. Cipto Mangunkusumo pada bulan Januari 2015 sampai Desember 2017. Analisis bivariat digunakan untuk mengetahui hubungan karakteristik demografi, klinis, laboratorium antara pasien HELLP dan preeklamsia sedangkan analisis multivariat untuk mengetahui karakteristik yang memengaruhi sindrom HELLP. Data dianalisis menggunakan SPSS 20. Terdapat 676 persalinan pada kelompok preeklamsia dengan atau tanpa perburukan dan 113 pasien dengan sindrom HELLP. Usia kehamilan, tekanan darah sistolik dan diastolik, hemoglobin, hematokrit, ureum, kreatinin, asam urat, dan albumin berbeda bermakna antara pasien sindrom HELLP dan preeklamsia. Riwayat hipertensi pada kehamilan sebelumnya dianggap sebagai faktor risiko terhadap sindrom HELLP (p=0,001); RR 2,33 (IK 95% 1,41-3,9). Berdasarkan usia kehamilan saat persalinan yang lebih awal dan bayi lahir lebih rendah pada sindrom HELLP (1442,5 g) dibandingkan preeklamsia (2400 g). Terdapat perbedaan bermakna pada usia kehamilan saat persalinan, tekanan darah, dan parameter laboratorium (ureum, kreatinin, asam urat, albumin) antara kelompok preeklamsia dan sindrom HELLP. Berdasarkan luaran neonatus, bayi dari sindrom HELLP lebih rendah berat lahirnya.
Kata kunci*: sindrom HELLP, preeklamsia, faktor risiko, luaran neonatus.*

Introduction

Worldwide, hypertensive disorder complicates 2–8% of all pregnancies. Preeclampsia, as a part of hypertensive disorders in pregnancy (HDP), is associated with conditions such as hemolysis, elevated liver enzymes, and thrombocytopenia.[1,2] Those symptoms were considered as a more severe form of preeclampsia and described as HELLP syndrome.[3,4]elevated liver enzymes (EL The incidence of HELLP syndrome was 4–18.9% among patients with severe preeclampsia, however it increases maternal and neonatal morbidity and mortality.[5]

Mortality rate of maternal and neonatal in pregnancy complicated by HELLP syndrome was 0–24% and 6.6–60%, respectively. Some studies stated that morbidity risk in HELLP syndrome is higher than in preeclampsia.[6] A wide range of complications, such as disseminated intravascular coagulation/DIC (5–56%), acute renal failure (7–36%), abruptio placenta (9–20%), and other such as eclampsia, severe ascites, cerebral and pulmonary edema, wound hematoma/infection, subcapsular liver hematoma, liver rupture, hepatic infarction, recurrent thrombosis, retinal detachment, cerebral hemorrhage, and maternal death. In perinatal, HELLP syndrome can contribute to preterm delivery (70%), intrauterine growth restriction/IUGR (38–61%), neonatal thrombocytopenia (15–50%), perinatal death (7.4–34%), and respiratory distress syndrome (5.7–40%).[6–9]Elevated Liver enzymes, Low Platelet (HELLP

Though preeclampsia could develop into HELLP syndrome, most patients do not develop into HELLP syndrome.[5,10] Haram et al[11] stated BcII polymorphism is related with development in HELLP syndrome but not in severe preeclampsia. Demographic and clinical factors, such as mother age, nulliparous, body mass index (BMI), history of chronic hypertension or gestational hypertension, diabetes, were linked to the development of HELLP syndrome.[4,12] On the other hand, there were not many prospective or retrospective studies that linked laboratory parameters as a risk factors for HELLP syndrome. Some studies stated that laboratory parameters such as lactate dehydrogenase (LDH), liver enzymes, bilirubin, and platelet did not influence the maternal outcome.[10,13,14] Therefore, this study aims to compare maternal characteristics, pregnancy and neonatal outcome between HELLP syndrome and preeclampsia.

Methods

The study was started after approved by The Ethics Committee of Faculty of Medicine, Universitas Indonesia (no. 957/UN2.F1/ ETIK/ 2017). This cross-sectional study was conducted in dr. Cipto Mangunkusumo Hospital from January 2015 to December 2017 by recruiting preeclampsia with or without severe features and HELLP syndrome patients consecutively. We excluded patients with gestational and chronic hypertension, superimposed preeclampsia, multiple pregnancies, history of diabetes, and cardiovascular disease.

Preeclampsia group consisted of preeclampsia without and with severe features. Preeclampsia was defined as 1) systolic blood pressure (SBP) of ≥140 mmHg or diastolic blood pressure (DBP) of ≥90 mmHg on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure and 2) proteinuria. Proteinuria was defined as ≥300 mg/24-hour urine collection or urinary dipstick proteinuria >1+.[15] Severe preeclampsia was defined as any of these findings: 1) SBP of ≥160 mmHg or DBP of ≥110 mmHg; 2) thrombocytopenia (platelet count less than 100,000/uL); 3) impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice the upper limit normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted by alternative diagnoses; 4) progressive renal insufficiency (serum creatinine >1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease); 5) pulmonary edema; 6) new onset headache unresponsive to medication and not accounted by alternative diagnosis; 7) visual disturbances. Criteria for preeclampsia and severe preeclampsia were based on ACOG criteria.[15]

HELLP syndrome criteria are: (1) LDH ≥ 600 U/L; (2) aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevated more than twice the upper limit of normal; (3) platelet count less than 100,000x10^9/L corresponding to Tennessee classification.[16]

Gestational age was defined using the last menstrual period date according to *Kesehatan Ibu dan Anak/KIA* (Mother and Child Health) book. If patients forget their last menstrual period or do not have *KIA* book, the gestational age was measured with first or early second trimester ultrasonography (USG) and physical examination. All laboratory parameters such as hemoglobin, hematocrit, platelet, AST, ALT, ureum, creatinine, uric acid, LDH, were analyzed by Clinical Pathology Department, dr. Cipto Mangunkusumo Hospital.

SPSS 20.0 for Windows was used for all analyses. Demographics, clinical, laboratory,

and neonatal outcome data were analyzed by Kolmogorov-Smirnov test to determine the distribution of variables. Maternal age was divided into two variables which is high risk (<20 years old or >35 years old) and non-high risk (20–35 years old); number of parity was divided into nullipara and multipara. Bivariate analysis was performed using chi-square or Mann-Whitney U test, continued with multivariate analysis using logistic regression. Confidence interval of 95% and power of 90% with p-values <0.05 was considered significant.

Results

In this study, there were 5,197 deliveries with 1,097 (21.1%) HDP cases, namely 256 cases were chronic and gestational hypertension, superimposed preeclampsia, lung edema, eclampsia, and 52 incomplete data. A total of 789 patients consist of 113 patients with HELLP syndrome (14.3%) and 676 patients with preeclampsia (85.6%).

Table 1 shows no significant difference (Mann Whitney U test, p>0.05) in maternal age, number of marriages, and number of gestation between groups; however, there was significant difference (Mann Whitney U test, p<0.05) in gestational age at delivery, blood pressure, and laboratory findings. There was no significant difference in high-risk age (p=0.990; RR 1.0; 95% CI 0.65-1.54) and parity (p=0.137; RR 1.4; 95% CI 0.9-2.18) between HELLP syndrome and preeclampsia group. Meanwhile there was significant difference in history of hypertension in previous pregnancy (p=0.001; RR 1.97; 95% CI 1.33-2.99).

Multivariate analysis among high-risk age, number of gestation, and history of hypertension in previous pregnancy showed that only history of hypertension was significantly difference (p=0.001) between HELLP syndrome and preeclampsia with coefficient correlation of 0.85 and relative risk (RR) of 2.33 (95%CI 1.41–3.9).

Table 1. The Association of Characteristics of the Subjects with HELLP Syndrome and Preeclampsia

Characteristics	HELLP syndrome (n=113) Median (min-max)	Preeclampsia (n=676) Median (min-max)	p
Demography			
Age (years old)	31 (17–43)	31 (14–46)	0.429
High risk age (n, %)	34 (30.1)	203 (30)	0.990*
Gestational age at delivery (weeks)	30 (21–40)	36 (21–42)	<0.001
Number of marriage(s)	1 (0–2)	1 (0–4)	0.726
Number of gestation	2 (0–9)	2 (0–12)	0.088
Nullipara (n, %)	31 (27.4)	233 (34.6)	0.001*
History of hypertension in previous pregnancy (n, %)	25 (22.3)	75 (11.1)	0.001
Blood pressure			
Systolic	180 (140–280)	170 (100–240)	<0.001
Diastolic	110 (80–160)	110 (70–220)	0.001
Laboratory			
Hemoglobin (g/dL)	13.2 (6.7–18.9)	12.4 (4.9–20.3)	<0.001
Hematocrit (%)	38.3 (21–55.2)	37.1 (4.8–54.7)	0.006
Platelet (1000/µL)	108 (9.9–309)	259 (116–630)	<0.001
Urea (mg/dL)	30 (9.4–73)	15.6 (0.6–186)	<0.001
Creatinine (mg/dL)	0.9 (0.2–35)	0.6 (0.1–24)	<0.001
Uric acid (mg/dL)	7.4 (2.9-15.2)	5.5 (1.3-15.5)	<0.001
AST (u/L)	79 (28–2943)	22 (6–1600)	<0.001
ALT (u/L)	70.5 (12–1264)	15.3 (3.0–776)	<0.001
Albumin (g/dL)	3.4 (1.4–5.3)	3.2 (1.4–4.3)	<0.001
LDH (u/L)	971 (538–5459)	493 (7.0–3389)	<0.001

*Chi-square test

Table 2 showed the neonatal outcome HELLP syndrome and preeclampsia group. There was significant association in baby condition between groups (p<0.001; RR 0.29; 95% CI 0.21-0.42). Based on data of gestational age at delivery which lower in HELLP syndrome, it showed lower median birth weight in HELLP syndrome (1442.5 g) compared with preeclampsia (2400 g).

Table 2. Neonatal Outcome of Pregnancy with HELLP Syndrome and Preeclampsia

Baby Condition	HELLP syndrome (n=113)	Preeclampsia (n=676)	p
Alive (n, %)	80 (70.8)	615 (91)	<0.001[a]
Died (IUFD or during hospital care) (n, %)	33 (29.2)	61 (9)	
Birth weight (g)*	1442.5 (300–3215)	2400 (270–4800)	<0.001[b]
Birth length (cm)*	39 (25–49)	46 (23–57)	<0.001[b]

*Median (min-max) a. Chi-square test b. Mann-Whitney U test

Discussion

In our study, the rate of preeclampsia and HELLP syndrome was 13% and 2.2% while among preeclampsia patients, the occurrence of HELLP syndrome reached 14.3%. It was higher compared with 0,17–0,85% a study by Prichard et al[17] and 0,24% by Malmstrom et al.[4] The occurrence of HELLP syndrome among preeclampsia patients was 16.7% similar with study by Turgut et al[5] which is 18%.

Gestational age at delivery was lower in patients with HELLP syndrome than preeclampsia with the median of 30 weeks and 26 weeks respectively. This result is similar to Kinay et al[6] and Abramovici et al[18] elevated liver enzymes, and low platelet count. This is not good since low gestational age is related to higher mortality for the neonate. Guzel et al[10] discovered that prematurity ≤35 weeks is the highest risk factor for perinatal mortality. Even 10% of HELLP syndrome can occur below 27 weeks of gestational age.[19] This will be a concern since delivery is still the best management for HELLP syndrome.[20]

SDP and DBP in preeclampsia and HELLP syndrome were different significantly (p<0.05) with median SDP was higher in HELLP and similar median DBP for both groups. Kinay et al[6] mean blood pressure was significantly higher in severe preeclampsia group at ≥34 weeks gestation (p=0.007) and it was not different for <34 week gestation. In preeclampsia, inadequate trophoblast invasion into maternal spiral arteries leads to impaired transformation of maternal vessels and uteroplacental circulation. Finally, it causes the increase of pressure in maternal heart contributing to left ventricular remodeling and diastolic dysfunction.[21]

Thrombocytopenia was more severe in HELLP as a diagnostic criteria. It was related to excessive platelet activation due to endothelial dysfunction and proinflammatory cytokines. It contributed to severe maternal morbidity. If the platelet count is in the range of 100–150,000/µl, the rate of maternal complications is 40%. For the range of 50–100,000/µl it is 54%, and for platelet count below 50,000/µl it is 64%.[22]preeclampsia (PE It could contribute to DIC. There are several mechanisms of developing DIC in patients with preeclampsia and HELLP syndrome: consumption coagulopathy in placental abruption due to complication of preeclampsia/HELLP syndrome, decreased production of clotting factors because of hepatic injury, and systemic maternal inflammatory response.[23]

Some laboratory parameters are worse in HELLP syndrome than preeclampsia such as higher level of urea and creatinine and lower level of albumin. In HELLP syndrome, the creatinine was higher than preeclampsia groups (p<0.001). Actually, in preeclampsia, there were histopathological changes including fibrin deposition, endothelial swelling, and loss of capillary space known as “glomerular endotheliosis”. It can lead to renal cortical necrosis of acute tubular necrosis as one of main causes for acute kidney injury (AKI) in pregnancy.[21] Chinese cohort showed that 17% of patients with preeclampsia/eclampsia and 60% of women with HELLP syndrome were diagnosed with AKI. It means that HELLP syndrome had higher impact to develop AKI.[24,25]

As criteria of HELLP syndrome, AST and ALT level in HELLP syndrome was higher than in preeclampsia group. Suresh et al[26] reported that overall incidence of hepatic dysfunction during

pregnancy was 3.2% and the most common causes of it were: preeclampsia (1.8%), eclampsia (0.6%), HELLP syndrome (0.24%), viral infection (0.19%), hyperemesis gravidarum (0.14%), ICP (0.13%), and chronic liver disease (0.03%). It could increase the risk of maternal mortality.[26]

Liver dysfunction during preeclampsia is related to endothelial dysfunction, which leads to hepatic microcirculatory deterioration and hepatocellular necrosis. Liver biopsies in women with HELLP syndrome have shown thrombotic microangiopathy.[27] The devastating complication was hepatic rupture with incidence of 1 per 2,000 patients with preeclampsia or HELLP syndrome. Vasoconstriction due to increased levels and sensitivity to circulating vasopressors such as endothelin and angiotensin II, lead to ischemia, necrosis, and rupture.[28]

Some studies suggest that uric acid involved in preeclampsia pathogenesis through promoting inflammation, oxidative stress and endothelial dysfunction. Uric acid could be used as risk marker for progression to preeclampsia and development of adverse maternal or infant condition.[29–31] Johnson et al[32] stated that uric acid more than 5.2 mg/dL had excellent sensitivity, specificity, and likelihood ratios for diagnosis and prognosis of preeclampsia.

Albumin level <3 g/dL was correlated with the severity of preeclampsia, although albumin does not predict perinatal and mother mortality, but this study shows median albumin levels between HELLP syndrome and preeclampsia group are similar and more than 3g/dL.[33] There are some factors that may affect serum albumin level, so albumin is not good to become an independent marker for severity of preeclampsia.

Multivariate analysis showed that only history of hypertension could be the risk factor associated with HELLP syndrome. History of hypertension is associated factor with RR 2.33 (95% CI 1.41–3.9). This result is similar to Malmstrom et al[4] that shows history of hypertension increased the risk of acquiring HELLP syndrome in the first and second pregnancy. The RR was even higher to develop HELLP syndrome in second pregnancy for women with hypertension than the first pregnancy.[4] This suggest for a better post pregnancy counseling and intensive monitoring in hypertensive and hyperuricemia women.

Regarding fetal outcome, birth weight in HELLP syndrome had median lower than preeclampsia group due to lower gestational age at delivery which similar to study by Rashwan.[5] Apart from that, the prevalence of baby died during hospital care was higher in HELLP syndrome group due to prematurity which was consistent between gestational age and neonatal morbidity and mortality. Based on high risk for preterm birth in HELLP syndrome, management and delivery of these cases should be performed at tertiary center equipped with highly trained neonatal and adult intensive care unit personnel and facilities. It is essential to improve both maternal and neonatal outcomes.

This study has some limitations because the HELLP syndrome was not divided into partial and complete as severity of diseases. The design of this study was cross-sectional, which makes it hard to find a causal relationship between the risk factors. Apart from that, bigger data with cohort studies collected from several centers should be performed to determine the laboratory risk factors associated with HELLP syndrome in preeclampsia patients. Meanwhile, this study could represent HELLP syndrome in this region because all complicated cases such as HELLP syndrome would be referred to this hospital. It was shown that 99.1% HELLP syndrome cases coming from outside. Performing bivariate and multivariate analyses to assess demographic risk factors of HELLP syndrome was essential for future in early detection and prompt treatment. This was the first original study assessing the risk factors of HELLP syndrome among preeclampsia patients. Cohort study based on demographic factors is needed to strengthen the causal relationship between the risk factors and incidence of HELLP Syndrome.

Conclusion

There is association in gestational age at delivery, nullipara, blood pressure, and laboratory findings (urea, creatinine, uric acid, albumin) between preeclampsia and HELLP syndrome group. History of hypertension in previous pregnancy is a significant risk factor for HELLP syndrome. Regarding neonatal outcome, baby born from HELLP syndrome has lower median birth weight.

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