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Risk Factors for Preeclampsia in Semarang City Indonesia

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ABSTRACT

Aims and Objectives: This study evaluates the risk factors that influence preeclampsia in Semarang Indonesia
Methods: The research was a case-control study involving 106 pregnancies with preeclampsia and 104 normal pregnancies without preeclampsia as controls who gave birth at KRMT Wongsonegoro Hospital Semarang City, Indonesia for the period January 2018 and December 2018. Data were taken from medical records, information about maternal characteristics, antenatal examination and delivery methods, and perinatal outcomes. Statistical analysis: The Mann-Whitney test was performed for numerical data and the continuity correction test for categorical data with a value of 0.05 to determine the differences in characteristics between the preeclampsia and control groups. To determine the relationship between preeclampsia and various risk factors, using Multinominal Logistic regression analysis with SPSS for Windows, version 22.
Results: the group of women without preeclampsia had a higher mean age than women with preeclampsia ($p < 0.001$). The percentage of primiparas in preeclampsia women is higher than in non-preeclampsia pregnancies ($p = 0.002$). Preeclampsia can be caused by several variables, including maternal age (OR 0.3; 95 percent CI 0.13-3.46), nullipara (OR 1.75; 95 percent CI 1.75-11.6), and a BMI of 25-29.9 kg/m2 (OR 0.4; 95 percent CI 0.21-0.85).
Conclusion: Preeclampsia can arise due to several risk factors, including maternal age, nulliparity, and obesity.

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INTRODUCTION

Preeclampsia is a major cause of maternal morbidity and mortality. This results in social, economic, and health problems in general. So, it is necessary to try to prevent and diagnose early so that optimal therapy can be carried out. Another important thing is the early identification of pregnant women who are at risk of developing preeclampsia, and clinical factors are a practical way to predict the occurrence of preeclampsia (Mayrink et al., 2019).

Preeclampsia is a condition of pregnancy after 20 weeks accompanied by signs of hypertension and proteinuria or if no proteinuria is found one of the signs of general edema, hematological disorders in the form of thrombocytopenia, or damage to vital organs including kidney disorders, abnormal liver function, pulmonary edema, brain edema, and visual disturbances (Chang et al., 2023). Approximately 2 to 4% of all pregnancies are complicated by preeclampsia and contribute to 46,000 maternal deaths and 500,000 fetal or 500,000 newborn deaths each year. The main drug choices for preeclampsia are antihypertensive agents and magnesium sulfate to help control so that clinical manifestations do not become severe (Laura A. Magee, M.D., Kypros H. Nicolaides, M.D., and Peter von Dadelszen, 2022).

Preeclampsia is still not known with certainty until now, several hypotheses have been made to explain its pathophysiology inadequate trophoblastic invasion leads to shallow placentation and poor uteroplacental perfusion, resulting in widespread endothelial dysfunction is one generally accepted theory, resulting in systemic clinical features (Roberts & Hubel, 2009).

Complications due to preeclampsia in the mother are antepartum hemorrhage caused by placental abruption, postpartum hemorrhage, kidney failure, liver disorders, eclampsia, stroke, HELLP syndrome, heart failure, DIC, and multiple organ failure (North et al., 2011, Ye et al., 2014). Fetal distress and fetal growth retardation intrauterine, preterm delivery, stillbirth, perinatal demise, and neonatal asphyxia are fetal complications that are often found (Osungbade & Ige, 2011, Yakasai & Morhason-Bello, 2013). Diabetes mellitus or gestational diabetes, obesity, twins-pregnancy, previously had preeclampsia, first pregnancy, chronic infection, maternal age over 35 years or under 20 years old, kidney disease, autoimmune disorders, and history of spontaneous abortion are risk factors that influence the onset of preeclampsia (Verma et al., 2017). This research is a preliminary study aimed to determine the various risk factors for the occurrence of preeclampsia in Indonesia, especially in the city of Semarang.

METHODS

Population study

A case-control study was conducted at the KRMT Wongsonegoro Hospital in Semarang City, Indonesia of all women who gave birth to a single baby (between January 2018 and December 2018) who was admitted to the obstetric ward. A total of 210 pregnant women were included in this study, with 106 having preeclampsia and 104 having normal pregnancies. Pregnant women over the age of 20 weeks who were admitted to the Obstetrics ward met the inclusion criteria. Pregnant women were separated into two groups in this study. Pregnancy with preeclampsia was a case and pregnancies without preeclampsia as a control group. Each subject recorded pregnancy history, medical history, delivery history, and perinatal outcome. All information was taken from hospital medical records. A total of 106 pregnant women with confirmed PE diagnosis

A systolic blood pressure of greater than or equal to 140 mm Hg, or a diastolic blood pressure of greater than or equal to 90 mm Hg, is considered preeclampsia. Which is only known at a pregnant age of more than 20 weeks with proteinuria is a sign of impaired glomerular function and is called proteinuria if the protein value is +2 by urine dipstick analysis, the protein level is more than 300 milligrams of a urine sample collected 24 hours, or the value is 0.3 mg/dL. However, if proteinuria is not found, then Preeclampsia is diagnosed if hypertension is found with one of the symptoms and abnormalities, including thrombocytopenia, kidney disorders (serum creatinine concentrations more than 1.1 mg/dL), liver problems, elevated transaminase concentrations to twice normal levels, and/or discomfort in the epigastric region of the abdomen/right upper portion of the abdomen, pulmonary edema, neurological symptoms (stroke, headache, visual disturbances), uteroplacental circulation disorders, oligohydramnios, and Fetal Growth Restriction (FGR) ("Practice Guidelines Gestational Hypertension and Preeclampsia: A Practice Bulletin from ACOG," 2019, Project, 2017).

Obesity is classified differently according to WHO and Asia Pacific. WHO defines BMI <18.5 kg/m2 as underweight, normal weight (18.5-24.9 kg/m2), overweight (25-29.9 kg/m2), and obesity (30 kg/m2). while Underweight (BMI <18.5 kg/m2), normal weight (18.5-22.9 kg/m2), overweight (23-24.9 kg/m2), and obesity (>25 kg/m2) is the classification used in the Asia Pacific (Lim et al., 2017).

Analytical statistics

To find out the differences in characteristics between the preeclampsia group and the control group, the Mann-Whitney test was used for numerical data because the data was not normally distributed, and the continuity correction test was used for categorical data with a value of α=0.05. To determine the relationship between preeclampsia and various risk factors, Multinominal Logistic regression analysis is used with a value of α=0.10 and displays the Odds Ratio (OR) value and 95% confidence interval (CI) for variables that are significant risk factors for preeclampsia.

RESULTS

The study involved 210 pregnant women consisting of 106 pregnant women with preeclampsia cases and 104 with normal pregnant cases without preeclampsia.

Table 1: Characteristics of the studied population's demographics

Characteristic	Preeclampsia (n=106)	control (n=104)	p-value
Age (years)	30.3 ± 5.6	33.8 ± 5.7	<0.001[a]
Body Mass Index (kg/m^2)	28.7 ± 6.5	28.2 ± 5.0	0.718[a]
Abortion No Yes	 91 (85.8%) 15 (14.2%)	 82 (78.8%) 22 (21.2%)	 0.250[b]
Parity Nulliparity Multiparity	 23 (21.7%) 83 (78.3%)	 6 (5.8%) 98 (94.2%)	 0.002[b]

[a] Mann-Whitney-test; [b]Continuity Correction-test

Table 1 indicates the demographic features of the respondents; the control group's mean age was higher than the preeclampsia group. The body mass index in both groups is relatively the same. Respondents in both groups tended to have never experienced an abortion. When compared to the control group, the percentage of primiparous preeclampsia women was significantly greater.

Table 2: Characteristics of Perinatal

Characteristics	Preeclampsia (n=106)	control (n=104)	p-value
Gestational age at delivery (weeks)	36.1 ± 3.3	37.5 ± 2.5	0.002[a]
Baby weight (grams)	2835.9 ± 546.3	2977.6 ± 437.8	0.099[a]
Baby weight < 2500 No Yes	 81 (76.4%) 25 (23.6%)	 93 (89.4%) 11 (10.6%)	0.020[b]
Preterm delivery No Yes	 46 (43.3%) 60 (56.6%)	 60 (57.7%) 44 (42.3%)	0.053[b]
Cesarean delivery No Yes	 42 (36.9%) 64 (60.4%)	 89 (85.6%) 15 (14.4%)	<0.001[b]
APGAR Score at 1 min <7	31 (29.2%)	7 (6.7%)	<0.001[b]
APGAR Score at 5 min <7	22 (20.8%)	4 (3.8%)	<0.001[b]

[a]Mann-Whitney-test; [b] Continuity Correction -test

Table 2 indicates the perinatal features; gestational age was considerably lower in women with preeclampsia than in pregnant women without preeclampsia, with babies born at 36 weeks on average. Furthermore, women with preeclampsia have a greater prevalence of low birth weight (birth weight 2500 g), preterm labor, cesarean delivery, and Apgar scores of 7 at 1 and 5 minutes.

Table 3: Preeclampsia Risk Factors

Risk Factors	Preeclampsia (n=106)	control (n=104)	p-value*
Age (years) <20 20-34 ≥35	 3 (2.85%) 73 (68.9%) 30 (28.3%)	 3 (2.9%) 49 (47.1%) 52 (50%)	 0.634 Reference 0.001
Parity Nulliparity Multiparity	 23 (21.7%) 83 (78.3%)	 6 (5.8%) 98 (94.2%)	 0.002 Reference
Previous Abortion No Yes	 91 (85.8%) 15 (14.2%)	 82 (78.8%) 22 (21.2%)	 Reference 0.185
BMI (kg/m^2) <20 20-24.9 25-29.9 ≥30	 1 (0.9%) 37 (34.9%) 30 (28.3%) 38 (35.8%)	 2 (1.9%) 23 (22.1%) 44 (42.3%) 35 (33.7%)	 0.351 Reference 0.016 0.267
History of chronic hypertension No Yes History of preeclampsia	 66 (62.3%) 36 (34%) 4 (3.8%)	 104 (100%) 0 (0%) 0 (0%)	 Reference 0.992 -
Diabetes mellitus No Yes	 98 (92.5%) 8 (7.5%)	 104 (100%) 0 (0%)	 Reference -

*Multinominal Logistic regression

Through multinominal logistic regression analysis, Table 3 displays risk variables in preeclamptic women and controls. Preeclampsia risk was considerably raised by age, BMI, and parity.

Table 4: Analysis results of Multivariate logistic regression

Risk Factors	Adjusted ORs	95% CI
Age ≥35	0.3	0.13 - 3.46
BMI 25-29.9 kg/m^2	0.4	0.21 – 0.85
Nulliparity	4.2	1.75 – 11.6

The findings of the multivariate logistic regression analysis are shown in Table 4. Age, BMI, and parity were all related to a significantly higher risk of preeclampsia. Women over 35 years old had a 0.3 times higher risk of developing preeclampsia than women under 35 years old, according to the odds ratio. Preeclampsia is four times more likely in women with a BMI of 25-29.9 kg/m2.

Preeclampsia was also shown to be 4.2 times more likely in primiparous women than in multiparous women.

DISCUSSION

If a woman has a history of hypertensive disease during a previous pregnancy or a maternal disease such as chronic kidney disease, autoimmune diseases, diabetes, or chronic hypertension, according to the 2019 National Institute for Health and Care Excellence (NICE) guidelines, she is at high risk of preeclampsia. If a woman is nulliparous, 40 years old, and has a body mass index (BMI) of 35 kg/m, she is at intermediate risk (Fox et al., 2019). In our study, it was found that maternal age ≥ 35 years, nulliparity, and a body mass index of 25-29.9 kg/m^2 were associated with an increased risk of developing preeclampsia.

Age as a risk factor for pre-eclampsia

Loss of vascular compliance reduced endothelial-dependent function and increased sympathetic nervous system activity are all biological impacts of aging, all of which led to arterial stiffness and the development of hypertension. An increase in vascular impedance in the uterine arteries of aged women was linked to adverse pregnancy status, according to a study. In older pregnant women, uterine artery remodeling and responsiveness may be reduced, thereby increasing the risk of pregnancy problems such as IUGR and preeclampsia. In pregnant women over 35 years, serum biochemical measurements revealed that soluble fms-like tyrosine kinase-1 (sFLT-1; inhibits vascular endothelial growth factor activity, causing endothelial dysfunction) and 8-epi-PGF2 (an oxidative stress marker) levels were significantly higher than in women under 30 years, Other pregnant women had much lower levels of placental growth factor and total antioxidant capacity (Cooke & Davidge, 2019).

Women of advanced age are more likely to develop atherosclerosis, which affects small arteries, such as those in the kidneys and uterus, leading to hypertension. Therefore, older pregnant women may easily develop preeclampsia. Recent studies demonstrated placental senescence in the placenta of preeclampsia cases. Therefore, maternal age may correlate with placental senescence (Arihiro Shiozaki and Shigeru Saito, 2018).

Several studies have shown the same results that the age of pregnant women ≥ 35 years have a greater risk of developing preeclampsia (Luealon & Phupong, 2010, Fox et al., 2019, Li et al., 2018, English et al., 2015). In our research, pregnant women aged ≥ 35 years have a 0.3 times risk than pregnant women aged <35 years. A study shows that pregnant women over the age of 35 have a 1.5 times risk of developing preeclampsia compared to those under 35 years of age (Lamminpää et al., 2012). Women who give birth at age 35 or older are referred to as "advanced maternal age" (AMA). Duckitt et al. explained that aged 35 years or more are at risk of preeclampsia because it may be associated with the aging of the uterine vessels and increased chorial villi reactions (Duckitt & Harrington, 2005).

BMI as a risk factor for preeclampsia

The placental formation, which begins early in pregnancy, has a strong link to early preeclampsia.

Late preeclampsia is often associated with adequate placental function; however, it can also be caused by maternal factors. A high BMI is one of the major risk factors for advanced preeclampsia.

Preeclampsia is characterized by a systemic inflammatory response in the mother that affects endothelial cell dysfunction components. Adipose tissue is a hormone-active tissue that releases various inflammatory mediators that might disrupt endothelial function, increasing the risk of pre-eclampsia in the mother. Obesity, as well as excessive weight gain during pregnancy, is linked to higher levels of inflammatory factors, which can lead to preeclampsia in women (Hutcheon et al., 2018).

Through metabolic alterations associated with obesity, such as hyperlipidemia, hyperinsulinemia, or hyperleptinemia, obesity can disrupt placental function and perfusion. Insulin resistance and hyperinsulinemia are two of the most essential characteristics of obesity, and it has been discovered that hyperinsulinemia and insulin resistance occur before the clinical signs of preeclampsia. Hyperinsulinemia causes shallower implantation sites and intrauterine growth suppression, according to studies, which are linked to changes in nitric oxide synthesis (Lopez-Jaramillo et al., 2018).

Regarding BMI risk factors for preeclampsia, our study shows that a BMI of 25-29.9 kg / m2 (obesity according to the Asia Pacific classification) has a 0.4 times higher risk of developing preeclampsia than non-obese. Other studies also report the same thing obesity is a risk factor for the onset of preeclampsia (English et al., 2015, Hutcheon et al., 2018, Mayrink et al., 2019). There is an association between maternal weight and preeclampsia. Obesity is one of the risk factors for preeclampsia. The progressive increase varied from 4.3% in women with a BMI <19.8 kg/m2 to 13.3% with a BMI of 35 kg/m2 (Lopez-Jaramillo et al., 2018, Phipps et al., 2016, Pramana et al., 2020).

Obesity appears to influence placental function and perfusion, as well as some of the metabolic abnormalities associated with hyperlipidemia, hyperinsulinemia, and hyperleptinemia, according to clinical findings and various research. Obese women have greater levels of these metabolic indicators, which are considerably higher in preeclampsia. Obesity also raises the risk of preeclampsia due to increased levels of triglycerides and free fatty acids (Lopez-Jaramillo et al., 2018).

Nulliparity as a risk factor for pre-eclampsia

Several studies have concluded that nulliparity is associated with the risk of preeclampsia (Duckitt & Harrington, 2005, Phipps et al., 2016, Paré et al., 2014, Lisonkova & Joseph, 2013). In our study, nulliparity had a 4.2 times higher risk than multigravidas (ORs 4.2; CI 1.75-11.6). This is almost like the study by Vorapong et al who reported that nulliparity was a risk factor for the development of preeclampsia (ORs 3.8; 95% CI 2.5-5.7) (Luealon & Phupong, 2010). Meanwhile, research by Paré, Emmanuelle et.al nulliparity was also a risk factor for preeclampsia (adjusted OR 1.73; 1.26–2.38) (Duckitt & Harrington, 2005). Disrupted trophoblast differentiation and invasion in early pregnancy induce oxidative stress and systemic

inflammatory response that results in preeclampsia (English et al., 2015). The circulating ratio of sFlt1 and sFlt1/PlGF in nulliparas is higher than in multiparous pregnancies, suggesting an angiogenic imbalanced relationship. Together with the pathogenic role of anti-angiogenic factors in preeclampsia, it is concluded from this explanation that nulliparity is a risk factor for the development of preeclampsia (Bdolah et al., 2014).

Research limitations

This research is a preliminary study, and the number of research samples is small, in case control, it is better to involve many samples. In this study, the authors have not divided the preeclampsia group into several subgroups such as early and late preeclampsia. Smoking habits have not been reported. And several other risk factors such as TNF-a and plasma protein-A levels in pregnancy have also not been reported. Some of the limitations in this study will be corrected and refined in future research.

CONCLUSION

Based on the results of our research, it can be concluded that maternal age over 35 years, nulliparity, and obesity are risk factors for increasing the incidence of preeclampsia. By knowing this information, obstetricians can provide counseling and screening for high-risk pregnant women. Women who are found to be at high risk can be prevented and treated properly so that no adverse complications arise.

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Ethical approval

This study has been approved by the Research Ethics Committee of the K.R.M.T. Wongsonegoro Hospital in Semarang, number No.070/4800/2019.

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Conflict of Interest

We declare there is no conflict of interest.

Informed Consent

There was no informed consent, because in a retrospective study the data were taken from medical records.

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