Risk Factor of Preeclampsia in a Secondary Indonesian Hospital: A Case-Control Study

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Risk Factor of Preeclampsia in a Secondary Indonesian Hospital: A Case-Control Study

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Abstract

Background: Preeclampsia is a form of hypertension in pregnancy that leads to morbidity and mortality. Although the etiology remains unclear, there are some risk factors that are suspected to be associated with the development ofpreeclampsia. **Objective**: To find out the risk factors associated with the incidence of preeclampsia inAirlangga University Hospital. **Method**: This studyconducted an analytical-observational study with the hospitalized unmatchedbased case-control approach. 165 pregnant women were included. Data were analyzed in univariate, bivariate, and multivariate regression logistic and performed using statistical package for the social science (SPSS), $p < 0.05$ was considered statistically significant. **Results:** Pregnant women with preeclampsia were about 18 to 44 years old, with the average BMIis 31.9 kg/m^2. There are significant relation between family history of hypertension ($p = 0.000$), maternal age ($p = 0.004$), BMI ($p = 0.000$), pregnancy interval ($p = 0.009$), and chronic hypertension ($p = 0.007$) with the incidence of preeclampsia. In the multivariate analysis using logistic regression, family history of hypertension was the most dominant factor with OR: 3.374 and 95% CI: 1.454 – 7.830 compared to other factors such as maternal age (OR: 2.885; 95% CI: 1.311 – 6.347; p: 0.008) , and BMI (OR: 2.590; 95% CI: 1.525 – 4.400; p: 0.000). **Conclusion:** Family history of hypertension, maternal age, BMI, pregnancy interval, and chronic hypertension have a significant relationship with the incidence of preeclampsia. In multivariate analysis, family history of hypertension is the most dominant risk factor among others.

Keywords: *Risk factor, Preeclampsia, Hypertension in pregnancy*

Introduction

Preeclampsia is a form of hypertension in pregnancy that has a high impact on morbidity and mortality. Based on WHO[1], the criteria for preeclampsia is characterized by persistent hypertension with diastolic pressure ≥90mmHg accompanied by substantial proteinuria (>0.3g/24 hours). Preeclampsia that is not handled properly can develop into eclampsia and cause maternal death. The maternal mortality rate in the world is very high, there are around 810 deaths in women due to complications of pregnancy or childbirth around the world every day[2]. Preeclampsia is one of the three factors that dominate the causes of maternal mortality in Indonesia with an increasing proportion[3]. The prevalence of preeclampsia in each region is different and preeclampsia is a worldwide concern due to its morbidity and mortality.

Preeclampsia is hypertension with a new-onset at or after 20 weeks with one or more symptoms such as proteinuria, acute kidney injury, liver complication, neurological complications, hematological complication, and uteroplacental dysfunction[4]. Preeclampsia is also characterized by placental dysfunction and endothelial activation and coagulation as a maternal response to systemic inflammation[5]. The pathogenesis of

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preeclampsia is still not fully explained, several theories explain the occurrence of preeclampsia, but the placenta is considered to play an important role in preeclampsia. Ischemic placenta caused by incomplete spiral artery remodeling and the release of antiangiogenic factors to maternal circulation are suspected as the cause of preeclampsia[6]. Besides, several risk factors can trigger preeclampsia. By knowing risk factors from an early stage, efforts can be made to prevent and treat them more quickly to reduce mortality and morbidity due to preeclampsia. This can improve the quality of life for maternal and infants and reduce maternal mortality. Risk factors from a place to another can be different because of differences in human characteristics that can be affected by geography, culture, and lifestyle. Therefore, this study aimed to determine the risk factors that are typical or often occur in Indonesian women associated with the incidence of preeclampsia.

Method

This studyconducted an analytical-observational study with the hospitalized unmatched based case-control approach. 165 pregnant women with and without preeclampsia who delivered and had the medical record in Airlangga University hospital from August 2017 to December 2018 were included. Sampling was carried out by purposive random sampling technique and 55 was obtained as the minimum sample size calculated using Lemeshow formula for case-control study, with P_1= 0.52, P_2= 0.19[7], then added 30%. By a ratio of 1:2, the number of case and control samples were 55 and 110, respectively. The instrument of the research used secondary data in the form of a medical record. Data were analyzed in univariate, bivariate, and multivariate regression logistic. Univariate analysis was performed to analyze the character of each variable. Bivariate analysis, utilized Chi Square test and for the ineligible variable utilized Fisher's exact test were to find out the relationship of each risk factorto preeclampsia. Furthermore, multivariate regression logistic was performed to connect several independent variables to dichotomous dependent variable.

All Statistics were performed using a statistical package for the social science (SPSS) and $p < 0.05$ was considered statistically significant.

Results

In this research, pregnant women with preeclampsia were about 18 to 44 years old, with a mean age of 31 years. Meanwhile, the age of pregnant women without preeclampsia were about 17 to 40 years old, with an average age of 28 years. Pregnant women with preeclampsia had an average body mass index (BMI) of 31.19 kg/m^2 and 27.66 kg/m^2 in pregnant women without preeclampsia.

Maternal Previous History

The previous history related to previous maternal pregnancies, such as a history of intra-uterine growth restriction (IUGR), previous stillbirth, previous placental abruption, and a history of preeclampsia can only be assessed in pregnant women with nonprimigravidas (multigravidas). From 110 control groups, there were 67 multigravida pregnant women (69.91%). Meanwhile, in the case group, 38 (69.09%) out of 55 were multigravida pregnancies. Whereas,the previous history related to family history of hypertension can be assessed in all available samples.

Table 1. Results and Analysis of Maternal Previous History with Preeclampsia Incidence

Variable	Category	Without preeclampsia n (%)	Preeclampsia n (%)	p value
Family history of hypertension	No	90 (81.82)	31 (56.36)	0.000*
	Yes	20 (18.18)	24 (43.64)	
History of preeclampsia	No	65 (97.01)	36 (94.74)	0.619
	Yes	2 (2.99)	2 (5.26)	
IUGR History	No	66 (98.51)	37 (97.37)	1.000
	Yes	1 (1.49)	1 (2.63)	

*showing significance level of p<0.05

Maternal Characteristic

Maternal characteristics assessed in the form of maternal age, nulliparous, primigravida, BMI, assisted reproductive technology (ART), pregnancy interval, and new partners are presented in the following table.

Table 2. Result and Analysis of Maternal Characteristic with Preeclampsia Incidence

Variable	Category	Without preeclampsia n (%)	Preeclampsia n (%)	p value
Maternal Age	<20 years	6 (5.45)	3 (5.45)	0.004*
	20 – 35 years	87 (79.09)	31 (56.36)	
	>35 years	17 (15.45)	21 (38.18)	
Nulipara	yes	46 (41.82)	17 (30.91)	0.174
	No	64 (58.18)	38 (69.09)	
Primigravida	yes	43 (39.09)	17 (30.91)	0.303
	no	67 (60.91)	38 (69.09)	
IMT	18.5 – 24.9	39 (35.45)	4 (7.27)	0.000*
	25.0 – 29.9	37 (33.64)	17 (30.91)	
	≥ 30	34 (30.91)	34 (61.82)	
Pregnancy interval	<2 years	12 (17.91)	1 (2.63)	0.009*
	2 – 4 years	23 (34.33)	8 (21.05)	
	>4 years	32 (47.76)	29 (76.32)	
New partner	no	62 (91.18)	33 (86.84)	0.518
	yes	6 (8.82)	5 (13.16)	

*showing significance level p < 0.05

Analysis result in table 2 showed that in maternal's characteristic, there was a significant relationship between maternal age, BMI, and pregnancy interval with the incidence of preeclampsia. Besides, all pregnant women with and without preeclampsia in this research had their pregnancies without assisted reproductive technology (ART).

Maternal Comorbid Disease

The frequency distribution of comorbid diseases and the relation with preeclampsia were presented in Table 3 below.

Table 3. Result and Analysis of Maternal Comorbid Disease with Preeclampsia Incidence

Variable	Category	Without preeclampsia n (%)	Preeclampsia n (%)	p value
Chronic hypertension	no	107 (97.27)	47 (85.45)	0.007*
	yes	3 (2.73)	8 (14.55)	
Diabetes mellitus	no	109 (99.09)	52 (94.55)	0.108
	yes	1 (0.91)	3 (5.45)	
Infection	no	100 (90.91)	50 (90.91)	1.000
	yes	10 (9.09)	5 (9.09)	

* showing significance level of p < 0,05

The results of this analysis indicatedthat in comorbid diseases, there wasa significant relationship between chronic hypertension and the incidence of preeclampsia. Meanwhile, diabetes mellitus and infection did not have a significant relation with the incidence of preeclampsia.

Fetal Factor

The number of fetuses that were conceived by pregnant women with preeclampsia and pregnant women without preeclampsia was single. Thus, there were no multiple pregnancies in all samples. Likewise, a hydatidiform molar pregnancy is not found in all pregnant women with preeclampsia and pregnant women without preeclampsia.

Multivariate Analysis

Multivariate analysis was performed using logistic regressi by including variables that had a p value <0.25. Variables that had a p value <0.25 consisted family history of hypertension (p = 0.000), maternal age (p = 0.004), nulliparous (p =0.174), BMI (p =0.000), diabetes mellitus (p =0.108) and chronic hypertension (p =0.007). The pregnancy interval had a value of p <0.25, but it was not included in the logistic regression because the pregnancy interval only involved samples that had been pregnant before. Thus, it did not apply to samples with first pregnancies.

The logistic regression results showed that the iteration history table in block 0 or before the independent variable was included in the model N = 165 the value of -2 log-likelihood was obtained: 210.050. Degree of freedom (DF) = N-1 = 165-1 = 164. Chi-square (X2) table on DF 164 with probability 0.05 = 194.8825. The value of -2 log-likelihood (210.050)> X2 table (194.8825). Thus, it rejected H0. It showed that the model before the independent variable includeddid not fit with the data. The -2 log-likelihood value after the independent variable is entered (in the iteration history table block 1) 168.018 and the X2 table value on DF 158 is 188.3317. The value of -2 log-likelihood <X2 table, then H0 2qw accepted. It indicated that the model after

inserting the independent variable, is fitted with the data. The results of the omnibus test showed a significance of 0.000 (<0.05). Thus, it rejected H0. It indicated that the addition of the independent variable was fit with the data. The Cox & Snell R Square value of 0.225 and Nagelkerke R Square of 0.312 showed the ability of the independent variable to explain the dependent variable of 0.312 or 31.2%. The Hosmer and Lemeshow Test obtained a significance value of 0.175 (>0.05), which indicated that there was no significant difference between the model and its observation value. Therefore, the model can be accepted. This test was a goodness of fit test (GoF) to determine whether the model formed is correct or not. Independent variables that have a significant value>0.05 were excluded from the table. Thus, table 4 is formed.

Table 4. Logistic Regression Result

	pvalue	OR	95% C.I. forOR	
			Lower	Upper
Family history of hypertension	0.005	3.374	1.454	7.830
Maternal age	0.008	2.885	1.311	6.347
IMT	0.000	2.590	1.525	4.400

Discussion

The Relation of Previous History and Preeclampsia Incidence

This study showed a significant relationship between family history of hypertension with the incidence of preeclampsia (p = 0.000). This was in line with the previous studies[8,9]. Shamsi et al.[10]suggested that a family history of hypertension was an important risk factor. Preeclampsia in female families had a strong association with an increased risk of preeclampsia at early and intermediate onset. In contrast, male families have only a weak relation with intermediate and late onset preeclampsia[11]. A family history of hypertension is an inexpensive and easy sign to obtain, thus, asking for a family history of hypertension can be used as an inexpensive and feasible screening tool to monitor preeclampsia in early pregnancy, a family history of hypertension reflects that genetic factors can predispose to an increase in risk factors for preeclampsia[10]. Maternal genes play a more important role than paternal genes, especially at early onset, this occur because, during pregnancy male contribution is limited to fetal gene expression that is obtained from the paternally, while in women, it affects pregnancy, both through the genotype and the fetal genes it inherits[11].

The analysis test results showed no significant relationship between the history of IUGR and the incidence of preeclampsia (p value = 1.000). This was in line with what Bartsch et al.[12]in a systematic review and meta-analysis that the relative risk for each risk factor is significantly greater than 1.0 except for historical IUGR. Health services for pregnant women, which were more easily accessed through the nearest public health center or other services, could increase maternal awareness of their pregnancy. Thus, fetal development is controlled.

History of preeclampsia did not significantly relate to the incidence of preeclampsia (p value = 0.619). The history of preeclampsia in previous pregnancies was very dependent on pregnant women's memory because this data wastaken at the time of subsequent pregnancies. The results of this research were different from previous studies[8,13]. Boyd et al.[11] revealed that the association was stronger for preeclampsia at early onset. Although preeclampsia history in this research did not have a significant relationship, in a sample of cases with a history of preeclampsia, preeclampsia could

return without a family history of hypertension, without chronic hypertension, or other comorbid diseases.

The Relation of Maternal Characteristic and Preeclampsia Incidence

In this study, maternal age has a significant relation with preeclamsia incidence (p=0.004). This research was in accordance with what Tessema et al.[9]stated that the development of preeclampsia increased in pregnancies with older maternal age of 35 years or over have a 4.5 times higher risk than those aged 25-29 years. Meanwhile, those aged 30-34 years were 3.3 times higher than those aged 25-29 years. Another research stated that the pooled unadjusted relative risk (RR) for maternal age over 35 years was 1.2 and for maternal age over 40 years was 1.5. It indicated an increase in risk with increasing age[12]. This can occur due to physiological changes in blood vessels[13]. As women get older, women tend to have cardiovascular problems that are closely related to aging of the uterine vessels and stiffness of the arteries, in addition, hemodynamic adaptation during pregnancy becomes more difficult[9]. Decreased physiological function and increased potential for disease increase the chances of problems during pregnancy, including the occurrence of preeclampsia.

The analysis showed that BMI also significantly related to the incidence of preeclampsia (p = 0.000). This result was in line with previous research[13]. Aliyu et al.[14]revealed that obesity increasedthe risk of preeclampsia and eclampsia in all women in the research and adolescents with obesity have the highest risk due to a combination of young age and obesity (AOR: 3.79; 95% CI: 3.15 - 4.55). This result was also in line with what Pare et al.[8]stated that overweight or obesity is an essential risk factor in their cohort study and is a major contributor to the incidence of preeclampsia and severe preeclampsia. This can be due to an increase in BMI associated with a tendency to develop hypertension, insulin resistance, diabetes mellitus, and affect chronic inflammatory conditions[15]. Two-thirds of obese people are estimated to have insulin resistance, and obesity is also a risk of cardiovascular disease and type 2 diabetes mellitus[13]. Obesity is a modifiable and avoidable risk factor to prevent preeclampsia and other disorders.

Pregnancy interval had a significant relation with the incidence of preeclampsia (p = 0.009). These results were in line with research conducted by Hercus et al.[16] that an increase in the pregnancy interval had a significant relationship to the incidence of preeclampsia with an OR of 1.39 at a 3-year interval (p = 0.042) and OR 2.05 at a 4-year interval (p = 0.002) and being an independent risk factor in multigravidas. This could be due to decreased modifying/stretching ability of the proximal spiral arteries due to previous pregnancies with increasing pregnancy intervals[16]. Another explanation stated that the pregnancy interval more than 10 years since the last time giving birth causes the number of paternal specific antigen Treg cells to decrease, thereby increasing the risk of preeclampsia in pregnancy[15].

Nulliparous and primigravida had no significant relation to preeclampsia incidence (p =0.174 for nulliparous and p=0.303 for primigravidas). In this study sample, the number of pregnant women with nulliparous and primigravida was less than those who were not. This study was in line with previous studies[8,17].Likewise, with the research of Shamsi et al.[10], the number of nulliparous women was less and not much different from the number of non-nulliparous women, and statistically showed that parity had no significant relation with the incidence of preeclampsia (p = 0.915). However, this result was different from the study conducted by Khader et al.[13]. They revealed that preeclampsia incidence was higher in primigravidas, and the risk of preeclampsia was 2.3 times higher in the first pregnancy compared to the second pregnancy onwards. This might occur due to immunological mechanisms, such as in subsequent pregnancies protected against paternal antigens. Although there was no significant relationship in this research, preeclampsia could occur in mothers with nulliparous and primigravida at a non-risk age and in the absence of comorbid diseases.

This study indicated that new partners did not significantly relate the incidence of preeclampsia (p = 0.518). Research conducted by Hercus et al.[16]revealed that women who had preeclampsia in previous pregnancies had an increased risk of subsequent pregnancies with both new and permanent partners. Yet, pregnancies with new partners for women with previous

normal pregnancies had a significantly risk of developing preeclampsia (OR : 2.27; p = 0.015). This may occur due to the low period of exposure to preconception semen because tolerance will be formed in long exposure with the same partner[9]. These results were not found in this research, and it could be because the data about the new partner obtained from the patient's medical record showed that the written husband was different from the previous pregnancy. This research also assumed that the pregnancy occurred with a partner as reported in the medical record.

The Relation of Comorbid Disease and Preeclampsia Incidence

The results of this study indicated that chronic hypertension had a significant relation with the incidence of preeclampsia (p = 0.007). This result was in line with the research of Pare et al.[8]who revealed that chronic hypertension affected the incidence of preeclampsia (AOR: 2.72; 95% CI: 1.78 - 4.13; p <0.01). Khader et al.[13]stated that high blood pressure significantly increases preeclampsia risk (OR: 11.9). Tessema et al.[9]also found that chronic hypertension had a relation with the incidence of preeclampsia (AOR: 4.3; 95% CI: 1.33 - 13.9). Chronic hypertension in preeclamptic women could increase the risk of pregnancy-associated stroke (PAS) (OR: 3.2; 95% CI: 1.8 - 5.5)[18]. This might occur due to the presence of cardiovascular blood vessel problems since before pregnancy. Thus, the elasticity of the blood vessels decreases and becomes a predisposing factor for preeclampsia.

Data analysis results showed that diabetes mellitus did not have a significant relation with the incidence of preeclampsia (p =0.108). This might be because the presence or absence of diabetes was asked after the mother had pregnancy, while before pregnancy the mother's ignorance of glucose levels could occur if there was no previous blood glucose examination. This study's results were in line with those of Nursal et al.[17]stated that there was no significant relationship between a history of diabetes mellitus and the incidence of preeclampsia (p =1.000). However, this result was different from previous research stating that pre-gestational diabetes was related to the incidence of preeclampsia[8,10]. Middleton et al.[19]stated that pregnant women with diabetes in the group with a loose glucose target (GDP 6.7 - 8.9 mmol/L) found more women with preeclampsia than the moderate target group (GDP 5.6 - 6.7 mmol / L) and tight (GDP ≤ 5.6 mmol/L).

The infection did not have a significant relationwith the incidence of preeclampsia (p = 1.000). In this research, the absence of a significant relation could be due to the various types of infection. Based on previous studi not all types of infections significantly affected the incidence of preeclampsia. From five pregnant women in the sample of cases who suffered from infection, only one mother (20%) had bacterial vaginosis, two mothers (40%) had hepatitis B infection, one mother (20%) had acute respiratory infections, and one other mother (20%) had not known the type of infection. Meanwhile, in the control sample, out of 10 mothers who experienced infection, there were two types of infection, hepatitis B infection (90%) and *S. pneumoniae* infection (10%). In chronic hepatitis B infection, Huang et al.[20]revealed that in Asian women, this infection can reduce the risk of preeclampsia because it had a negative significant relation (OR: 0.77, 95% CI: 0.65 - 0.90; p = 0.002), this is due to disruption immune response or increased immune tolerance caused by hepatitis B virus infection. Minassian et al.[21]found that other infections such as the respiratory tract were also not related with preeclampsia (AOR: 0.91; 0.72 - 1.16), in contrast with urinary tract infections (AOR: 1.22; 1.03). - 1.45). In another research, Miller et al.[18]revealed that infection can increase the risk of developing PAS in preeclamptic women.

The Relation of Fetal Factor and Preeclamptic Incident

In this research, all pregnancies were singleton pregnancies. Thus, the relation with the incidence of preeclampsia was not known. The result of this research was in line to the previous study[22].They stated that all respondents had single pregnancies. When compared with single pregnancies, multiple pregnancies can increase the risk of preeclampsia by 2.36 times, and preeclampsia will occur in 30% of pregnancies[22]. This result was different from the previous research that multiple pregnancy had a significant relation with the incidence of preeclampsia[8,13]. The incidence of preeclampsia increased in multiple pregnancies not due

to incompatibility of maternal HLA with the fetus, but because of fetal antigens twice as many as in single pregnancies[15].

In this research, there was no pregnancy with hydatid mole. This was presumably because the samples in the research were pregnant women who delivered, while in the hydatidiform molar pregnancy the fetus was absent/ unable to survive, thus, there was no birth. Hydatidiform moles developed from pregnancy tissue were divided into two types: complete hydatidiform moles and partial hydatidiform moles. The total hydatidiform mole was a type that often occurred and there was no fetus, while in the partial hydatidiform mole, there was a defective or non-viable formation[23]. Min et al.[24] in their study, argued that compared to the normal placenta in early pregnancy, the hydatidiform mole produced more vascular endothelial growth factor (VEGF), increased angiogenic factors VEGF could lead to the development of preeclampsia with very early onset.

Multivariate Analysis

Multivariate analysis using logistic regression showed that family history of hypertension (OR: 3.374; 95% CI: 1.454 – 7.830; p: 0.005), maternal age (OR: 2.885; 95% CI: 1.311 – 6.347; p: 0.008), and BMI (OR: 2.590; 95% CI: 1.525 – 4.400; p: 0.000), were independent variables that significantly affected the dependent variable. Family history of hypertension was the most dominant factor among other independent variables, with a p value of 0.005 and an OR value of 3.374, which means that pregnant women who had a family history of hypertension had a risk of developing preeclampsia 3.374 times compared to pregnant women without a family history of hypertension.

Conclusion

Family history of hypertension, maternal age, BMI, pregnancy interval, and chronic hypertension have a significant relation to preeclampsia incidence. In multivariate analysis, family history of hypertension is the most dominant risk factor among others.

Further study is needed to conduct regarding risk factors for preeclampsia, especially those related to emotional, social, and cultural conditions, so that risk factors can be obtained holistically.

Conflict of Interest: The authorsdeclare that there is no conflict of interest.

Ethical Clearance: This study had been approvedby the research ethics committee of Airlangga University Hospital with the number 159 / KEP / 2019.

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