A 5 YEAR REVIEW OF PRE-ECLAMPSIA IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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Nor Fatimah Zakiah bt Hanafi

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1.2 List of tables

1.3 List of abbreviations

AFI	Amniotic fluid index
ALT	Alanine aminotransferase
AMA	Advanced maternal age
AST	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
CNS	Central nervous system
CS	Caesarean section
CTG	HELLP
CVS	Cardiovascular system
DIC	Disseminated intravascular coagulopathy
DM	Diabetes Mellitus
EOP	Early onset pre-eclampsia
FGR	Fetal growth restriction
GDM	Gestational diabetes melitus
HELLP	Hemolysis, elevated liver enzyme, and low platelet
HTN	Hypertension
ICU	Intensive care unit
IUGR	Intrauterine growth restriction
LOP	Late onset pre-eclampsia
NA	Not available
NICE	National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit

PAC	Patient admission centre
PE	Pre-eclampsia
PIGF	Placental growth factor
SGA	Small for gestational age
SPSS	Statistical Package for the Social Sciences
VEGF	Vascular endothelial growth factor

1.5 Abstrak

Objektif: Menentukan kadar pre eklampsia awal pada kehamilan kurang dari 34 minggu dan pre eklampsia lewat selepas 34 minggu, dan menentukan ciri ciri pesakit dan kesudahan ibu dan kandungan pesakit, dan faktor penyebab kesan buruk kepada pesakit pesakit pre eklampsia yang bersalin di Hospital Universiti Sains Malaysia.

Metodologi: Kajian retrospektif ini melibatkan semua pesakit dengan kehamilan singleton yang bersalin di Hospital Universiti Sains Malaysia yang mempunya pre eklampsia, dalam tempoh Januari 2016 hingga Disember 2020. Semua butir butir demografi, sejarah perubatan, aduan klinikal, keputusan pemeriksaan, keputusan makmal, cara bersalin dan kesudahan ibu dan anak yang dikandung didapati dari fail pesakit, direkod dan di analisa. Data kategori di analisa melalui peratusan dan data pernomboran dianalisa melalui purata dan median. Faktor penyebab kesan buruk kepada ibu dan kandungan di analisa melalui regresi logistik. Variabel variable yang mempunyai *p-value* < 0.25 kemudian dianalisa dengan regresi logistik multiple, dan variabel dengan *p-value* <0.05 adalah dikira signifikan.

Keputusan: . Kadar prevalen di kalangan populasi kami adalah sebanyak 1.4%. Sebanyak 108 (30.8%) daripada 351 kes merupakan pre-eklampsia awal, manakala 243 (69.2%) merupakan pre-eklampsia lewat. Wanita yang lanjut umur merangkumi 43.5% di kalangan pre-eklampsia awal, manakala 24.3% dalam kalangan pre-eklampsia lewat. 58.3% wanita di kalangan pre-eklampsia awal mempunya sejarah pre-eklampsia, dan mereka kebanyakannya mempunyai BMI > 30 (59.3% vs 46.1%). Wanita yang mempunyai sejarah penyakit darah tinggi mempunyai risiko pre-eklampsia awal yang signifikan. Wanita pada kehamilan pertama lebih cenderung mendapat pre-eklampsia lewat walaupun tidak signifkan secara statistik. Wanita yang mempunyai pre-eklampsia awal lebih cenderung mendapat komplikasi. Malahan, bayi kepada ibu-ibu yang mempunyai pre-eklampsia awal lebih cenderung mendapat komplikasi,

ataupun kematian. Di kalangan wanita yang mempunyai pre-eklampsia awal, mereka didapati mempunyai sejarah pre-eklampsia ataupun obesiti. Di kalangan wanita yang mempunya pre-eklampsia lewat, mereka kebanyakannya adalah merupakan kandungan kali pertama ataupun mempunyai jarak di antara kandungan yang pendek (kurang 2 tahun).

Di antara wanita yang mempunyai pre-eklampsia awal dan mendapat komplikasi kepada bayi, didapati mereka merupakan wanita yang lanjut umur dan mengandung pada kali pertama. Di antara wanita yang mempunyai pre-eklampsia lewat yang mendapat komplikasi kepada bayi, mereka didapati menghidap Diabetes Mellitus dan obesiti. Walaubagaimanapun, perbezaan ini adalah tidak signifikan.

Kesimpulan: Prevalens pre-eklampsia di kalangan populasi merupakan 1.4%, adalah setanding dengan hasil dapatan negara Asia lain. Kebanyakan faktor risiko adalah lazim untuk pre-eklampsia awal dan pre-eklampsia lewat, namun begitu beberapa faktor risiko adalah berbeza mengikut subklasifikasi pre-eklampsia. Pre-eklampsia menyebabkan kesan komplikasi yang signifikan kepada wanita hamil, lebih-lebih lagi pre-eklampsia awal. Kesan kepada bayi lebih buruk untuk wanita yang mempunyai pre-eklampsia awal jika dibanding dengan pre-eklampsia lewat. Secara keseluruhan, wanita yang mempunyai pre-eklampsia lewat mempunyai keputusan yang lebih baik kepada ibu mahupun bayi.

1.6 Abstract

Objective: To determine the rate of early onset pre-eclampsia (onset of pre-eclampsia before 34 weeks) and late onset pre-eclampsia (onset of pre-eclampsia after 34 weeks) in patients who delivered in Hospital Universiti Sains Malaysia, the risk factors, the maternal and fetal outcomes for both groups and the associated factor for poor maternal and neonatal outcomes of both groups.

Methodology: This retrospective observational study involved all patients with singleton deliveries in Hospital Universiti Sains Malaysia, with the diagnosis of pre-eclampsia from January 2016 until December 2020. The demographic data, co-morbid, clinical presentation, clinical assessment, laboratory results, mode of delivery, and outcome were retrieved from the case notes and recorded and analyzed. Categorical data were analyzed by n (percent) and numerical data were analyzed by mean (SD) and median (IQR). Simple logistic regression testing was used to test for factors associated with poor maternal and fetal outcomes in pre-eclampsia. Any significant variables with a p-value <0.25 were included in multiple logistic regression for further analysis, and variables with p-value <0.05 were considered significant.

Results: 108 (30.8%) of 351 cases had early onset pre-eclampsia, 243 (69.2%) had late onset pre-eclampsia. The prevalence rate of pre-eclampsia in our centre was 1.4%. Advanced maternal age occurs in 43.5% of the early onset pre-eclampsia group vs 24.3% in the late onset group. 58.3% of women in the early onset group had a history of pre-eclampsia in a previous pregnancy, and they were likely to be obese (59.3% vs 46.1%). Chronic hypertension significantly increased the risk for early onset pre-eclampsia. Nulliparous women were more likely to develop late onset pre-eclampsia although not statistically significant. Women with early onset pre-eclampsia had a higher percentage of the poor maternal outcome (33% vs 21%). In addition, their babies had significantly increased rates of morbidity and mortality. Among

women with early onset pre-eclampsia that had a maternal complication, they were more likely to have a history of pre-eclampsia and obese, although not statistically significant. Furthermore, among women with late onset pre-eclampsia that had a maternal complication, they were likely to be nulliparous or had a shorter interpregnancy interval of less than 2 years, although not statistically significant.

Among women with early onset pre-eclampsia that had poor perinatal outcomes, there was a higher percentage of advanced maternal age and nulliparous women, and among women with late onset pre-eclampsia that had poor perinatal outcomes, there was a higher percentage of patients with Diabetes Mellitus and obese. However, these differences failed to reach statistical significance.

Conclusion: The prevalence of pre-eclampsia in the general population was 1.4% which was comparable to other Asian countries. Some risk factors were common to both early and late onset pre-eclampsia, however, several risk factors had quantitatively different associations with the 2 subtypes of pre-eclampsia**.** Pre-eclampsia causes significant maternal complications, especially early onset pre-eclampsia. Outcomes of babies of women with early onset pre-eclampsia are significantly worse than for those who presented later. Overall, women presenting with pre-eclampsia after 34 weeks have generally good maternal and fetal outcome.

2. INTRODUCTION

2.1 Introduction and literature review

Hypertensive disorder of pregnancy affects 10% of pregnancies. They account for 18% of maternal mortality worldwide. (Hutcheon, Lisonkova and Joseph, 2011)

There are broad categories in the classification of hypertensive disorder in pregnancies. According to the Malaysian Ministry of Health Guidelines which is based on International Society for the Study of Hypertension in Pregnancy (ISSHP), they can be classified as chronic hypertension, gestational hypertension, pre-eclampsia (de novo or superimposed on chronic hypertension), and white coat hypertension. (Brown *et al.*, 2018)

Chronic hypertension refers to high blood pressure diagnosed before pregnancy. As many women will not have had their blood pressure measured close to pregnancy, in practice, we rely upon the first-trimester blood pressure to define normal or high blood pressure in these women. (Brown *et al.*, 2018)

Gestational hypertension is defined as de novo hypertension after 20 weeks gestation, in the absence of proteinuria and without biochemical or hematological abnormalities. (Brown *et al.*, 2018)

Pre-eclampsia is diagnosed by hypertension and the co-existence of one or more of the following new-onset conditions, which are; proteinuria, evidence of maternal organ dysfunction, and/or uteroplacental insufficiency. (Brown *et al.*, 2018)

Pre-eclampsia is a major cause of maternal morbidity. This includes a 2 to 4-fold increased risk of long-term hypertension, a doubling of the risk of cardiovascular mortality and major cardiovascular events, and 1.5 fold increased risk of stroke. It is also associated with adverse fetal outcomes including intra uterine growth restriction, preterm birth, placenta abruption, fetal distress, and fetal death in utero. Most of the morbidity is concentrated among pregnancies

complicated by pre-eclampsia or eclampsia, and for every woman who dies, approximately 20 others suffer severe morbidity. (Abalos *et al.*, 2014)

The crude incidence of pre-eclampsia was 2.3%, ranging from 1.2% to 4.2% across regions. In a review by WHO, the incidence of pre-eclampsia was 2.3% in a developing region and 0.8% in a developed region. (Abalos *et al.*, 2014)

Based on the Malaysia Clinical Research Centre (CRC) review of hypertensive disorder in pregnancy in the years 2011 & 2012, the incidence of hypertensive disorder in the group was 4.3% and 3.8% respectively. The data showed that the incidence of pre-eclampsia/eclampsia was 19% and chronic hypertension with superimposed pre-eclampsia was 6%. (Rohani *et al.*, 2012)

The prevalence of pre-eclampsia in Hospital Universiti Sains Malaysia was about 1.4 % (Mahamooth, 2018)

Pre-eclampsia is a multisystem disorder without unknown cause that is specific to human pregnancy. It is characterized by the abnormal vascular response to placentation that is associated with increased systemic vascular resistance, enhanced platelet aggregation, activation of the coagulation system, and endothelial cell dysfunction. (Sibai, Dekker and Kupferminc, 2005)

The clinical presentation of pre-eclampsia can exhibit as either a maternal syndrome (hypertension and proteinuria with or without other multisystem abnormalities) or fetal syndrome (fetal growth restriction, reduced amniotic fluid, and abnormal oxygenation). (Sibai, Dekker and Kupferminc, 2005)

The disorder is heterogenous for which pathogenesis can differ in women with various risk factors. Pathogenesis of pre-eclampsia in nulliparous women may differ from that in women with preexisting vascular disease, multifetal gestation, diabetes Mellitus, or previous pre-

eclampsia. Additionally, the pathophysiology of the disorder leading to onset before 34 weeks' gestation could differ from that developing at term, during labour, or postpartum.(Sibai, Dekker and Kupferminc, 2005)

So far, a limited number of studies are available in the literature that analyzed in detail the differences between early onset pre-eclampsia and late onset pre-eclampsia, taking into account the International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria. Although the diagnostic criteria for early onset pre-eclampsia and late onset pre-eclampsia are the same, the are some uncertainties about the maternal and fetal outcomes. It is thought that EOP poses a high risk to both mother and fetus, whereas LOP may present with less severe clinical symptoms

2.1.1 Hypertension in pregnancy

Hypertension in pregnancy should be defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90mmHg, based on the average of at least two measurements, taken at least 15 minutes apart, using the same arm. (Magee *et al.*, 2014)

According to Malaysian Ministry of Health Guideline, which was base on the International Society for the Study of Hypertension in pregnancy (ISSHP), the hypertensive disorder in pregnancy can be classified as:

1. Hypertension known before 20 weeks; chronic hypertension, white coat hypertension, and masked hypertension
2. Hypertension arising de novo at/after 20 weeks; transient gestational hypertension, gestational hypertension, and pre-eclampsia (de novo or superimposed on chronic hypertension)

Chronic hypertension refers to high blood pressure diagnosed prior to pregnancy. As many women will not have had their blood pressure measured close to pregnancy, in practice, we rely upon first-trimester blood pressure to define normal high blood pressure in these women. Most cases of chronic hypertension will be due to essential hypertension, usually accompanied by a family history of hypertension and often overweight or obesity. Other secondary causes of hypertension are less common and in this age group are usually underlying primary renal parenchymal disorders and less commonly fibromuscular hyperplasia of the renal arteries or primary hyperaldosteronism. (Magee *et al.*, 2014)

A transient hypertensive effect should be defined as office systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90mmHg which is not confirmed after rest, or on repeat measurement on the same or subsequent visit. (Magee *et al.*, 2014)

A white coat hypertensive effect refers to blood pressure that is elevated in the office pressure (ie, systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90mmHg) but ambulatory or home blood pressure monitoring systolic BP is < 135mmHg and diastolic BP is < 85mmHg. (Magee *et al.*, 2014)

Gestational hypertension is defined as de novo hypertension after 20 weeks gestation, in the absence of proteinuria and without biochemical or hematological abnormalities.

A masked hypertensive effect refers to BP that is normal in the office (ie, systolic BP < 140 mmHg or diastolic BP ≥ 90mmHg) but elevated by ambulatory or home blood pressure monitoring (ie, systolic BP ≥ 135 mmHg or diastolic BP ≥ 85mmHg) (Magee *et al.*, 2014)

Pre-eclampsia is diagnosed by hypertension and the co-existence of one or more of the following new onset conditions, which are:

1. Proteinuria (spot urine protein/creatinine ≥30mg/mmol or ≥300mg/day or at least 1gm/L [2+] on a dipstick testing)
2. Maternal organ dysfunction:
    - renal insufficiency (creatinine ≥ 90umol/L or 1.02mg/dL)
    - liver involvement (elevated transaminases at least twice upper limit of normal ± right upper quadrant or epigastric abdominal pain)
    - neurological complications (examples include eclampsia, altered mental status, blindness, stroke, more commonly hyperreflexia when accompanied by clonus, severe headache when accompanied by hyperreflexia, persistent visual scotomata)
    - hematological complications (thrombocytopenia - platelet count < 150000/dL, DIC, hemolysis)

3. Uteroplacental dysfunction (fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, or stillbirth)

Pre-eclampsia superimposed on chronic hypertension is diagnosed when a woman with chronic essential hypertension develops any of the maternal organ dysfunction consistent with pre-eclampsia. (Magee *et al.*, 2014)

Early onset pre-eclampsia is the occurrence of pre-eclampsia before 34 weeks gestation and late onset pre-eclampsia develops at or after 34 weeks gestation (Tranquilli *et al.*, 2013).

2.1.2 Prevalence of pre-eclampsia

The crude incidence of pre-eclampsia was 2.3%, ranging from 1.2% to 4.2% across regions. In a review by WHO, the incidence of pre-eclampsia was 2.3% in a developing region and 0.8% in a developed region. (Dolea and Abouzahr, 2003)

In a study done by Seema Das et all, the incidence of pre-eclampsia in Nepal is about 1.8%. (Das *et al.*, 2019)

A secondary analysis of the WHO Global Survey on Maternal and Perinatal Health showed that the prevalence of pre-eclampsia/eclampsia is about 4%, however, there are variations between countries. Across the region, the prevalence ranged from less than 1% in Angola to 8% in Brazil. In general, the prevalence in Asian countries is about 3%, with the highest in the Philippines which is 5.6%, and the lowest in Vietnam which is 1%. (Bilano *et al.*, 2014)

They attributed the variation of the prevalence were due to the variability in maternal risk factors distribution and also the differences in facility and countries characteristic such as diagnostic capacities or accessibility of services. (Bilano *et al.*, 2014)

Based on the Malaysia Clinical Research Centre (CRC) review of hypertensive disorder in pregnancy in the years 2011 & 2012, the incidence of hypertensive disorder in the group was 4.3% and 3.8% respectively. The data showed that the incidence of pre-eclampsia/eclampsia was 19% and chronic hypertension with superimposed pre-eclampsia was 6%. (Rohani *et al.*, 2012)

The prevalence of pre-eclampsia in Hospital Universiti Sains Malaysia based on a previous study was about 1.4 % (Mahamooth, 2018)

2.1.3 Pathogenesis of pre-eclampsia

The widely accepted pathogenesis of pre-eclampsia is a deficiency of trophoblastic invasion that leads to endothelial dysfunction and exaggerated inflammatory response. (Raymond and Peterson, 2011). In pre-eclampsia, there is lacking physiological change in myometrial segments of the spiral arteries because of reduced trophoblastic invasion. The spiral arteries remain narrow and the mean external diameters of the spiral arteries in women with pre-eclampsia are less than half of the similar vessels from uncomplicated pregnancies (Myatt and Webster, 2009). Blood supply to the fetus is then restricted, leading to deficient uteroplacental circulation and a poorly perfused ischemic and hypoxic placenta (Carty, Delles and Dominiczak, 2008). The poorly perfused and hypoxic placenta is thought to synthesize and release increased amounts of vasoactive factors, disrupt syncytial architecture, and contribute to endothelial cell dysfunction. This leads to an exaggerated inflammatory response by inducing an alteration in the balance of circulating levels of several factors, including angiogenic factors, pro-inflammatory cytokines, and other immunological factors Chronic hypoxia triggers oxidative stress and increases placental apoptosis, necrosis, and shedding of placental-produced debris (Grill *et al.*, 2009).

Abnormal placental development is believed to be more strongly associated with early onset pre-eclampsia, whereas late onset pre-eclampsia is believed to occur secondary to maternal microvascular disease, such as long-term hypertension, or to reflect maternal genetic disposition. This distinction is further supported by the fact that late onset pre-eclampsia is usually associated with a normally grown baby with no signs of growth restriction, normally or slightly altered behavior of uterine spiral arteries, and no change in blood flow of umbilical arteries (Oudejans *et al.*, 2007)

In contrast, early onset pre-eclampsia is usually associated with fetal growth restriction, inadequate and incomplete trophoblast invasion of spiral arteries, changes in blood flow within the placental bed, and increased peripheral resistance of placental vessels. Placenta from early onset pre-eclampsia also has been demonstrated to be associated with abnormal placenta morphology (Huppertz, 2008).

Another factor contributing to the pathogenesis of pre-eclampsia is an imbalance in the factors promoting angiogenesis. Among all, the vascular endothelial growth factor (VEGF) system has gained the most attention concerning pre-eclampsia. VEGF and placenta growth factor (PIGF), are thought to contribute to normal trophoblast proliferation and implantation. VEGF stabilizes endothelial cells in mature blood vessels, and PIGF is predominantly expressed by trophoblasts and is thought to stimulate angiogenesis under the condition of ischemia, inflammation, and wound healing (Wang, Rana and Karumanchi, 2009). VEGF and PIGF are found to be significantly reduced in women with pre-eclampsia. And multiple studies show that second and third-trimester levels of PIGF seem to be lower in women with early onset pre-eclampsia than in those with late onset pre-eclampsia (Wang, Rana and Karumanchi, 2009).

Soluble Fms like tyrosine kinase (sFlt1) is a circulating anti-angiogenic protein that acts as an antagonist by binding VEGF and PIGF, preventing interaction with their receptor. It has been hypothesized that sFlt1 may cause the maternal endothelial dysfunction that is characteristic of pre-eclampsia. Placental expression of sFlt1 is increased in pre-eclampsia. Although both early and late onset pre-eclampsia is associated with the altered plasma level of sFlt1, the alterations are more pronounced in early onset versus late onset pre-eclampsia (Masuyama *et al.*, 2006).

Dysregulation of the immune system is also thought to play a key role in the pathogenesis of pre-eclampsia. In normal pregnancy, the female immune system undergoes significant changes to allow for immunologic survival of the fetus for the duration of the pregnancy, manifested

by activation of monocytes and granulocytes of the endothelium, in addition, to an increase in systemic oxidative stress. However, the response is exaggerated in pre-eclampsia, believed due to maternal-fetal immune maladaptation (Myatt and Webster, 2009)

Syncytiotrophoblast microparticles (STBMs), are believed to be one of the stimuli for the systemic response and endothelial cell damage observed in pre-eclampsia. It is shed into maternal circulation in a higher amount compared with normal pregnancy. Early onset pre-eclampsia has been associated with increased STBM levels compared with normal pregnancy, whereas, in late onset pre-eclampsia, the value has not been found to differ significantly from controls (Goswamia *et al.*, 2006).

Many other studies looking at the factors thought to play a role in normal placental development, such as PIGF, sFlt, VEGR-1, endostatin, and PP-13, have been found to be more regulated or better predictors of early onset pre-eclampsia in the comparison with late onset pre-eclampsia (Raymond and Peterson, 2011).

2.1.4 Risk factors pre-eclampsia

Risk factors for eclampsia represent a bewildering array of causative antecedents that reflect the disease's complexity. Nulliparous women have a three-fold higher risk of pre-eclampsia compared with multiparous women (Hutcheon, Lisonkova and Joseph, 2011). However, the frequency and severity of the disease are substantially higher in women with multifetal gestation, chronic hypertension, previous pre-eclampsia, pregestational Diabetes Mellitus, and pre-existing thrombophilia. Older maternal age and obesity also increase the risk of pre-eclampsia. (Hutcheon, Lisonkova and Joseph, 2011)

A study by Seema Das et all in Nepal found that there is an increased risk for pre-eclampsia for women with maternal age above 35 years old, gestational age below 37 weeks, twin pregnancy, chronic hypertension, urinary tract infection, gestational diabetes, and primiparous.

The secondary analysis of the WHO Global Survey on Maternal and Perinatal Health showed that the risk factors for pre-eclampsia to be a history of chronic hypertension, BMI more than 35kg/m2, severe anemia, underlying cardiac or renal disease, and nulliparity. (Bilano *et al.*, 2014)

2.1.4.1 Nulliparity

Pre-eclampsia has long been considered a disorder of primigravid women. Nullipara is six to eight times more susceptible to pre-eclampsia than multipara (Badria and Amarin, 2005). One of the etiological theories of pre-eclampsia is the involvement of the immune system. It has been postulated that maternal immune maladaptation to her fetus is a possible cause for the increased risk of pre-eclampsia in nulliparae. The protective effect of multiparity is however lost with the change of partner.

One meta-analysis of 26 original studies that were carried out found that there is a 1.4-5.5 higher risk of pre-eclampsia was observed in primiparous women in all studies (Luo *et al.*, 2007).

2.1.4.2 Age

The causes of pre-eclampsia have been linked to multiple factors. One of the suggested risk factors for pre-eclampsia is advanced maternal age. In western countries, maternal age at first delivery has been steadily increasing. In a study on primiparous women in Finland, the women more than 35 years old were 1.5 times more likely to have pre-eclampsia compared to women under 35 years of age. They also found that among pre eclamptic women, adverse pregnancy outcome was more common in women more than 35 years of age, such as Caesarean section, preterm deliveries, and impaired fetal growth (Lamminpää *et al.*, 2012).

In another study by Phupong V, they found that maternal age of more than 35 years carried an increased risk of developing pre-eclampsia. This may be related to the progressive vascular endothelial damage that occurs with maternal aging and obstruction of maternal spiral arteriolar lumina by atherosis (Luealon and Phupong, 2010).

A study conducted by Bestari et al found that maternal age above 35 years old increases the risk of poor maternal and neonatal outcomes in a pre-eclamptic patient. Advanced maternal age indeed increased the maternal outcome in pre-eclamptic patients 3 fold higher. They have found that there was an increased risk of postpartum hemorrhage and an increased rate of Caesarean section within this group (Dianing Tyas *et al.*, 2019)

2.1.4.3 Obesity

High BMI has been associated with an increased risk of pre-eclampsia. In a study by Mostello et al, there is a progressive increase in the risk of pre-eclampsia as BMI increases to the overweight and obese range (Mostello *et al.*, 2002)

Some authors have proposed a pathophysiologic connection between obesity, insulin resistance, and pre-eclampsia. Both obesity and pre-eclampsia may be manifestations of insulin resistance syndrome. Insulin, at the high levels that are associated with the insulin resistance of obesity, may regulate intracellular cation pumps that affect vascular tone and blood pressure, stimulate the sympathetic nervous system, or induced hypertrophy of vascular smooth muscle. Increased levels of vasoconstrictive peptides that are associated with hyperinsulinemia may contribute to the endothelial injury that is characteristic of both pre-eclampsia and the insulin resistance syndrome.

In a study by E Pare et al, they found that there was a dose-response effect between BMI and pre-eclampsia (Paré *et al.*, 2014). Even being overweight is independently associated with an increased risk of pre-eclampsia and severe pre-eclampsia. Their study found that being overweight or obese was the most important risk factor for pre-eclampsia with an attributable risk percent for BMI greater than 25 of 64.9%. However, following analysis for early pre-eclampsia, obesity was not significantly associated with early onset pre-eclampsia.

Sibai et al found that the risk of pre-eclampsia increased with the percent above the desirable weight.

2.1.4.4 Chronic hypertension

The 2019 National Institute for Health and Care Excellence (NICE) guidelines classify a woman as at high risk of pre-eclampsia if there is a history of hypertensive disease during previous pregnancy or a maternal disease including chronic kidney disease, autoimmune disease, diabetes, or chronic hypertension.

In a study by Chappell et all, involving 822 women with chronic hypertension, the incidence of superimposed pre-eclampsia was found to be 22%. Of note, 44% of this 22% developed superimposed pre-eclampsia before 34 weeks of gestation, a rate that stands in contrast to the pattern seen in women without chronic hypertension, who more commonly developed pre-eclampsia closed to term (Chappell *et al.*, 2008)

A study by Lisonkova and Joseph found that older maternal age, unmarried status, and male sex of infant are typical of both early onset and late onset pre-eclampsia. However, they have found that chronic hypertension, congenital anomalies, and African American race are strongly associated with early onset pre-eclampsia (Lisonkova and Joseph, 2013).

Moreover, in a study by Aksornphusitaphong and Phupong, a history of chronic hypertension was significantly associated with an increased risk of only early onset pre-eclampsia (Aksornphusitaphong and Phupong, 2013a)

2.1.4.5 Diabetes Mellitus

Preexisting diabetes is a risk factor for pre-eclampsia. In comparison to the relatively low incidence of pre-eclampsia in non-diabetic women (2-7%), pre-eclampsia is diagnosed in 15-20% of pregnancies in women with type 1 diabetes and 10-14% in women with type 2 diabetes. Obesity is a shared risk factor for both pre-eclampsia and type 2 diabetes, however, the greater pre-eclampsia risk among women with type 2 diabetes persists even when women are matched for BMI (Weissgerber and Mudd, 2015)

In a population-based study of deliveries in Washington state, preexisting diabetes was a risk factor for both early onset and late onset pre-eclampsia.

In a retrospective investigation of 647 392 pregnancies in the German Perinatal Quality Registry examining the relation between GDM and pre-eclampsia while controlling for common risk factors, the authors found that the odds of pre-eclampsia were increased among women with GDM. These findings concur with other birth registry studies in Canada and Sweeden, confirming that GDM is an independent risk factor for pre-eclampsia.

When compared to women with healthy pregnancies, researchers have identified many maladaptations to pregnancy that are present in both pre-eclampsia and GDM. This includes endothelial dysfunction, angiogenic imbalance, increased oxidative stress, and dyslipidemia.

2.1.5 Maternal outcome of pre-eclampsia

Pre-eclampsia is associated with substantial maternal complications both acute and long term. Women with pre-eclampsia and eclampsia had a 3 to 25 fold increased risk of severe complications such as abruptio placenta, thrombocytopenia, disseminated intravascular coagulation, pulmonary edema, and aspiration pneumonia (Ghulmiyyah and Sibai, 2012).

Severe pre-eclampsia is associated with an increased risk of maternal mortality (0.2%) and increased rates of maternal morbidities such as convulsions, pulmonary edema, acute renal or liver failure, liver hemorrhage, disseminated intravascular coagulopathy, and stroke. These complications are usually seen in women who develop pre-eclampsia before 32 weeks gestation and in those with preexisting medical conditions (Ghulmiyyah and Sibai, 2012).

Bellamy et al showed that after a pregnancy complicated by pre-eclampsia, women had an increased risk of hypertension, ischemic heart disease, stroke, and venous thromboembolism. (Bellamy *et al.*, 2007)

The death that occurs secondary to pre-eclampsia mainly results from eclampsia, uncontrolled hypertension, or systemic inflammation. Most of these maternal deaths are caused by intracerebral hemorrhage (Bellamy *et al.*, 2007).

2.1.6 Perinatal outcome of pre-eclampsia

The pathogenesis of pre-eclampsia is complex and not fully understood, however, it is known to involve dysfunctional placentation, systemic inflammation, and oxidative stress. Abnormal placentation occurs due to the failure of appropriate remodeling of the spiral arteries, resulting in higher resistance to placental blood flow and hypoperfusion of the placenta. This causes chronic ischemia and reduced blood flow to the developing fetus. These maladaptive processes can precipitate fetal hypoxia and adverse outcome include IUGR, preterm birth, oligohydramnios, placental abruption, fetal distress, and fetal death in utero. The frequency of fetal complications differs depending on the onset of pre-eclampsia. Early onset pre-eclampsia has been associated with significantly higher rates of adverse outcomes for the fetus, including IUGR, oligohydramnios, and fetal death (Fox *et al.*, 2019).

2.1.7 Early onset pre-eclampsia and late onset pre-eclampsia

A review by Raymond and Peterson in 2011 found that pre-eclampsia has been characterized by 2 different disease entities; which are early onset and late onset pre-eclampsia. Early onset is usually defined as pre-eclampsia that develops before 34 weeks of gestation whereas late onset occurs at or after 34 weeks' gestation. They are associated with different maternal and fetal outcomes, biochemical markers, risk factors, heritability, and clinical features (Raymond and Peterson, 2011).

Early onset pre-eclampsia is considered a fetal disorder that is typically associated with placenta dysfunction, reduction in placental volume, intrauterine growth restriction, abnormal uterine and umbilical artery Doppler evaluation, low birth weight, multiorgan dysfunction, perinatal death, and adverse maternal and neonatal outcomes. (Raymond and Peterson, 2011)

Meanwhile, late onset pre-eclampsia is considered a maternal disorder, a result of maternal constitutional disorder which is more often associated with a normal placenta, larger placenta volume, normal fetal growth, normal uterine and umbilical artery Doppler evaluation, normal birth weight, and more favorable maternal and neonatal outcome (Raymond and Peterson, 2011).

Lisonkova et al looked at the risk factors and outcomes of early onset and late onset pre-eclampsia and found that even though they share some etiological features, there are differences in regard to several risk factors and lead to different outcomes (Lisonkova *et al.*, 2014)

The results showed that the effect of risk factors such as race, nulliparity, chronic hypertension, and diabetes vary according to the subtype of pre-eclampsia. For instance, they found that congenital anomalies were more strongly associated with early onset disease, suggesting the

presence of associated placental abnormalities that affect perfusion and result in early onset disease.

On the contrary, a stronger positive association between diabetes Mellitus and late onset pre-eclampsia suggests that relative placental insufficiency is more likely to occur in diabetic pregnancies with a larger fetus.

In another study done by Lisonkova et al, regarding the maternal morbidity associated with early and late onset disease, they have found that the rate of severe maternal morbidity was highest among women with early onset pre-eclampsia, particularly respiratory, cardiovascular, and acute renal failure when compared with women without early onset disease (Lisonkova *et al.*, 2014).

A study by Anna Wojtowicz et al. also support these findings whereby women with early onset pre-eclampsia have a more frequent occurrence of severe cardiorespiratory complication, hematological, hemolysis, adverse fetoplacental conditions, and severe fetoplacental complication than women with late onset pre-eclampsia (Wójtowicz *et al.*, 2019)

Nevertheless, their study found that early onset and late onset pre-eclampsia share a common risk factor which is primiparity. However, they found no difference in risk factors between these 2 groups.

On the contrary, Lisonkova et al. found that African American race, chronic hypertension, and congenital anomalies were more strongly associated with early onset pre-eclampsia, whereas younger maternal age, nulliparity, and Diabetes Mellitus were more strongly associated with late onset disease. (Lisonkova and Joseph, 2013)

Adisorn et al. also found that chronic hypertension increased the risk of early onset pre-eclampsia, while a family history of chronic hypertension was associated with late onset pre-eclampsia. Their study found that both early and late pre-eclampsia share other risk factors

such as a family history of diabetes Mellitus, high pre-pregnancy body index ≥ 25kg/m^2, and weight gain ≥ 0.5kg/ week (Aksornphusitaphong and Phupong, 2013a)

Karuna Kanta et al. also concluded that all the maternal complications like eclampsia, sepsis, systemic disorder, ICU admission, and maternal deaths were higher in early onset pre-eclampsia as compared to late onset. Primiparity, high BMI, family history of pre-eclampsia, and male sex of fetus were found to be an important risk in the development of early onset pre-eclampsia (Kanta Das *et al.*, 2018)

A study conducted by F. Petitt et al found that early onset pre-eclampsia is associated with worse neonatal outcomes than later onset pre-eclampsia. However maternal complications including the development of severe hypertension, neurological, renal, hepatic, and thrombocytopenic complication occurred with similar frequency across all gestation of presentation with gestational age (Pettit *et al.*, 2015)

A study done by Julie et al, regarding the severity of placental findings in women according to gestational age, they have found that the rates of the placental lesion in pre eclamptic patients were significantly higher than the normotensive control subjects, particularly in the early gestational age (Moldenhauer *et al.*, 2003)

2.2 Justification of study

Although many studies have quantified the effects of pre-eclampsia on maternal and neonatal outcomes, maternal morbidity and mortality rates associated with early onset and late onset pre-eclampsia have not been thoroughly evaluated. The majority of the literature on pre-eclampsia are evaluating late onset pre-eclampsia. This will not be representing the whole spectrum of pre-eclampsia.

In addition, although the studies that were done found a significant difference in regards to maternal outcome and perinatal outcome between these early and late onset groups, other studies have been published that have conflicting results.

The limited number of studies and reviews focusing on early versus late onset pre-eclampsia makes it difficult to make any firm conclusions regarding the differences between these two groups.

In addition to the limited numbers of literature comparing early versus late pre-eclampsia worldwide, specifically in Malaysia, there is no published data available regarding gestational age-specific incidence, risk factors, and outcome of early onset and late onset pre-eclampsia yet.

This particular study goes into detail on the factors associated with poor maternal and perinatal outcomes in early onset pre-eclampsia.

Based on the outcome of this study, we will be able to tailor our management according to the age-specific onset of pre-eclampsia.

3. OBJECTIVES

3.1 General objectives

To study the patients diagnosed with pre-eclampsia who were delivered in Hospital Universiti Sains Malaysia, Kubang Kerian from 2016 to 2020.

3.2 Specific objectives

1. To determine the rate of early, and late onset pre-eclampsia in Hospital USM
2. To determine the risk factors between early and late onset pre-eclampsia.
3. To determine the maternal outcome of early and late onset pre-eclampsia and fetal outcome of early and late onset pre-eclampsia.
4. To determine the associated factors for poor maternal and perinatal outcomes for early and late onset pre-eclampsia.

4. METHODOLOGY

4.1 Study designs, setting, and duration

This study was conducted in the Department of Obstetrics and Gynaecology in Hospital Universiti Sains Malaysia. It is a tertiary hospital and one of the referral center for all the hospitals in Kelantan. This study was conducted from January 2016 until December 2020.

4.2 Study population

Study participants include all singleton deliveries in Hospital Universiti Sains Malaysia, with the diagnosis of pre-eclampsia.