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Clinical risk factor of preeclampsia: a five-year retrospective study in Bali Royal Hospital, Bali-Indonesia

Abstract

Prevalence of preeclampsia worldwide is quite high, treatment for preeclampsia currently does not give satisfying result, overcome the risk factor are the key to prevent the disease. The aim of this study is to explore the clinical risk factor of preeclampsia in Bali Royal Hospital. A case control study was conducted in Bali Royal Hospital between June 2013-June 2018. Consecutive methods are used to find samples in the study. Total of 80 samples was involved in current study, divided into two groups evenly (case and control group). Statistical analysis using chi-square test, odds ratio calculation, and logistic regression models were used. This study found an association of clinical risk factors with the occurrence of preeclampsia. Chronic hypertension is the most important risk factor for the occurrence of preeclampsia (adjusted OR: 8.44; p = 0.008). Therefore, advanced maternal age, obesity, history of preeclampsia, chronic hypertension, multiple fetal pregnancies, and nulliparity showed to be the risk factors for preeclampsia.

Keywords: *pregnancy, hypertension, preeclampsia, risk*

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Introduction

Preeclampsia in pregnant women occurs around 3% -8% worldwide. Pregnant women with preeclampsia could cause mortality if not treated properly. Mothers die more than 60,000 worldwide due to preeclampsia and its complication. In the United States approximately 20% of maternal deaths with preeclampsia appears each year. In developing countries, prevalence starts from 1.8% to 16.7%[(1)].

The percentage of maternal deaths due to hypertension exceeds other causes of death in mothers such as 2% sepsis, 8% abortion, and 13% bleeding. Pregnancy with preeclampsia has many complications, can affect the current pregnancy, maternal safety, causing low birth weight in newborn infant, preterm birth to perinatal death. Women with severe preeclampsia have a large impact on the fetus. The impact on the fetus is malnutrition resulting from uteroplacental vascular insufficiency, resulting in growth retardation[(2,3)].

Many theories have been developed to explain the mechanism of the occurrence of preeclampsia such as immunological theory, trophoblast invasion disorder, genetic, hormonal and inflammatory factors, hypoxia and oxidative stress, but until now there has been no theory that can clearly explain the occurrence of preeclampsia[(4)].

Treatment for preeclampsia is currently unable to overcome problems in pregnant women properly so we need to know the risk factors for preeclampsia so that it can be avoided. Research conducted by Quan et al. in China shows the risk factors affecting pregnant women with preeclampsia such as history of hypertension, hyperlipidemia, excess body mass index (BMI), history of diabetes mellitus, and advanced age[(5)].

Mothers with preeclampsia are at risk for fatal ischemic heart disease, because preeclampsia is a risk factor for cardiovascular disease. Preeclampsia is also closely related to the risk of kidney disease. This high risk of cardiovascular and kidney diseases causes mothers with a history of preeclampsia to modify their lifestyles in order to reduce the risk of complications[(6,7)].

Research conducted by Widhyaningrum et al. in Sanglah General Hospital Denpasar, Bali-Indonesia found 195 mothers with preeclampsia with the highest prevalence in 35 years old. Knowing the risk factors for preeclampsia makes it easier to make an early detection in high-risk mothers to provide an opportunity for proper monitoring and clinical management, as well as identifying early complications[(8)].

Bali Royal Hospital is one of the public hospitals in Denpasar city, Bali-Indonesia that provides comprehensive obstetric and gynecology services. Data on pregnant women in this hospital are still limited. Information about emergency cases and complications in pregnancy such as preeclampsia in this hospital are also still limited, so based on the description above this study was conducted with the aim to determine the clinical risk factors for preeclampsia.

Methods

Study design using case-control model evaluated the clinical risk factors of preeclampsia through medical records investigation at Bali Royal hospital during the period June 2013 to June 2018. Clinical risk factors performed in this study were advanced maternal age, BMI, multiple pregnancy, chronic hypertension, previous history of preeclampsia, and parity. Total sample study involved is 80, divided into two equal groups evenly, case group (person with preeclampsia) and the control group (person without preeclampsia). Sampling in this study was conducted through consecutive methods. The inclusion criteria in this study were complete medical record files with a complete diagnosis of preeclampsia and its clinical risk factors. Exclusion criteria in this study are other conditions that resemble preeclampsia such as epilepsy, chronic kidney disease, and malignancy. The analysis in this study using SPSS version 25.0 software. Chi-square test and odds ratio calculation were used to assess the role of clinical risk factors for preeclampsia on the incidence of preeclampsia, as well as logistic regression analysis that was used to see the most dominant clinical risk factors in the occurrence of preeclampsia.

Results

Current study used a case-control design to explore the clinical risk factors for preeclampsia in the Bali Royal Hospital in the period from June 2013 to June 2018. Data were collected through medical record search in 40 pregnant patients with preeclampsia as a case group and 40 pregnant patients without preeclampsia as control group. Subject characteristics can be seen in Table 1.

There was seen a difference in the mean age of mothers during pregnancy who have preeclampsia and those without preeclampsia. Maternal age at pregnancy with preeclampsia (31.50 ± 5.22) was greater than those without preeclampsia (27.97 ± 4.69) (p=0.002). In the BMI there are mean differences between preeclampsia mothers and those without preeclampsia. The BMI of mothers with preeclampsia (25.61 ± 2.29) was greater compared with those without preeclampsia (24.30 ± 1.70) (p=0.005). The results of the analysis of gestational age also have a mean difference between the groups of women with preeclampsia (35.42 ± 2.13) compared to the group of women who did not experience preeclampsia (36.72 ± 2.21) (p = 0.009) (Table 1).

Overall patients with preeclampsia as many as 42.5% were in the age group ≥35 years while of all study subjects who did not experience preeclampsia only 10% were in the age group ≥35 years. There was a significant association between age and preeclampsia in pregnant women (p=0.001). Odd ratio analysis obtained a value of 6.65 (95% CI: 1.98-22.27), which showed that mothers with a gestational age of ≥35 years were six times more likely to experience preeclampsia compared to mothers at <35 years. In the study subjects who had preeclampsia, as many as 45% had a history of preeclampsia before while only 10% of subjects who did not experience preeclampsia had a history of preeclampsia before. Previous history of preeclampsia had a significant association with the incidence of preeclampsia (p=<0.001). Odd ratio analysis obtained a value of 7.36 times (95% CI: 2.21-24.61) greater for preeclampsia than subjects who did not have a history of preeclampsia before (Table 2).

Based on the history of chronic hypertension, 57.5% of preeclampsia subjects had a history of hypertension before pregnancy while only 7.5% had no history of hypertension from the control group. There was a significant relationship between the history of hypertension with preeclampsia (p≤0.001). Through odd ratio analysis, it was obtained a value of 16.67 (95% CI: 4.40-63.30), subjects with a history of hypertension had a 16 times greater risk of experiencing preeclampsia compared with subjects who did not have a history of hypertension. Furthermore, subjects who experienced preeclampsia, as much as 65% were obese while subjects who did not experience preeclampsia were only 22.5% with obesity. There was a significant relationship between obesity and preeclampsia (p≤0.001). Through odds ratio analysis, it was obtained a value of 6.39 (95% CI: 2.38-17.15), subjects with obesity had a six times greater risk of experiencing preeclampsia compared with subjects who were not obese. In subjects who had preeclampsia, there were 35% of subjects with multiple fetal pregnancies while there were 12.5% of subjects who did not experience preeclampsia with multiple fetal pregnancies. Multiple fetal pregnancies with preeclampsia have a significant relationship (p=0.018). Odd ratio analysis obtained a value of 3.77 (95% CI: 1.21-11.79), which showed that multiple fetal pregnancies have a risk three times greater for preeclampsia compared with mothers of single fetal pregnancies. In subjects who experienced preeclampsia 32.5% had primiparous parity, whereas in the group of mothers who did not experience preeclampsia only 14.7% had multiparity, there was a significant relationship between parity with the incidence of preeclampsia (p=0.023), mothers with primiparous parity had 2.8 times more risk large to experience preeclampsia compared with mothers who have multiparity status (Table 2).

The multivariate model shows that all variable has a significant value as a risk factor for preeclampsia, but there is one of the most important factors as a risk factor for preeclampsia, namely chronic hypertension (adjusted OR: 8.44; p=0.008), but based on the determinant coefficient in this study, value of 0.544 was found which showed that all variables in this study are only able to explain its role as a risk factor for preeclampsia by 54.4% while there are still 45.6% other variables that influence the incidence of preeclampsia outside of this study (Table 3).

Discussion

Advance Age and Preeclampsia

Findings of current study show age ≥35 years that is a risk factor for the occurrence of preeclampsia. Advanced maternal age has been associated with a higher risk for

Table 1 Subject characteristics

Characteristics	Preeclampsia (n=40)	Without preeclampsia (n=40)	*p*
Maternal age at pregnancy (years)	31.50 ±5.22	27.97 ±4.69	0.002
Body mass index (kg/m^2)	25.61±2.29	24.30±1.70	0.005
Gestational age (weeks)	35.42±2.13	36.72±2.21	0.009

Table 2 Analysis of clinical risk factor of preeclampsia in Bali Royal Hospital

Risk factor		Preeclampsia				OR	CI 95%	p
		Yes	%	No	%			
Age	≥35 years	17	42.5%	4	10%	6.65	1.98-22.27	0.001*
	<35 years	23	57.5%	36	90%			
Previous history of preeclampsia	Yes	18	45%	4	10%	7.36	2.21-24.61	<0.001*
	No	22	55%	36	90%			
Chronic hypertension	Yes	23	57.5%	3	7.5%	16.67	4.40-63.30	<0.001*
	No	17	42.5%	37	92.5%			
Obesity (BMI≥ 25 kg/m^2)	Yes	26	65.0%	9	22.5%	6.39	2.38-17.15	<0.001*
	No	14	35.0%	31	77.5%			
Multiple preganancy	Yes	14	35%	5	12.5%	3.77	1.21-11.79	0.018*
	No	26	65%	35	87.5%			
Nulliparity	Yes	13	32.5%	6	14.7%	2.80	1.43-12.46	0.023*
	No	27	67.5%	35	85.3%			

**significant (p<0.05)*

preeclampsia. Research by Mostello et al. regarding the incidence of preeclampsia in 17,773 pregnant women in USA, found that age over 36 years had a risk of 1.16 times greater for preeclampsia compared with 18-25 years of age (95% CI: 1.16-1.33; p<0.05)[9].

Aging is a result of genetic and epigenetic interactions in different cells and tissues during life, characterized by low levels chronic inflammation of arterial walls (pro-inflammation), stiffness, and elevated blood pressure. This situation is affected by modifications that occur in vascular smooth muscle cells (VSMC) and endothelial cells. An animal model study conducted by Sehgel et al. found a significant difference in VSMC stiffness between young mice with older mice, VSMC stiffness was four times greater in rats with old age compared to rats at a young age[10].

Intrinsic rigidity of VSMC will increase with age, apart from that the worsening condition is an increase in matrix metalloproteinase (MMP) along with aging. MMP increase is associated with an increase in Angiotensin-II (Ang II) which triggers vasoconstriction, water and salt retention of the kidneys and raises blood pressure. All of these mechanisms have a final impact on a failure of cardiovascular adaptation with age[11].

Table 3 Multivariate model of clinical risk factor in preeclampsia

Risk Factors	Coefficient	S.E	Wald	df	Adjusted OR	CI 95%	p
Age ≥35 years	1.62	0.81	3.97	1	5.06	1.02-24.94	0.046*
Previous history of preeclampsia	1.85	0.78	5.63	1	6.39	1.38-29.57	0.018*
Chronic hypertension	2.13	0.81	7.03	1	8.44	1.74-40.86	0.008*
Obesity (BMI≥25 kg/m^2)	1.48	0.67	4.89	1	4.40	1.18-16.32	0.027*
Multiple pregnancy	1.52	0.67	4.89	1	4.59	1.02-20.62	0.046*
Nulliparity	1.36	0.54	4.43	1	3.28	1.04-18.43	0.048*

**significant (p<0.05), R2=0.544*

Regarding the increased risk of preeclampsia in old age can be explained by the failure of cardiovascular adaptation that occurs at an older age. Under normal conditions the blood vessels will be refractory to the presence of various vasopressor stimuli such as MMP, Ang II, and norepinephrine, but in preeclampsia there is an overresponse from stimulation of vasopressor mediators, this condition is also influenced by the predisposition of older age which increases stiffness from VSMC, so that the whole thing will increase the risk of preeclampsia in pregnant women with older age[12].

Previous History of Preeclampsia

In this study, a previous history of preeclampsia was a risk factor for the occurrence of preeclampsia in subsequent pregnancies. An epidemiological cohort study conducted by Diaz et al. found that mothers with preeclampsia in their first pregnancy had a risk of 14.7% to experience preeclampsia in the second pregnancy, and mothers who had preeclampsia in the first and second pregnancies had 31.9% chance to experience preeclampsia in the third pregnancy. This gives an idea that the likelihood of preeclampsia will increase if a person has a history of preeclampsia in a previous pregnancy[13].

A study conducted by Wong et al. on clinical risk factors for preeclampsia in Germany, found that the history of preeclampsia in previous pregnancies was the most important factor for the occurrence of preeclampsia (OR: 2.94; 95% CI: 1.25-6.91; p=0.013) compared to others clinical risk factor such as obesity, multiple fetal pregnancies, diabetes, and autoimmune diseases[14].

Chronic Hypertension

Preeclampsia is a response to the mechanism of vasospasm. The basic change in the pathophysiology of preeclampsia involves vasospasm from systemic arterioles, endothelial dysfunction, and systemic target organ damage that results in various clinical symptoms due to decreased blood flow. A study by Quan et al. regarding clinical risk factors for preeclampsia in 558 patients with preeclampsia found that a history of hypertension was a clinical risk factor that most contributed to the occurrence of preeclampsia (adjusted OR: 7.487; 95% CI: 2.54-11.24; p=0.004)[5].

The study conducted by Villa et al. is a cohort study of 903 pregnant women with risk factors for preeclampsia. Mothers with chronic hypertension before pregnancy had a five times greater risk of experiencing mild preeclampsia (RR: 5.3: CI 95%: 2.4-9.8). Women with chronic hypertension have a 10-25% risk of developing preeclampsia compared to the general population who do not have chronic hypertension. This risk increases to 31% if the duration of chronic hypertension is more than four years[15].

Obesity and Preeclampsia

A study led by Wie et al in the population of pregnant women in Korea, found a significant difference (p<0.001) in the incidence of preeclampsia in the group of women with a low BMI (1.5%), in women with a normal BMI (1.9%), in women with an excess BMI (3.0%), and in women with obesity BMI (4.8%)[16].

Obesity and a high-fat diet will directly affect vascular remodeling and uteroplacental blood flow, which can cause ischemia and hypoxia to placenta. Under normal conditions of pregnancy vascular endothelial growth factor (VEGF) binds to VEGF receptor 1 (Flt 1) to increase triggers of neovascularization which will increase uteroplacental blood flow. However, there is a decrease in placental VEGF receptor interaction in conditions of pregnancy accompanied by obesity. This change causes reduction in uteroplacental perfusion and causes placental ischemia. The condition of placental hypoperfusion will increase the production of interleukin (IL)-6 and tumor necrosis factor (TNF)-α as pro-inflammatory maternal mediators who will later contribute to the onset of preeclampsia[17].

The condition of the placenta in obese person has a narrower villous area, a greater number of macrophages in placental villous tissue, and higher CD14 expression. Apart from that, higher amounts of

proinflammatory cytokines (i.e. leptin, IL-6, TNF-α and C-reactive protein) are also found in placentas of pregnant women who are obese[18]. In normal conditions, there is an increase in the secretion of TNF-α and VEGF, which is believed to trigger angiogenesis in the placenta to ensure blood flow to the uteroplacental circulation. TNF-α also has a role in regulating trophoblast; in the first trimester high TNF-α levels will cause apoptosis of the trophoblast. This has become a basic link of obesity to the occurrence of preeclampsia which is associated with the theory of trophoblast invasion failure[19].

Multiple Pregnancy and Preeclampsia

Findings of current study showed multiple fetal pregnancies were clinical risk factors for preeclampsia. Multiple fetal pregnancies have been known to be associated with an increased risk of preeclampsia. In mothers at the first pregnancy with a double fetus have a 12.3% chance of experiencing preeclampsia[13]. A population study conducted by Gudnadottir et al. found a higher proportion of multiple fetal pregnancies in the maternal group with preeclampsia (9.5%) compared to the maternal group without preeclampsia (5.2%) (p=0.004)[20].

Nulliparity and Preeclampsia

Nulliparity has been shown to be a risk factor for preeclampsia, the state of nulliparity increases the risk of preeclampsia up to three times greater (OR: 2.91; 95% CI: 1.29-6.61) based on systematic review[21]. New paternity also increases the risk of preeclampsia in a subsequent pregnancy. The association between nulliparity and preeclampsia suggests an immunological mechanism such that later pregnancies are protected against those paternal antigens[22]. Supporting this concept, previous pregnancy loss, increased duration of sexual activity before pregnancy, or prolonged pre-pregnancy cohabitation confer a lower risk of preeclampsia. Conversely, the risk of preeclampsia is increased with the use of barrier contraceptives, new paternity, and with donor sperm insemination[23].

Study Limitation

This study is only able to provide an overview of the clinical risk factors for preeclampsia, the use of medical records makes the causal value of this study to be reduced because of the possibility of recall bias. Furthermore, all of these variables are only able to explain 54.4% role as a risk factor for preeclampsia, further research is needed to explore other risk factors that play a role in preeclampsia beyond the variables explored in this study.

Conclusions

Advanced maternal age, obesity, history of preeclampsia, chronic hypertension, multiple fetal pregnancies, and nulliparity were showed to be the risk factors for preeclampsia. Furthermore, chronic hypertension showed to be the most dominant risk factor for the occurrence of preeclampsia. ■

Conflict of interests: The authors declare no conflict of interests.

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