THE SEVERITY OF PREECLAMPSIA AND ITS ASSOCIATED FACTORS IN HOSPITAL UNIVERSITI SAINS MALAYSIA

NURDIYANA FARHANA BINTI MAT TAMIZI

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by

NURDIYANA FARHANA BINTI MAT TAMIZI

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LIST OF ABBREVIATIONS

ACOG	American Congress of Obstetricians and Gynecologists
AIC	Akaike Information Criterion
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BIC	Bayesian Information Criterion
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CPG	Clinical Practice Guideline
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
GDM	Gestational Diabetes Mellitus
Hb	Haemoglobin
HELLP	Hemolysis, Elevated Liver enzymes, Low Platelet count
HPT	Hypertension
IQR	Interquartile Range
JEPeM	Jabatan Etika Penyelidikan Manusia
LR	Likelihood Ratio
MC	Multicollinearity
NICE	National Institute for Health and Care Excellence

O&G	Obstetrics and Gynaecology
OLS	Ordinary Least Square
OR	Odds Ratio
PE	Preeclampsia
PS	Power and Sample size software
ROC	Receiver Operating Characteristic
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SGA	Small Gestational Age
SPSS	Statistical Package for the Social Sciences
USM	Universiti Sains Malaysia
VIF	Variance Inflation Factor
WHO	World Health Organization

LIST OF SYMBOLS

α	Level of significance
1-β	Power
p	Proportion
p	Probability
Δ	Precision
z	z-statistic distribution
n	Sample size
m	Ratio of control to cases group
δ	Estimated difference from population mean
σ	Standard deviation
P_0	Proportion of exposed factor in mild disease
P_1	Proportion of exposed factor in more severe disease
b	Regression coefficient
P	P-value
%	Percentage
=	Equal to
<	Less than
>	More than
≥	More than or equal to

≤	Less than or equal to
| |	Modulus
n	Covariate pattern
h	Leverage
dx2	Hosmer-Lemeshow Delta chi-squared influence statistic
dd	Hosmer-Lemeshow Delta-D influence statistic
db	Pregibon Delta-Beta influence statistic
K	Constant
μ	Micro

TAHAP KETERUKAN PREEKLAMPSIA DAN FAKTOR-FAKTOR YANG BERKAITAN DI HOSPITAL UNIVERSITI SAINS MALAYSIA

ABSTRAK

Latar belakang kajian: Preeklampsia (PE) adalah salah satu punca utama kepada kematian dan mobiditi ibu di seluruh dunia. PE berlaku selepas 20 minggu kehamilan dengan kehadiran tekanan darah tinggi dan protin dalam air kencing. Kajian ini dijalankan bertujuan untuk menentukan peratus dan faktor-faktor penyebab PE berdasarkan tahap keterukan dalam kalangan pesakit di Hospital USM. **Metodologi:** Kajian rentas ini dijalankan ke atas 200 pesakit yang didiagnosa sebagai PE antara tahun 2011 hingga 2016 yang mengikuti rawatan susulan semasa kehamilan hingga proses kelahiran. Pesakit yang dirujuk dari hospital lain di Kelantan dan negeri lain yang terdekat juga dikira sebagai sampel kajian. Selain itu, pesakit yang menghidapi tekanan darah tinggi kronik sebelum PE, sindrom hemolisis, enzim hati yang tinggi, dan kiraan platelet rendah (HELLP) dan eklampsia juga termasuk dalam kriteria kajian. Pengkelasan tahap keterukan dibahagikan kepada ringan, sederhana dan teruk seperti yang ditetapkan oleh garis panduan Institut Kecemerlangan Kesihatan dan Penjagaan Kebangsaan (NICE). Regresi logistik ordinal telah digunakan untuk menganalisis. **Dapatan kajian:** Peratus pesakit yg menghidapi PE tahap ringan adalah sebanyak 34.7%, tahap sederhana sebanyak 30.2% dan tahap teruk sebanyak 35.1%. Asid urik yang tinggi didapati meningkatkan risiko untuk mendapat PE pada tahap yang lebih teruk (nisbah odds terlaras: 1.05, 95% selang keyakinan (SK): 1.02, 1.07). Tekanan darah tinggi kronik (nisbah odds terlaras: 2.36, 95% SK: 1.28, 4.33) dan

diabetes semasa hamil (nisbah odds terlaras: 0.53, 95% SK: 0.30, 0.96) juga didapati mempunyai kaitan dengan tahap keterukan PE. **Kesimpulan:** Mereka yang mengalami tahap PE yang ringan dan teruk didapati lebih tinggi berbanding tahap sederhana dalam populasi kajian ini. Pesakit dengan asid urik yang tinggi dan tekanan darah tinggi kronik lebih berisiko untuk mendapat PE yang teruk, manakala pesakit yang mengalami diabetes semasa hamil lebih cenderung mendapat PE yang ringan. Asid urik, tekanan darah tinggi kronik dan diabetes semasa hamil adalah berkaitan dengan bererti mengikut tahap keterukan PE dalam kalangan pesakit di Hospital USM. Pemeriksaan berkala terhadap tekanan darah dan protein dalam air kencing perlu diamalkan pada setiap pemeriksaan antenatal seperti yang dicadangkan oleh Pertubuhan Kesihatan Sedunia.

Kata kunci: preeklampsia, tahap keterukan, peratus, asid urik, tekanan darah tinggi, diabetes semasa hamil

THE SEVERITY OF PREECLAMPSIA AND ITS ASSOCIATED FACTORS IN HOSPITAL UNIVERSITI SAINS MALAYSIA

ABSTRACT

Background: Preeclampsia (PE) is one of the leading cause of maternal mortality and morbidity worldwide. It occurs after 20 weeks of gestation with the presence of hypertension and proteinuria. The aim of this study was to determine the proportion and the associated factors of PE according to its severity among patients in Hospital USM. **Methods:** A cross-sectional study involving 200 patients diagnosed with PE between years of 2011 to 2016 who were followed up and delivered in Hospital USM were included in this study. Patients from other referral hospitals in Kelantan and nearer states were also included to be the study samples. We also include those of chronic hypertension with superimposed PE, hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, and eclampsia. The severity classification of mild, moderate and severe PE was determined based on the National Institute of Health and Care Excellence (NICE) guideline. Ordinal logistic regression was used for analyzing. **Results:** The percentage of PE among patients in Hospital USM were found to be 34.7% in mild, 30.2% in moderate and 35.1% in severe cases. Higher uric acid resulted in greater odds of getting severe versus mild PE (Adjusted odds ratio (OR): 1.05, 95% CI: 1.02, 1.07) after adjusted for other variables. Patients having chronic hypertension (Adjusted OR: 2.36, 95% CI: 1.28, 4.33) and gestational diabetes mellitus (GDM) (Adjusted OR: 0.53, 95% CI: 0.30, 0.96) were also found to be associated with the severity of PE. **Conclusion:** Those who developed

mild and severe PE was higher compared to moderate PE in this population. Patients with high uric acid and chronic hypertension have higher chances to get severe PE, while those with GDM was more likely to have mild PE. Uric acid, chronic hypertension, and GDM were significantly found to be associated with the severity of PE among patients in Hospital USM. A routine screening for PE based on BP and urine protein measurement should be practiced and done at every antenatal visit as recommended by World Health Organization (WHO).

Keywords: preeclampsia, severity, proportion, uric acid, chronic hypertension, GDM

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Hypertensive disorders of pregnancy remain one of the leading causes of maternal and perinatal morbidity and mortality for about 3-8% worldwide (Carty *et al.*, 2010). Preeclampsia (PE) is a common disorder characterized by hypertension in pregnancy and complicates about 2-8% of all pregnancies in the developed world (Steegers *et al.*, 2010). Maternal systolic blood pressure (SBP) $\geq$ 160 mm Hg and/or diastolic blood pressure (DBP) $\geq$ 110 mm Hg was defined as severe PE and if remains untreated, it could lead toward more serious condition known as eclampsia (Al-Jameil *et al.*, 2013). Severe PE was associated with an increased risk of adverse outcomes in pregnancy (Wilkinson, 2011). Women who did not reach BP of 140 or 90 mmHg, but had been detected a rise of > 30/15 mmHg from booking or preconception BP, had in the past been considered useful in diagnosing PE instead of relying on an absolute value (CPG, 2013; Lowe *et al.*, 2015).

Based on the Malaysia Clinical Research Center (CRC) review of hypertensive disorders in pregnancy from the year 2011 until 2012, the data showed that incidence of PE was 19.6%, chronic hypertension was 18.6%, chronic hypertension of superimposed PE was 6.7% and gestational hypertension of 53.3%, which was the commonest type of hypertensive disorders in pregnancy among Malaysian women (Yadav, 2012).

A recent study done in three hospitals in Riyadh, Saudi Arabia found that PE occurred in 1.2% among Saudi women (Wahabi *et al.*, 2016), and 2.23% among women who referred to Dilla University Referral Hospital, Ethiopia (Vata *et al.*, 2015).

Consequently, PE can affect both mother and the baby. Anderson *et al.* (2012) noted that PE women was 25.8% higher chance of delivering preterm infants and 28.5% of getting small gestational age (SGA) infants compared to those without PE. The rate of Neonatal Intensive Care Unit (NICU) admission was significantly higher for those mother with PE than in those from mother with gestational hypertension (38.8% versus 25.7%). Fetal and neonatal death was also noted to be higher in PE group compared to the gestational hypertension group (Shiozaki *et al.*, 2013).

Hence, the major complications for women with PE include central nervous system (CNS) injuries such as seizures (eclampsia), hemorrhagic and ischemic strokes, hepatic damage ranging from transaminase elevation known as HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), hepatic failure, and renal dysfunction (Mustafa *et al.*, 2012).

1.2 Problem Statement

The assessment of the severity of PE in pregnancy was based on the clinical examination of patient with the presence of proteinuria. Different investigations would determine different level of the severity of PE among patients. However, the severity classification of mild, moderate and severe PE had not been specified in Hospital USM medical birth register. Whereas the information on the severity of PE and their associated factors were lacked among pregnant Malaysian women.

1.3 Justification of the Study

There would be some benefits of doing this study, not only for the researchers but mainly very useful for clinicians as the information obtained can help them in identifying the associated factors of PE according to the severity of either mild, moderate or severe. From this information, they can educate patients and increase patients' knowledge and awareness about PE and its consequences. This study would also provide them with the proportion of developing PE among patients in Hospital USM. The severity of PE was classified into mild, moderate and severe referring the National Institute of Health and Care Excellence (NICE) as a main guideline. In addition, since no similar study had been done on the factors associated with the severity of PE, the finding could help in providing extra information on the severity of PE in the local population.

CHAPTER 2

OBJECTIVES

2.1 Research Question

1. What was the proportion of the severity of preeclampsia patients in Hospital USM?
2. What were the associated factors of the severity of preeclampsia patients in Hospital USM?

2.2 General Objective

To determine the proportion and the associated factors of the severity of preeclampsia patients in Hospital USM.

2.3 Specific Objectives

Specifically, the objectives of the study were:

1. To determine the proportion of the severity of preeclampsia patients in Hospital USM.
2. To identify the associated factors of the severity of preeclampsia patients in Hospital USM.

2.4 Hypothesis Statement

There were significant associations between socio-demographics, clinical characteristics and laboratory parameters with the severity of PE among patients in Hospital USM.

CHAPTER 3

LITERATURE REVIEW

3.1 Hypertensive Disorders in Pregnancy

Hypertensive disorders in pregnancy include chronic hypertension, gestational hypertension, preeclampsia (PE), and chronic hypertension with superimposed PE. They can affect both mother and the baby and thus result in substantial maternal morbidity and increase the chance of having cardiovascular disease later in future. Chronic hypertension occurs before 20 weeks of gestation including women with hypertension before pregnancy (pre-existing hypertension). Gestational hypertension occurs after 20 weeks of gestation without proteinuria assessment or any systematic findings. While PE presents after 20 weeks of gestation with significant proteinuria or any symptoms of end-organ damage. Chronic hypertension with superimposed PE occurs when women with pre-existing hypertension also develops PE during the course of their pregnancy (NICE, 2013).

In addition, Surapaneni *et al.* (2013) classified hypertension in pregnancy into chronic hypertension, gestational hypertension, preeclampsia (PE), eclampsia and HELLP syndrome. Hypertension was defined as a systolic blood pressure (SBP) of $\geq$ 140 mmHg and/or a diastolic blood pressure (DBP) of $\geq$ 90 mmHg, taken on at least two measures over several hours (Brown *et al.*, 2001). Eclampsia occurs when women with PE develop seizures and HELLP syndrome represents the occurrence of hemolysis, elevated liver enzymes and low platelets among women with severe PE (Lowe *et al.*, 2015).

3.2 Diagnosis of Preeclampsia and Its Severity

A guideline from the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) defined PE as a raised in blood pressure during pregnancy with the involvement of other clinical manifestations (Lowe *et al.*, 2015). They indicated that the presence of proteinuria was not mandatory for clinical diagnosis of PE. A diagnosis of PE was determined when increased in blood pressure occurs after 20 weeks gestation and was accompanied by any of the maternal organ dysfunction involving either renal insufficiency (a spot urine protein/creatinine ratio ≥ 30mg/mmol or serum creatinine > 90 μmol/L), hematological complications (thrombocytopenia or haemolysis), liver involvement (raised serum transaminases or severe epigastric and/or right upper quadrant pain), neurological complications (convulsions, persistent headache or visual disturbances), and uteroplacental dysfunction of fetal growth restriction.

These symptoms of PE diagnosis were similar with the International Society for the Study of Hypertension in Pregnancy (ISSHP). However, for severe PE, the recent ISSHP statement suggested that determining severity include the difficulty in controlling blood pressure and worsening clinical condition such as HELLP syndrome, impending eclampsia, thrombocytopenia or fetal growth restriction with less concern regarding increased of proteinuria (Tranquilli *et al.*, 2014). The criteria for diagnosing severe PE were in line with several other studies (RCOG, 2006; American College of Obstetricians and Gynecologists (ACOG), 2013; CPG, 2013).

The assessment of the severity of PE during pregnancy was based on the clinical examination of the patients with the presence of proteinuria (Prakash *et al.,* 2012). The American College of Obstetricians and Gynaecologists (ACOG) defined proteinuria as the excretion of 300 mg or more protein in a 24-hour urine collection or a protein/creatinine ratio of at least 0.3 mg/dL. If this approach is not readily available, diagnosis of proteinuria can be determined based on dipstick test of 1+ as a cut-off point (American College of Obstetricians and Gynecologists (ACOG), 2013). Recently, some guidelines (American College of Obstetricians and Gynecologists (ACOG), 2013; CPG, 2013; Tranquilli *et al.*, 2014; Lowe *et al.,* 2015) no longer requires proteinuria for the diagnosis of PE, leaving only the British National Institute for Health and Care Excellence (NICE) guideline with this requirement (NICE, 2013). The measurement of proteinuria in pregnancy-induced hypertension has been reviewed by Lindheimer and Kanter (2010). The presence of 2+ or 3+ proteinuria or repeated 1+ dipstick testing increased both sensitivity and specificity, thus was considered to represent significant proteinuria until proven otherwise by confirmatory tests.

Some of the pregnancy guidelines classified PE as mild and severe or mild-moderate and severe (American College of Obstetricians and Gynecologists (ACOG), 2013; CPG, 2013; Magee *et al.*, 2014; Lowe *et al.*, 2015). A guideline which classified PE into mild, moderate and severe was NICE with inclusion of proteinuria assessment (NICE, 2010). They defined PE as a new onset of hypertension taken at least four hours apart on two measurements with the presence of significant proteinuria. The diagnosis of the severity of PE in this study was based on NICE guideline. Hence, PE was classified into three groups of mild,

moderate, and severe. Mild PE was diagnosed if SBP was between 140 to 149 mmHg and/or DBP was between 90 to 99 mmHg. While moderate was when SBP between 150 to 159 mmHg and/or DBP was between 100 to 109 mmHg. Those with BP above 160/110 mmHg were considered as having severe PE (NICE, 2013).

3.3 Prevalence of the Severity of Preeclampsia among Pregnant Women

PE affected about 6.4% among pregnant Iranian women (Allahyari *et al.*, 2010) and 3.3% in New Zealand multiethnic pregnant women (Anderson *et al.*, 2012). From a study done by Xiao *et al.* (2014) in China involving three hospitals, 2.35% of pregnant women developed PE, with 74.1% developed mild PE and the rest 25.9% were diagnosing of severe PE. Hence the prevalence of mild PE was 1.42% and that of severe PE was 0.49%. As compared with Caucasians, the prevalence of PE in this Chinese population was low due to better lifestyle practice such as diet, caloric intake, physical activity, geographical location, and genetic factors in China. For example in terms of dietary intake, they consumed a lot of tofu, one of the popular food in China with calcium-rich made from soy beans. Calcium supply in tofu has been shown to reduce the incidence of PE by up to 50% as reported by Hofmeyr *et al.* (2006).

A previous study by Sohlberg *et al.* (2012) demonstrated that PE occurred in 4.8% among primiparous women who delivered a singleton baby in Sweden. The percentage for mild to moderate PE was 3.2% and 1.6% for severe PE in the population. They demonstrated that women of short stature and increase of body mass index (BMI) had higher risks of

both mild and severe PE. Those with BMI of more than 35 kg/m^2 were four times higher chance to develop mild PE and three times of getting severe PE. Since it was reported that most of the women in the study were obese, then the proportion of getting mild was higher than severe PE.

In addition, Direkvand-Moghadam *et al.* (2012) found out the prevalence of PE was 9.5% out of 610 pregnant women included in the study done at Mustafa Hospital of Ilam in the west of Iran. The prevalence of developing mild and severe PE was 1.3% and 8.2% respectively. Higher prevalence of severe PE in this population was found to be associated with history of PE, hypertension, and infertility as well as low level of education among women.

3.4 Proportion of the Severity of Preeclampsia among PE women

Based on a study done by Alsnes *et al.* (2014) in Stavanger University Hospital, Norway, they discovered that the proportion of mild PE were 0.33, moderate PE was 0.42 and severe PE was 0.25. They noted that there was a decreased level of insulin resistance in severe group compared to the others, hence proven their hypothesis that women with mild and moderate PE were more likely deviated in metabolism and those of severe PE were mostly due to placental issue (Vatten and Skjaerven, 2004).

Meanwhile, in a study done by Vata *et al.* (2015) at Dilla University Referral Hospital, Ethiopia, the proportion of PE was noted to be 0.66 in mild group, 0.17 in severe group and the rest 0.17 in eclampsia group. It was noted that PE occurred in 10% of pregnancies in low-income countries including Africa, which considered higher compared to global average of approximately only 2% (Nakimuli *et al.*, 2014).

3.5 Factors Associated to the Severity of Preeclampsia

3.5.1 Socio-Demographic Characteristics

3.5.1.1 Maternal Age

Various studies have shown a significant relationship between maternal age and the incidence of PE. Advanced of maternal age have been associated with a higher risk of developing PE. Trogstad *et al.* (2011) reported that the risk of developing more severe PE was almost twice for women aged 40 years and older compared to those of younger age. In addition, Tessema *et al.* (2015) pointed out that women aged 35 and above were 4.5 times higher odds of experiencing PE than those aged 25 to 29 years (Adjusted OR: 4.5, 95% CI: 1.56, 12.8), while those of 30 to 34 years were 3.3 times higher odds of developing PE than women with 25 to 29 years old (Adjusted OR: 3.26, 95% CI: 1.35, 7.8).

A study done in Finland by Lamminpää *et al.* (2012) classified PE women aged 35 years and above as older age and compared to those under 35 as younger. They reported that women of advanced maternal age exhibited 9.4% more often of having more severe PE than younger women (6.4%). This was due to the fact that women with older age were at

higher risk of getting chronic diseases such as hypertension and DM and thus affect their pregnancies with deliveries of preterm or small gestational age infants.

Vata *et al.* (2015) observed that 88.37% of PE women in their study group were in age of below 30 years old and the rest 11.63% were above 30. Conversely, they found a significant trend of association between women with younger age with increasing PE severity. They had concluded that younger women were more likely to develop severe PE compared to the elder one. It was mainly because of younger women had low level of awareness and knowledge on occurrence of PE during pregnancy.

3.5.1.2 Pre-Pregnancy Body Mass Index (BMI)

BMI was calculated as the ratio of maternal weight and height (kg/m^2) at the first booking visit. According to the World Health Organization (WHO), overweight and obesity in adults were defined as an abnormal or excessive fat accumulation that may impair health status where an individual BMI respectively were 25 to 29.9 and above 30 kg/m^2. However, WHO stated that the BMI classification for Asian/Indian women was different as the BMIs for normal, overweight and obese were 18.5 to 22.9, 23 to 27.4 and above 27.5 kg/m^2, respectively (WHO Expert Consultation, 2004). The prevalence of obese women (BMI $\geq$ 30 kg/m^2) aged 18 and above in 2014 were 27.9% in Australia, 15.9% in Malaysia, 11.4% in Thailand, 8.2% in China, 8.1% in Indonesia, and about 5.1% in India (WHO Global Health Observatory data, 2016).

Several studies have highlighted the relationship between maternal obesity and PE. Based on the study done by Xiao *et al.* (2014), they found out that BMI was associated with the prevalence of PE among Chinese where 18.3% were overweight and 2.9% were obese. However, there was no significant association between mild and moderate PE with obesity. Being overweight and obese among women in China were less frequent as compared to European or American women (WHO Expert Consultation, 2004). Better consumption of dietary intake contributed to low prevalence of obesity among Chinese.

While in Pittsburgh, Pennsylvania population, it was estimated that the prevalence of PE caused by obesity was 30% (Jeyabalan, 2013). Obesity increased risk of getting both mild and severe PE in the population as well as development of cardiovascular disease later in future (Roberts *et al.,* 2011). In a retrospective cohort study of recorded maternity data from 2006 to 2009 in Auckland, New Zealand, Anderson *et al.* (2012) examined BMI of more than 27.5 kg/m^2 was associated with a 2.6 fold increase in the risk of PE. Besides, Paré *et al.* (2014b) proved that those with BMI more than 25 kg/m^2 were 64.4% greater risk of having severe PE.

In addition, Sohlberg *et al.* (2012) proved that obesity with BMI $\geq$ 35 kg/m^2 was associated with a 4 fold increase risk of mild to moderate PE and 3 fold increase risk of severe PE. This association showed that increasing BMI lead to a milder form of PE than severe. They also came up with a finding that women with a short stature had a greater chance of getting PE in pregnancy compared to those with tall stature (Adjusted OR: 1.3, 95% CI: 1.2, 1.5). There were stronger associations of short stature for severe than for mild to moderate PE

since they also claimed that women of short stature were at increased risk of cardiovascular disease.

3.5.1.3 Parity

Bai *et al.* (2002) defined parity as the number of how many times a woman had given birth to an infant from 20 weeks of gestation or weighed more than 0.4 kg. Nulliparity was a strong risk factor of PE (Adjusted OR: 2.4, 95% CI: 2.01, 2.86) as reported by Anderson *et al.* (2012). They noticed that there was no significant association between multiparous woman and risk of developing PE in the population. Other authors also demonstrated that nulliparous women were more likely to have severe PE than multiparous women (Kumar *et al.*, 2014; Paré *et al.*, 2014a).

Furthermore, Xiao *et al.* (2014) stated that 81.5% of total women involved in their study were nulliparous. Hence, the prevalence of PE for nulliparous women was 1.92% and among all nulliparous PE women from the population, 74.1% developed mild PE and 25.9% of women developed severe PE. Less development of severe PE in this population was due to high consumption of fruits and better daily lifestyle diet practiced among these women.

3.5.1.4 Multiple Gestations

The incidence of PE in women with multiple gestations has been shown to be two to five times that of singleton pregnancy (Lazarov *et al.*, 2016). They also reported that 15-20% of women with twins will develop PE in their pregnancy. In a retrospective cohort study to evaluate the risk of preterm delivery among PE women conducted by Henry *et al.* (2013), they showed that twin pregnancies were significantly more likely to develop severe PE and delivered preterm babies than singletons (RR: 5.7, 95% CI: 4.47, 7.26). Clinicians claimed that it was difficult in balancing the needs of a mother and her babies as preterm severe PE carried high morbidity. Besides, Paré *et al.* (2014a) also found that women with multiple gestations were three times higher odds of developing severe PE than those with a singleton pregnancy (Adjusted OR: 3.17, 95% CI: 1.78, 5.66). Thus, they suggested that multiple gestations need to be prevented when assisted reproductive technologies were used.

3.5.1.5 Marital Status

Some previous studies have evaluated the relationship between paternity change and risk of developing an adverse pregnancy outcome like PE. Bandoli *et al.* (2012) concluded that the odds of having PE in pregnancy were 2.75 times higher for women with partner changing compared to those who had not (Adjusted OR: 2.75, 95% CI: 1.33, 5.68). This finding was similar to a study done on pregnant women in Maryam Hospital located in Tehran, Iran as they found out that those with marriage more than once were 2.65 times

more likely to be associated with the development of a more serious PE condition (Allahyari *et al.*, 2010).

Tessema *et al.* (2015) proved that unmarried women were 3 times more likely to develop PE than those who were married (Adjusted OR: 3.03, 95% CI: 1.12, 8.20). This was due to the possibility of low preconception period seminal fluid exposure among unmarried women which could increase the risk of PE during pregnancy.

3.5.2 Clinical Characteristics

3.5.2.1 Previous PE History

Women with PE history in their previous pregnancy had a significantly higher chance of developing another PE in next pregnancy with OR of 9.4, 5.46, and 3.63 respectively (Kashanian *et al.*, 2011; Direkvand-Moghadam *et al.*, 2012; Paré *et al.*, 2014b). Recently, Sharami *et al.* (2017) asserted that the odds of developing PE were 3.2 times higher among women with previous PE history. They found that those with history of PE were 3.9 and 4.2 times higher chance of getting both mild and severe PE respectively in the subsequent pregnancy (Adjusted OR: 3.93, 95% CI: 1.69, 9.14 vs Adjusted OR: 4.2, 95% CI: 1.58, 11.3). This reflected that there was an association between PE and future risk of hypertension and heart diseases (Garovic and August, 2013).

Wong *et al.* (2013) observed that those with severe PE in previous pregnancy was 53.3% greater chance of getting PE in next pregnancy compared to those with mild PE in the previous pregnancy (16.7%). They concluded that previous PE history was proven to be a strong independent factor for gestational hypertensive disorders among high-risk pregnant women (Adjusted OR: 2.89, 95% CI: 1.18, 7.08).

3.5.2.2 Chronic Hypertension

Chronic hypertension is a prior problem in developing countries and it can increase the incidence of PE (Macdonald-Wallis *et al.*, 2011). Paré *et al.* (2014b) reported that women with chronic hypertension were 3.2 times higher odds of developing severe PE compared to those without prior hypertension (Adjusted OR: 3.20, 95% CI: 2.06, 4.98). In addition, women with underlying chronic hypertension were 8.32 and 12.06 times more likely to develop PE and eclampsia with 95% CI of 7.13-9.72 and 8.40-17.31 respectively (Abalos *et al.*, 2014). Direkvand-Moghadam *et al.* (2012) also found a significant association between chronic hypertension with the severity of PE (Adjusted OR: 2.34, 95% CI: 1.03, 4.40).

3.5.2.3 Family History of Hypertension and DM

Tessema *et al.* (2015) concluded higher chance of PE was found among women in Ethiopia with family history of hypertension for about seven-fold (Adjusted OR: 7.17, 95% CI: 3.4, 15.2), while odds of developing PE were 2.4 times higher among those with a family

history of DM (Adjusted OR: 2.40, 95% CI: 1.09, 5.6). Paré *et al.* (2014b) claimed that those with family history of PE was 74% higher odds of having severe PE in pregnancy than mild PE (Crude OR: 1.74, 95% CI: 1.10, 2.74).

This result was supported by a study done by Bezerra *et al.* (2010) where they proved that women whose mothers had a history of hypertension (Adjusted OR: 1.46, 95% CI: 1.13, 1.88), PE (Adjusted OR: 2.08, 95% CI: 1.22, 3.55), or eclampsia (Adjusted OR: 3.23, 95% CI: 1.06, 9.81) were at higher odds of getting severe PE. The chance of severe PE was also high when the woman had a sister with a history of hypertension (Adjusted OR: 2.60, 95% CI: 1.60, 4.21), PE (Adjusted OR: 2.33, 95% CI: 1.58, 3.45), or eclampsia (Adjusted OR: 2.57, 95% CI: 1.28, 5.16). Notably, there was a significant association of getting severe PE among women with both mother and sister having a history of hypertension (Adjusted OR: 3.65, 95% CI: 1.65, 8.09).

3.5.2.4 History of Abortion

Recently, Sepidarkish *et al.* (2017) stated that higher number of previous spontaneous abortion was associated with higher chance of developing PE among pregnant women (Adjusted OR: 1.28, 95% CI: 1.03, 1.59). In a cross-sectional study conducted in Alzahra Hospital, Rasht, Sharami *et al.* (2017) demonstrated that history of abortion was 2.72 times higher odds of developing mild PE (Adjusted OR: 2.72, 95% CI: 1.33, 1.56), and there was a significant mean difference among healthy pregnant and mild PE ($P<0.019$), as well as mild and severe PE ($P<0.008$).

3.5.2.5 History of Established DM and Gestational DM (GDM)

Several studies demonstrated that there were significant associations between pre-existing DM and GDM among PE women. In a recent study conducted by Yang *et al.* (2017), those with GDM during pregnancy was about 16 fold more likely to develop PE (Adjusted OR: 15.54, 95% CI: 5.82, 41.49). Besides, pre-existing DM was 3.88 times higher odds of getting PE when controlling for other confounders (Adjusted OR: 3.88, 95% CI: 2.08, 7.26) (Paré *et al.*, 2014b). These were supported by a previous study done by Anderson *et al.* (2012) where GDM as well as type 1 and type 2 diabetes were significantly higher among PE women referred to Auckland City Hospital in New Zealand.

3.5.2.6 Laboratory Parameters

The combination of clinical data as well as the laboratory routine tests such as uric acid, creatinine, albumin, platelet count, urea, hemoglobin, AST, and ALT were very helpful in determining the severity of PE during pregnancy. Somani *et al.* (2015) concluded that serum uric acid level were usually elevated during pregnancy with PE and significantly higher among PE women ($p<0.005$). This was supported by other previous studies (Hawkins *et al.*, 2012; Wu *et al.*, 2012; Enaruna *et al.*, 2014). Previously, Egwuatu (1986) claimed that overproduction of uric acid was due to excessive cellular activity associated with placental ischemia. They found that plasma urea and uric acid concentration were higher in patients with severe PE than those of mild/moderate PE, but no significant mean

difference between plasma creatinine and the severity of PE. Consequently, an increase in uric acid and urea among PE women had led to the complications of the fetus.

Manaj *et al.* (2011) reported that PE occurred if platelet count was less than 100,000/µL. Hyperuricemia was found associated with PE and usually was tested early to predict later onset of PE. A serum uric acid level greater than 5 mg/dL was considered abnormal and was predicted as a marker of tubular dysfunction in PE. Usually serum creatinine was less than 0.8 mg/dL during pregnancy, thus higher levels suggest intravascular volume contraction or renal involvement in PE. Moreover, elevated levels of serum transaminases would lead to hepatic involvement in PE such as HELLP syndrome; a liver-related disorder. Features of PE occur in the majority of patients presenting with HELLP syndrome. Ten to 20% of patients with severe PE will develop HELLP (Hammoud and Ibdah, 2014).

Murakami *et al.* (2000) suggested that the presence of hemoconcentration was due to hemoglobin level of more than 13 g/dL, while low level may be due to microangiopathic haemolysis or iron deficiency. Anemia was defined as haemoglobin level of less than 11 g/dL (McLean *et al.*, 2009). Ali *et al.* (2011) estimated the prevalence of PE and eclampsia for about 8.2% and 3.3% among women with severe anaemia respectively. PE was just significantly increased in severe anaemia group (Adjusted OR: 3.6, 95% CI: 1.40, 9.10) compared to the mild group, while there was no increase in risk for eclampsia among women with anaemia. After adjusted for all potential confounders, Taner *et al.* (2015) demonstrated that women with anaemia were 55% higher chance of developing PE

(Adjusted OR: 1.55, 95% CI: 1.03, 2.1) compared to those who did not. However, Kashanian *et al.* (2011) claimed that anaemia was protective for PE since there was no significant association between them.

In a recent study done by Maged *et al.* (2017) among pregnant women in Cairo, Egypt, they found out that the platelet count was significantly lower in those of severe PE compared to mild, while there was no significant difference between creatinine, uric acid, urea, and AST between both mild and severe PE groups. However, the ALT level was noted to be significantly higher among women with severe PE than mild.

3.6 Ordinal Logistic Regression

The statistical analysis applied in this study was the ordinal logistic regression. It is an extension of the binary logistic regression. The interest of logistic regression is to estimate the relationship between the binary outcome (dependent) variable and more than one explanatory (independent) variables which consist of the combination of numerical and categorical variables and also known as covariates. The main goal of the analysis of logistic regression is to find the best fit and most parsimonious, as well as biologically plausible model to explain the relationship between an outcome variable and the independent variables (Hosmer *et al.*, 2013).

A method of ordinal logistic regression is designed to take full advantage for analysing ranked outcomes and several associated factors. The primary characteristic of ordinal data

is that the numbers assigned to successive categories of the variable being measured represent differences in magnitude, or a "greater than" or "less than" quality (Stevens, 1951).

In this study, the severity of PE was assessed with scale categories of mild, moderate, and severe which showed an ordered ratings of the outcome variable. Knapp (1999) explained that the severity of illness categories represent increasing the severity, in the sense that "moderate" is more critical than "mild," and "severe" is more critical than "moderate." The rating given to the "severe" case does not imply that "severe" is three times as critical than "mild," only that the severity of illness in the "severe" category is greater than the severity of illness for those in the "mild" category and greater still than those in the "moderate" category.

Data that were used to be collected using an ordinal scale were rarely analysed as such since the methods of analysing ordinal data have not been widely applied (Scott *et al.*, 1997). Hence, they reported that ordinal data often be treated as nominal, with proportions calculated for each level of outcome. Chi-square tests of association are used to test the differences in proportions. However, chi-square tests have less optimal power, since they ignore the ordinality of the data which may yield to incorrect inferences. Some limitations of chi-square tests are, they are not amenable to statistical adjustments; the results are sample-size dependent, and no measure of association is produced.

The ordinal scale is usually collapsed into a dichotomous one and treated as a binary logistic model. The ordinal outcome will be forced into two levels, thus discarded some important information. Hence, it may lead to erroneous statistical inferences.

Otherwise, the ordinal scale is quantified and treated as continuous and linear. Applying linear regression models to ordinal outcomes is troublesome as one of the assumption is that the variance of the outcome must be homogenous. However, the variance of ordinal data with an underlying multinomial distribution is not homogenous. Ordinary least square (OLS) regression is applied to this data, but the corresponding estimates of variance are biased and inconsistent (Lipsitz and Buoncristiani, 1994).

Thus, fitting an ordinal logistic regression is preferable so that no information is lost. This analysis is powerful and the estimates produce a broad parameter interpretation that summarizes the effect between groups of all level of the outcome.

There are various models in ordinal logistic regression. Hosmer *et al.* (2013) discussed that the most commonly used models are the adjacent-category, the continuation ratio, and the proportional odds models. In this study, only the proportional odds model was applied in assumption checking. Some other models that are less frequently used are the unconstrained partial-proportional odds, the constrained partial-proportional odds, and the stereotype logistic models.

In the ordinal model, outcomes needed to be decided to compare and determine what the most reasonable model is for the logit. If each response to the next larger response is compared, then the model that should be applied is the adjacent-category logistic model. It is a constrained version of the baseline logits. However, the continuation-ratio logistic model is about comparing each response to all lower responses that is $Y = k$ versus $Y < k$ for $k = 1,2,\ldots, K$.

The third most frequently used model for ordinal logistic regression is the proportional odds model (McCullagh, 1980; Hosmer *et al.*, 2013). It is meant for comparing the probability of an equal or smaller response, $Y \leq k$, to the probability of a larger response, $Y > k$, for $k = 0,1,\ldots, K-1$. It describes a less than or equal versus more comparison. It is also called the constrained cumulative logit model. The constrained placed on the model is that the log odds does not depend on the outcome category as the inferences from fitted proportional odds models are more on the direction of response rather than on specific outcome categories. Proportional odds model is derived via categorization of an underlying continuous response variable. Thus, some concepts from linear regression modeling is allowed to be used. One advantage of the proportional odds model that almost similar to the binary logistic model is that the direction of the model can be reversed by changing the signs of the coefficients to get the estimated odds ratio. Hence, the model chosen for ordinal logistic regression should consider an assessment of the model adequacy and which odds ratios are most informative for the problem.