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Preeclampsia severity and associated factors in Kelantan, Malaysia

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ABSTRACT

Aims: Preeclampsia is a significant disorder that poses serious risks to maternal and fetal health. This study aimed to identify the severity of preeclampsia and associated factors in a University Hospital in Malaysia.

Methods: A cross-sectional study was conducted among preeclampsia patients at the Hospital Universiti Sains Malaysia (USM), Kelantan, Malaysia, between 2011 and 2016. Preeclampsia patients with chronic hypertension, hemolysis, elevated liver enzymes, low platelet (HELLP) syndrome, and eclampsia were included, whereas patients with chronic kidney disease were excluded. Preeclampsia severity was classified into mild, moderate, and severe.

Results: The study included 202 patients [mean (standard deviation) maternal age: 30.49 (6.18) years]. Most patients were multigravida (134) and multipara (134). Sixty-five (32.2%) patients had a history of preeclampsia. The proportion of patients with mild preeclampsia was 35% [95% confidence interval (CI): 30%, 40%], moderate preeclampsia was 30% (95% CI: 25%, 35%), and severe preeclampsia was 35% (95% CI: 30%, 40%). High levels of uric acid [adjusted odds ratio (OR): 1.05, 95% CI: 1.02, 1.07, p=0.001], chronic hypertension (adjusted OR: 2.36, 95% CI: 1.28, 4.33, p=0.006), and gestational diabetes mellitus (adjusted OR: 0.53, 95% CI: 0.30, 0.96, p=0.035) were the factors associated with the severity of preeclampsia.

Conclusions: Higher levels of uric acid, chronic hypertension, and gestational diabetes mellitus were significantly associated with the severity of preeclampsia among patients in the USM.

Introduction

Preeclampsia is defined as hypertension accompanied by proteinuria that occurs after 20 weeks of pregnancy (1). The parameters for initial identification of preeclampsia are a systolic blood pressure of 140 mmHg and higher or diastolic blood pressure of 90 mmHg and higher twice at least 4 hours apart; or shorter interval timing of systolic blood pressure of 160 mmHg and higher or diastolic blood pressure of 110 mmHg and higher, after 20 weeks of gestation (2).

Other significant findings that may or may not be a part of the clinical presentation include proteinuria, signs of end-organ damage, such as thrombocytopenia, impaired liver function, severe persistent right upper quadrant or epigastric pain (excluding all other alternative diagnoses), new-onset headache unresponsive to all forms of management, pulmonary edema, or renal insufficiency with abnormal laboratory values (3).

The prevalence of preeclampsia varies from 0.2% to 6.7% in Asia, 0.5% to 2.3% in Africa, 2.8% to 5.2% in Europe, 2.8% to 9.2% in Oceania, 1.8% to 7.7% in South America and the Caribbean, and 2.6% to 4.0% in North America (4). In Asian regions the prevalence of preeclampsia was reported by 2.1% in China, 1.2% in Japan, 2.2% in Thailand, and 0.6% in Nepal (5). Based on the Malaysia Clinical Research Centre review of hypertensive

disorders in pregnancy from 2011 to 2012, the incidence of preeclampsia was 19.6% (6). Globally, preeclampsia is diagnosed in 8.5 million women annually (7). Preeclampsia affects 1-5% of pregnancies, resulting in severe maternal and neonatal morbidity and mortality (8,9). Annually, preeclampsia results in 70,000 maternal deaths and more than 500,000 fetal and neonatal deaths worldwide (9). Thus, preeclampsia poses serious risks to the health of women.

Risk factors for preeclampsia include obesity, diabetes and chronic hypertension. Other risk factors for the illness include nulliparity, adolescent pregnancy, and disorders that cause hyperplacentation and large placentas (e.g. twin pregnancy) (10). In Malaysia, primigravid women carrying multiple pregnancies, older than 35 years, had their last pregnancy more than 10 years ago, had a body mass index (BMI) greater than 35 kg/m^2, or had a family history of preeclampsia are categorized as having intermediate risk (11,12). A pregnant woman is accepted at high risk with the presence of at least one high-risk factor, such as chronic kidney disease, systemic lupus erythematosus, antiphospholipid syndrome, type 1 or type 2 diabetes mellitus, or chronic hypertension (11,12).

Preeclampsia and associated issues should be prevented by early detection and early intervention in women at high risk (13,14). Primary health clinics that offer prenatal care are essential for the early detection and prevention of steps to manage preeclampsia and its consequences (13). Additionally, Malaysia offers pre-pregnancy care that includes preconception counseling, reliable contraception, the management of underlying comorbid diseases, and treatment alterations before conception, all of which are crucial precautions for women at risk of preeclampsia (13).

Preeclampsia continues to be a major cause of morbidity and mortality in both mothers and infants. However, information on the factors associated with preeclampsia based on its severity is limited among pregnant Malaysian women. Therefore, this study aimed to assess the severity of preeclampsia and associated factors among hospitalized pregnant women in a university hospital.

Methods

Study design and sample size

This retrospective cross-sectional study was conducted among pregnant women who received routine antenatal care and delivered at the Universiti Sains Malaysia (USM) Hospital in Kelantan, Malaysia from 1st January 2011 until 31 December 2016. The study included hospitalized patients aged between 15 and 49 years who had chronic hypertension with superimposed preeclampsia, hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, and had eclampsia.

This study involved patients with a minimum age of 15 years. Muslim girls below the age of 18 are still allowed to marry with the Syariah court's permission. Under Malaysian law, underage marriage for non-Muslims is governed by civil marriage law, whereas underage marriage for Muslims is governed by Islamic family law in the Syariah courts. Under this dual legal system, the legal minimum age of marriage for Muslim men is 18 and 16 for women; for non-Muslim men and women, the legal minimum age is 18. This study excluded patients with chronic kidney disease and incomplete data.

Patients with preeclampsia were identified in the medical record unit and hospital database known as the Laboratory Information System and recruited using a simple random sampling method. There were 756 preeclampsia patients at the Hospital USM. Using Power and Sample Size Calculation (PS) software, the required sample was calculated as 216 patients.

Based on this number, we first entered all preeclampsia patients into the software and then randomly selected 216 patients. After applying the inclusion and exclusion criteria, 202 patients were considered eligible for the study.

Outcome variable

The outcome variable was the severity of preeclampsia. The severity of preeclampsia was categorized into mild, moderate, and severe (15). Mild preeclampsia is defined as a systolic blood pressure of 140 to 149 mmHg and/or 90 to 99 mmHg diastolic blood pressure with proteinuria (15). Moderate preeclampsia is defined as systolic blood pressure of 150 to 159 mmHg and/or 100 to 109 mmHg diastolic blood pressure with proteinuria (15). Severe preeclampsia is defined as systolic blood pressure higher than 160 mmHg and/or diastolic blood pressure higher than 110 mmHg with proteinuria (16). Significant proteinuria in pregnancy is defined as ≥300 mg protein in a 24-h urine sample or a protein-creatinine ratio of 30 mg/mmol in a spot urine sample, or at least persistent 1+ dipstick proteinuria (17).

Statistical Analyses

Stata Special Edition version 14 was used for data entry and analysis (StataCorp, 2015. Stata Statistical Software, Release 14. College Station, TX, USA: StataCorp LP). Results are presented as frequency (n) and percentage (%) for categorical variables and mean and standard deviation (SD) for numerical variables. Descriptive analyses were performed for sociodemographic characteristics, clinical characteristics, and laboratory parameters.

The independent variables were sociodemographic characteristics (maternal age, BMI, gravidity, parity, number of fetuses, marital status), clinical characteristics (history of preeclampsia, family history of hypertension, family history of diabetes mellitus, history of small for gestational age, gestational diabetes mellitus, chronic hypertension, patients on

hypertension medications, history of abortion), and laboratory parameters [uric acid, creatinine, albumin, platelet, aspartate aminotransferase, alanine transaminase, urea, and hemoglobin (Hb)].

The severity of preeclampsia was assessed as a ratio and 95% confidence interval (CI). The factors associated with the severity of preeclampsia were studied using simple and multiple ordinal logistic regression analysis.

Simple ordinal logistic regression models followed by the selection of backward and backward stepwise methods were used to select the variables (p=0.05 for entry and p=0.10 for removal). Variables showing an association at p<0.25 in the univariate analysis or clinically associated variables with the outcome were included in the full model. Dummy variables were created for categorical variables with more than two levels. Multicollinearity, interactions, and linear-to-logit transformations (if applicable) were examined. Assumptions, goodness of fit, outliers, and influential cases were appropriately assessed. The crude and adjusted odds ratio (OR), regression coefficient (b), 95% CI, and p-value were reported. P<0.05 was accepted as statistically significant.

Results

Characteristics of the patients

The study included 202 patients [mean (SD) maternal age: 30.49 (6.18) years]. Mean (SD) pre-pregnancy BMI of 28.83 (5.60) kg/m^2. The majority of patients were in their first marriage (94.1%), multigravida (66.3%), and multiparous (59.9%). Eight patients had twins during their pregnancy. A history of preeclampsia was recorded in 65 patients, whereas the remaining 137 had preeclampsia for the first time. A total of 73 patients were diagnosed with chronic hypertension. More than half of the preeclampsia patients had no family history of hypertension or diabetes mellitus. Thirty-seven patients had a history of a small gestational age in a previous pregnancy (Table 1).

Laboratory parameters

Uric acid, creatinine, and urea levels were higher in patients with severe preeclampsia, with mean (SD) values of 433.64 (105.23) µmol/L, 76.97 (13.28) µmol/L, and 3.99 (1.49) mmol/L, respectively (Table 2). Overall, the mean (SD) albumin level was 32.59 (3.18) g/L. The mean Hb level was lower in patients with mild preeclampsia**.**

Associated factors for more severe preeclampsia

The proportion of patients with mild preeclampsia was 35% (95 % CI: 30%, 40%), moderate preeclampsia was 30% (95% CI: 25%, 35%), and severe preeclampsia was 35% (95% CI: 30%, 40%). High uric acid levels, chronic hypertension, and gestational diabetes mellitus were factors associated with the severity of preeclampsia. Every 10 µmol/L increase in uric acid was associated with a 5% higher risk of developing more severe preeclampsia versus mild preeclampsia (adjusted OR; 1.05; 95% CI: 1.02, 1.07; p=0.001) after controlling for chronic hypertension and gestational diabetes mellitus (Table 3).

Pregnant women with chronic hypertension had 2.4 fold higher risk of developing severe preeclampsia versus mild preeclampsia than those without chronic hypertension (adjusted OR: 2.36, 95% CI: 1.28, 4.33, p=0.006) with adjustment for uric acid level and gestational diabetes mellitus.

Those with gestational diabetes mellitus had 47% lower odds of severe preeclampsia versus mild preeclampsia after controlling for chronic hypertension and uric acid.

Discussion

The study revealed that uric acid levels were significantly associated with the severity of preeclampsia, demonstrating that individuals with elevated uric acid levels were at a greater risk of developing severe preeclampsia than those with mild preeclampsia. This study was similar to that of Ugwuanyi et al. (18) who showed that higher levels of uric acid were associated with the severity of preeclampsia and associated with poorer perinatal outcomes. Women with abnormal uric acid levels were four times more likely to have severe preeclampsia than those with normal serum uric acid levels (18). In addition, previous research conducted in India, Bangkok, and Southeast Nigeria revealed that uric acid was a good marker of the severity of preeclampsia (19-21).

Furthermore, uric acid levels were significantly higher in women with preeclampsia than without preeclampsia (22). In addition, a previous study involving 877 preeclampsia women and 580 normotensive women reported that an increase in uric acid levels was seen only in patients with preeclampsia, whereas, among normotensive women who developed preeclampsia later, serum uric acid was not significantly high (23). The study pointed out that uric acid may increase because of preeclampsia but is not a biomarker or risk factor for preeclampsia (23). Uric acid synthesis may be increased in preeclampsia patients due to hypoxia and ischemia of the placenta, and increased cytokine production (24).

A higher uric acid level may be associated with poor maternal and fetal outcomes (25). Preterm birth, intrauterine growth restriction, fetal death, and neonatal death are all possible outcomes (23,26). Therefore, monitoring uric acid levels throughout pregnancy may help in the early detection of preeclampsia and reduce its serious effects.

In this study, chronic hypertension was significantly associated with severe preeclampsia. The findings of the current study were in line with a previous meta-analysis that concluded that patients with chronic hypertension were at a more than two-fold higher risk of developing preeclampsia than those without

Table 1. Characteristics of preeclampsia patients based on the severity (n=202)

Variables	Severity of preeclampsia		
	Mild	Moderate	Severe
Gravidity, n (%)			
Primigravida	24 (35.3)	19 (27.9)	25 (36.8)
Multigravida	46 (34.3)	42 (31.3)	46 (34.3)
Parity, n (%)			
Nullipara	28 (34.6)	24 (29.6)	29 (35.8)
Multipara	42 (34.7)	37 (30.6)	42 (34.7)
Number of fetuses, n (%)			
Singleton	67 (34.5)	59 (30.6)	68 (35.1)
Multiple	3 (37.5)	2 (25.0)	3 (37.5)
Marital status, n (%)			
Unmarried	1 (33.3)	1 (33.3)	1 (33.3)
First marriage	65 (34.2)	56 (29.5)	69 (36.3)
Second marriage	4 (44.4)	4 (44.4)	1 (11.2)
History of preeclampsia, n (%)			
No	49 (35.6)	43 (31.4)	45 (32.9)
Yes	21 (32.3)	18 (27.7)	26 (40.0)
Chronic hypertension, n (%)			
No	47 (36.4)	44 (34.1)	38 (29.5)
Yes	23 (31.5)	17 (23.3)	33 (45.2)
Family history of hypertension, n (%)			
No	32 (31.4)	37 (36.3)	33 (32.3)
Yes	38 (38.0)	24 (24.0)	38 (38.0)
Family history of diabetes mellitus, n (%)			
No	37 (31.4)	37 (31.4)	44 (37.2)
Yes	33 (39.3)	24 (28.6)	27 (32.1)
History of small gestational age, n (%)			
No	61 (37.0)	49 (29.7)	55 (33.3)
Yes	9 (24.3)	12 (32.4)	16 (43.2)
Gestational diabetes mellitus, n (%)			
No	40 (32.3)	34 (27.4)	50 (40.3)
Yes	30 (38.5)	27 (34.6)	21 (26.9)
History of abortion, n (%)			
No	56 (34.6)	50 (30.8)	56 (34.6)
Yes	14 (35.0)	11 (27.5)	15 (37.5)
Patients on medication, n (%)			
No	48 (35.3)	38 (27.9)	50 (36.8)
Yes	22 (33.3)	23 (34.9)	21 (31.8)

Table 2. Laboratory assessment of preeclampsia patients based on the severity (n=202)

Variables	Severity of preeclampsia		
	Mild	Moderate	Severe
Uric acid (μmol/L), mean (SD)	375.42 (90.58)	403.98 (112.56)	433.64 (105.23)
Creatinine (μmol/L), mean (SD)	73.40 (15.38)	73.63 (11.73)	76.97 (13.28)
Albumin (g/L), mean (SD)	32.91 (2.56)	32.97 (2.64)	31.98 (3.97)
Platelet (10^3/UL), mean (SD)	247.16 (97.09)	253.62 (70.24)	229.82 (85.72)
Hemoglobin (g/dL), mean (SD)	11.95 (1.54)	12.02 (1.53)	12.42 (1.70)
Urea (mmol/L), mean (SD)	3.43 (1.47)	3.50 (1.48)	3.99 (1.49)
AST (U/L), mean (SD)	20.0 (12.0)	20.0 (8.0)	26.0 (13.0)
ALT (U/L), mean (SD)	13.0 (9.0)	11.0 (7.0)	18.0 (12.0)

SD: Standard deviation, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

Table 3. Factors associated with the severity of preeclampsia (n=202)

Variables	b (SE)	Adjusted OR (95% CI)	p-value
Uric acid (μmol/L)	0.04 (0.01)	1.05 (1.02, 1.07)	0.001
Chronic hypertension	0.86 (0.31)	2.36 (1.28, 4.33)	0.006
Gestational diabetes mellitus	-0.63 (0.30)	0.53 (0.30, 0.96)	0.035

[b]Coefficient regression.
SE: Standard error, OR: Odds ratio, CI: Confidence interval

chronic hypertension (27). However, patients may develop other types of chronic diseases, such as diabetes mellitus and renal disease, which can affect the maternal end organs. Patients who have chronic hypertension or any other pre-existing medical condition should be paid more attention during routine antenatal care visits, and additional precautions should be taken even before pregnancy to avoid serious consequences (27).

Paré et al. (28) indicated that chronic hypertension was a significant predictor of severe preeclampsia. Women with chronic hypertension had a 3.2 higher chance of developing severe preeclampsia than those without prior hypertension. This finding is consistent with a study conducted by Direkvand-Moghadam et al. (29), in which they reported that chronic hypertension was significantly associated with the severity of preeclampsia. They claimed that chronic hypertension was the strongest predictor of preeclampsia in the Iranian population. However, they found that chronic hypertension was only a significant factor in women with mild preeclampsia; there was no association between chronic hypertension and severe preeclampsia.

The current study also found that women with gestational diabetes mellitus had 47% lower odds of developing severe preeclampsia than those with mild preeclampsia. A link between gestational diabetes mellitus and preeclampsia has been reported in a study from the German birth registry (30). This finding was consistent with another birth registry study in Alberta, Canada, which confirmed that gestational diabetes mellitus was a significant risk factor for preeclampsia (31).

In contrast, a study using national perinatal data of Slovenian pregnant mothers found that gestational diabetes mellitus was not associated with the development of preeclampsia (1). The contrast in the results was explained by the fact that the insult that causes preeclampsia most likely occurs early in pregnancy, whereas gestational diabetes mellitus develops during mid-gestation (9,32). Furthermore, Slovenian pregnant mothers received appropriate antenatal care through a targeted program for diabetic pregnancies beginning in the early 1980s, which included preconception consulting, management of gestational diabetes mellitus, and regular screening for gestational diabetes mellitus.

Study Limitations

Several limitations of the current study should be addressed. Medical records were incomplete or not applicable for some patients, resulting in deviations in the results obtained. In addition, the findings of this study may not be applicable to the general population because this was a hospital-based study. On the other hand, these findings could provide new information on the severity of preeclampsia in the local population because, to our knowledge, there is no similar study in the literature on the factors associated with the severity of preeclampsia in Kelantan.

Conclusion

This study showed that uric acid, chronic hypertension, and gestational diabetes mellitus were significantly associated with the severity of preeclampsia. Pregnant mothers should be encouraged to seek medical attention so that preeclampsia can be diagnosed early to prevent complications.

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Ethics

Ethics Committee Approval: Ethical approval was obtained from the Human Research Ethics Committee of the School of Medical Sciences Universiti Sains Malaysia (USM) with JEPeM code USM/JEPeM/16090273 on 9th January 2017. Permission to review the medical records was obtained from the Director of Hospital USM.

Informed Consent: Consent form was filled out by all participants.

Authorship Contributions

Concept: N.F.M.T., S.A., S.A.A.H., F.J., W.N.A.W.A., Design: N.F.M.T., S.A., S.A.A.H., F.J., W.N.A.W.A., Data Collection or Processing: N.F.M.T., S.A.A.H., W.N.A.W.A., Analysis or Interpretation: N.F.M.T., S.A., S.A.A.H., W.N.A.W.A., Literature Search: N.F.M.T., S.A.A.H., W.N.A.W.A., Writing: S.A.A.H., W.N.A.W.A.

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