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Original Research Article

The relationship between high risk factors for preeclampsia and the incidence of preeclampsia in pregnant women at The Medan City Community Health Center

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ABSTRACT

Background: The maternal mortality rate (MMR) is a major issue in health development with total 305 per 100,000 live births in 2015. Preeclampsia (PE) affects about 3.4% of all pregnant women and is one of the leading causes of maternal and fetal morbidity.
Methods: This study is an observational analytical study with a cross-sectional design to assess the relationship between high-risk factors for preeclampsia present at <20 weeks of gestation and the incidence of preeclampsia based on blood pressure and proteinuria examinations at >20 weeks of gestation. This research was conducted at the Medan City Health Center. The research population consists of pregnant women receiving antenatal care services at the Medan City Health Center. Data were analyzed descriptively to see the frequency distribution. For bivariate analysis, the chi-square test is used. For multivariate analysis, logistic regression is used. The analysis results are considered significant if $p<0.05$.
Results: The majority of the research subjects are aged 31-35 years with a parity status of multigravida, an education level of high school, an employment status of unemployed, and a BMI classified as normoweight. Parity and education status were significantly related to preeclampsia ($p<0.005$). Bivariate analysis can be concluded that multipara status with preeclampsia, multiple pregnancies, gestational diabetes, chronic hypertension, and kidney disease are statistically significantly related to the occurrence of preeclampsia ($p<0.05$). There are five independent variables that significantly affect preeclampsia in this study, namely parity, multipara with preeclampsia, multiple pregnancies, diabetes in pregnancy, and chronic hypertension. Based on the regression equation, the probability is 27%.
Conclusions: There are five independent variables that significantly affect preeclampsia in this study, namely parity, multipara with preeclampsia, multiple pregnancies, diabetes in pregnancy, and chronic hypertension.

Keywords: Hypertension, Preeclampsia, Proteinuria, Risk factors

INTRODUCTION

The maternal mortality rate (MMR) is a major issue in health development. The government continues to strive to accelerate the reduction of Maternal Mortality Rate (MMR). The 2015 SUPAS data shows an MMR of 305 per 100,000 live births, while the target of the National Medium-Term Development Plan (RPJMN) for 2020-2024 is 183 per 100,000 live births, requiring an acceleration of reduction efforts by 5.5% per year. The acceleration of MMR reduction in Indonesia, as set in the Sustainable Development Goals (SDGs) 2030, is an MMR of 70 per 100,000 live births. There are several factors that influence the increase in MMR, including the "Four Too Many," namely, too young, too frequent, too close, and too old pregnancies.[1] Healthy pregnancy planning is one of the

efforts to reduce high-risk pregnancies that have the potential to lower Maternal Mortality Rate (MMR). Maternal and Child Health (MCH) efforts are one of the priority programs at community health centers (Puskesmas) expected to reduce maternal mortality rate (MMR), neonatal mortality rate (NMR), infant mortality rate (IMR), and under-five mortality rate (U5MR). The government, both internally and in collaboration with UNICEF (United Nations International Children's Emergency Fund), has made efforts to reduce maternal mortality, which are outlined in the Safe Motherhood program. This program aims to reduce maternal mortality and ensure that every mother has the opportunity to give birth to a baby in a safe and healthy condition. The examination of pregnant women, postpartum women, breastfeeding mothers, infants, and toddlers conducted by midwives or doctors is part of the health services that can be accessed by all Indonesian citizens who are participants in the National Health Insurance in accordance with the Minister of Health Regulation No. 28 of 2014 on the Guidelines for the Implementation of the National Health Insurance Program.[2]

Regular assessment of proteinuria during pregnancy is a key step to rule out or diagnose severe conditions associated with high morbidity and mortality, particularly preeclampsia.[3] Preeclampsia (PE) affects about 3.4% of all pregnant women and is one of the leading causes of maternal and fetal morbidity. Preeclampsia is a pathological condition in pregnancy associated with new-onset hypertension, most often occurring after 20 weeks of gestation and generally approaching term. The classification of preeclampsia is into early-onset and late-onset groups according to gestational age (GA). The cutoff for gestational age in preeclampsia is early onset (GA <34 weeks), late onset (GA >34 weeks), preterm (GA <37 weeks), and term (GA >37 weeks). PE is associated with an increased risk of perinatal death and accounts for about 10% of stillbirths and 15% of preterm births. Preeclampsia occurs in 2% to 8% of pregnant women and is one of the leading causes of maternal and perinatal morbidity and mortality. Worldwide, 76,000 women and 500,000 babies die each year due to preeclampsia. Additionally, preeclampsia is associated with an increased risk of long-term cardiovascular and chronic diseases in mothers and children from pregnancies with preeclampsia. Babies born to mothers who have experienced preeclampsia are also at risk of developing medium- and long-term complications, such as neurodevelopmental disorders, insulin resistance, diabetes mellitus, coronary heart disease, and hypertension. The main risk factors include a history of preeclampsia, multiple pregnancies, chronic hypertension, pregestational diabetes mellitus, renal disorders, autoimmune disorders, antiphospholipid syndrome, and obesity.[4] Metabolomic studies conducted on the serum of women at 11-13 weeks of pregnancy who later developed late-onset pre-eclampsia identified that insulin resistance and metabolic syndrome, mitochondrial dysfunction, energy metabolism disorders, oxidative stress, and lipid dysfunction occur at the late onset of pre-eclampsia, allowing these disorders to be identified early in the disease process.[5] Based on this background, this research aims to examine the relationship between high-risk factors for preeclampsia and the incidence of preeclampsia at the Medan City Health Center.

METHODS

This study is an observational analytical study with a cross-sectional design to assess the relationship between high-risk factors for preeclampsia present at <20 weeks of gestation and the incidence of preeclampsia based on blood pressure and proteinuria examinations at >20 weeks of gestation. This research was conducted at the Medan City Health Center starting from the date the Ethical Clearance was issued by the Medical and Health Research Ethics Committee of the University of North Sumatra.

The research population consists of pregnant women receiving antenatal care services at the Medan City Health Center. The research sample includes pregnant women with a gestational age of >20 weeks who receive antenatal care services at the Medan City Health Center during the period of January-July 2024. Sample collection was conducted using the consecutive sampling technique. Determination of the sample size is conducted based on statistical calculations with a confidence level set at 95%. The sample size is 100 samples.

Inclusion criteria include pregnant women with a gestational age >20 weeks who receive antenatal care services at the Medan City Health Center during the period of January-July 2024, with complete medical record data for high-risk preeclampsia factors in the KIA book, who are willing to participate in the study, and Puskesmas that are willing to be visited. Exclusion criteria are pregnant women with an incomplete KIA book. The dependent variable is the incidence of preeclampsia assessed at a gestational age >20 weeks based on blood pressure ≥ 140 mmHg/90 mmHg, proteinuria with a value >300 mg/dl of protein in a 24-hour urine collection or with a urine dipstick with a value ≥+1, and other supporting examinations for the diagnosis of preeclampsia in the complete medical record. The independent variables include multipara with a history of previous PE, multiple pregnancies, diabetes in pregnancy, chronic hypertension, kidney disease, autoimmune diseases, and antiphospholipid syndrome.

Data were analyzed descriptively to see the frequency distribution of research subjects based on the characteristics of the research sample. Before conducting bivariate analysis, a normality test is first performed using the Kolmogorov Smirnov test. For bivariate analysis, the chi-square test is used, and if the data is not normally distributed, the Fisher exact test is used. The magnitude of the influence of each related risk factor will be tested using logistic regression analysis. The analysis results are considered significant if $p<0.05$, with a 95% confidence level.

RESULTS

In Table 1, it shows the characteristics and their relationship with preeclampsia risk factors. The majority of the research subjects are aged 31-35 years with a parity status of multigravida, an education level of high school, an employment status of unemployed, and a BMI classified as normoweight. The analysis of differences in characteristics was continued using the chi-square test to analyze the variables of age, parity, education, occupation, and body mass index in relation to the incidence of preeclampsia. It was found that parity and education status were significantly related to preeclampsia ($p<0.005$).

Table 1: The association between patients's characteristic and preeclampsia incidence.

Variable	Total	No preeclampsia	Preeclampsia	*P value
Age in years				
20-25	66	59	25	0.203
25-30	99	52	31	
31-35	137	100	35	
Parity				
Primigravida	124	106	18	0.001
Multigravida	165	96	69	
Grandemultigravida	13	9	4	
Education				
Elementary school	14	6	8	
Junior high school	37	29	8	0.040
Senior high school	163	109	54	
Bachelor	88	66	21	
Occupation				
Yes	230	148	67	0.540
No	72	63	24	
Body mass index				
Underweight	29	22	6	
Normoweight	157	109	46	0.638
Overweight	86	59	27	
Obesity	30	21	12	

Table 2: The association between high risk factors and preeclampsia incidence.

Variable	Total	No preeclampsia	Preeclampsia	P value
Multiparity with PE history				
Yes	68	10	58	0.001
No	111	95	16	
Primiparity	124	106	18	
Multiple pregnancy				
Yes	17	5	12	0.001
No	285	206	79	
Gestational diabetes				
Yes	16	7	9	0.019
No	286	204	82	
Chronic hypertension				
Yes	20	8	12	0.003
No	282	203	79	
Renal disorders				
Yes	5	1	4	0.014
No	297	210	87	
Autoimmune disorders				
Yes	13	7	6	0.198
No	289	204	85	
Antiphospholipid syndrome				
Yes	35	27	18	0.118
No	257	184	73	

Table 2 shows high-risk factors and their relationship to the incidence of preeclampsia. From Table 2, the majority of the study subjects were multiparous without a history of preeclampsia, not multiple pregnancies, and were not diagnosed with diabetes during pregnancy, chronic hypertension, kidney disease, autoimmune diseases, or antiphospholipid syndrome. Bivariate analysis using the chi-square test can be concluded that multipara status with preeclampsia, multiple pregnancies, gestational diabetes, chronic hypertension, and kidney disease are statistically significantly related to the occurrence of preeclampsia (p <0.05).

Table 3: Multivariate analysis of preeclampsia risk factors on preeclampsia incidence.

Variable	B	P value	Exp (B)	95% CI for Exp (B)	
				Lower	Upper
Selection-I					
Age	0.089	0.724	1.094	0.665	1.797
Parity	-2.753	0.001	0.064	0.017	0.242
Education	-0.484	0.062	0.616	0.371	1.024
Occupation	-0.253	0.604	0.777	0.299	2.019
Body mass index	0.128	0.596	1.136	0.709	1.821
Multiparity with PE history	-3.535	0.001	0.029	0.012	0.071
Multiple pregnancy	-2.982	0.001	0.051	0.013	0.195
Gestational diabetes	-2.004	0.004	0.135	0.035	0.526
Chronic hypertension	-1.760	0.005	0.172	0.050	0.592
Renal disorders	-1.436	0.271	0.238	0.018	3.069
Autoimmune disorders/SLE	-0.999	0.230	0.368	0.072	1.885
Antiphospholipid syndrome	-0.981	0.048	0.375	0.142	0.992
Constant	-31.931	0.000	7.373E+13		
Selection-II					
Parity	-2.685	0.001	0.068	0.019	0.243
Multiparity with PE history	-3.501	0.001	0.030	0.013	0.072
Multiple pregnancy	-2.829	0.001	0.059	0.016	0.213
Gestational diabetes	-2.093	0.002	0.123	0.034	0.451
Chronic hypertension	-1.899	0.001	0.150	0.047	0.482
Antiphospholipid syndrome	-0.894	0.059	0.409	0.162	1.034
Constant	25.669	0.001	1.406E+11		
Selection-III					
Parity	-2.619	0.001	0.073	0.021	0.255
Multiparity with PE history	-3.442	0.001	0.032	0.014	0.075
Multiple pregnancy	-2.718	0.001	0.066	0.019	0.232
Gestational diabetes	-1.952	0.003	0.146	0.019	0.521
Chronic hypertension	-2.086	0.001	0.124	0.039	0.396
Constant	-15.222	0.001	1.827E+10		

Table 3 shows the characteristics and their relationship with the occurrence of preeclampsia. Using the enter method, which involves removing one independent variable at a time starting from the variable with the highest p-value >0.05, it was found that there are five independent variables that significantly affect preeclampsia in this study, namely parity, multipara with preeclampsia, multiple pregnancies, diabetes in pregnancy, and chronic hypertension. Based on the regression equation, the probability of a pregnant woman with multiparity characteristics, multipara with a history of preeclampsia, multiple pregnancies, diabetes during pregnancy, and chronic hypertension experiencing preeclampsia is: 27%.

DISCUSSION

In this study, the majority of the research subjects were aged 31-35 years, both in the preeclampsia and control groups. Research by Bej et al reported that the majority of subjects were aged 20-29 years.[6] Research by Nie et al reported that the average age of patients was around 32-33 years.[7] Similarly, research by Pare et al also reported the average age of study subjects as 31 years.[8] Age did not have a significant relationship with preeclampsia in this study. This is in line with the research by Nie et al.[7] Based on parity status, the majority of preeclampsia patients were multigravida, while in the control group, the majority were primigravida. A study in East Java by Zainiyah et al found that the majority of both preeclampsia and control patients

were primigravida.[9] In this study, most patients were multigravida. Analysis of characteristic differences using the chi-square test showed that parity status and education level were significantly related to preeclampsia (p<0.005). This is in line with the research by Silva et al,[10] which states that women with lower education levels have a higher risk of suffering from preeclampsia than the group of women with higher education (OR: 1.30; 95% CI: 0.80, 2.12). In this study, the mother's level of education does not directly affect the risk of gestational hypertension, but is likely to act through other risk factors, known as mediators. Some of these factors can be potential mediators involving substance use, namely smoking, alcohol consumption, and drug use, a history of pre-existing diabetes, the mother's anthropometric status, and the mother's blood pressure. This is supported by Fondjo et al,[11] who state that a higher level of education (high school and above) is significantly associated with knowledge of PE, thereby reducing the risk of PE occurrence (OR = 4.45, 95%CI (2.18-9.10), p<0.0001). In this study, education also includes knowledge of ANC, media broadcasts, and national education programs.[11] A cohort study by Solee et al concluded that maternal education history is associated with the incidence of pregnancy hypertension. Higher education reduces the risk of preeclampsia/eclampsia by 34% (adjusted OR 0.66, 95% CI 0.62-0.69), compared to women with secondary education. Education reflects socioeconomic status because it is less likely to be influenced by diseases that occur in adults compared to other variables such as income and employment. Our research found that, regardless of birthplace or parity, women with the lowest education levels do not have an increased risk of pregnancy hypertension.[12]

Regarding parity, a study by Maeda et al stated that multiparity is significantly associated with a lower risk of preeclampsia (OR: 0.08; 95% CI: 0.01-0.95).[13] The lower risk of preeclampsia among multiparous women has been linked to desensitization after exposure to antigens in the placenta during previous pregnancies. A lower risk is also associated with a more subtle trophoblast invasion after maternal spiral artery modification.[14]

These study results are also consistent with research by Luo et al, where primiparous women are more likely to experience preeclampsia with an OR of 2.42 [95% CI 2.16, 2.71].[15] However, this is not in line with the study by Tran et al, where women with recurrent multiparous preeclampsia showed more severe pregnancy hypertension. Persistent hypertension in women with a history of preeclampsia is a risk factor for recurrent preeclampsia, and these patients should be monitored more closely (OR 2.05, p = 0.002).[16] Several variables that fall into the high-risk factor category include multipara with a history of preeclampsia, multiple pregnancies, diabetes in pregnancy, chronic hypertension, kidney disease, autoimmune diseases, and antiphospholipid syndrome. Women who have previously experienced preeclampsia in a prior pregnancy have a higher risk of experiencing preeclampsia in subsequent pregnancies, even if they are multiparous. Both a family history and a maternal history of preeclampsia were found to be associated with the occurrence of preeclampsia in the study by Pare et al. Women with a history of preeclampsia in pregnancy are at 3.28 times higher risk, while women with a family history of preeclampsia are at 1.65 times higher risk.[38] In several other studies, the risk of recurrent preeclampsia in multiparous women with a history of preeclampsia ranges from 20-30%, depending on the severity and timing of the onset of preeclampsia in previous pregnancies. Other factors such as the mother's medical conditions or long intervals between pregnancies can also increase the risk of recurrent preeclampsia.[17]

Multiple pregnancies (e.g., twins or more) increase the risk of preeclampsia due to the greater burden on the mother's body. A larger placenta and increased circulatory load can cause higher vascular stress and inflammation, contributing to the development of preeclampsia. Preeclampsia occurs more frequently in multiple pregnancies compared to single pregnancies, with a prevalence up to three times higher.[11] Pare et al found that women with multiple pregnancies are 2.91 times more likely to experience preeclampsia compared to those with a single fetus.[18] The study by Pare et al showed that women with gestational diabetes are associated with the occurrence of preeclampsia and are 4.86 times more likely to experience preeclampsia.[18] Gestational diabetes, as well as type 1 or type 2 diabetes, increases the risk of preeclampsia. Chronic hyperglycemia can cause damage to blood vessels, endothelial dysfunction, and insulin resistance, all of which contribute to the pathogenesis of preeclampsia. Women with diabetes during pregnancy have a higher risk of preeclampsia, especially if diabetes is not well-controlled.[18]

In the study by Yusihda and Zahara, it was found that hypertension is associated with the risk of preeclampsia. Women with hypertension are at 2.5 times higher risk of developing preeclampsia in this study.[19] In the study by Pare et al, it was found that chronic hypertension, gestational diabetes, multiple pregnancies, a family history of preeclampsia, and multiparous pregnancies with a history of preeclampsia are associated with the occurrence of preeclampsia. Women with chronic hypertension risk 4.32 times more likely to experience preeclampsia.[18] From the above studies, it can be concluded that women with chronic hypertension before pregnancy have a greater risk of experiencing preeclampsia. Chronic hypertension can cause damage to blood vessels, and pregnancy can worsen this condition, thereby increasing the likelihood of developing preeclampsia. In addition, chronic hypertension is also often associated with other complications such as impaired kidney function and endothelial dysfunction, all of which play a role in preeclampsia.[20]

Chronic kidney disease is one of the main risk factors for preeclampsia, as kidneys with impaired function are more

susceptible to increased blood pressure and fluid imbalance during pregnancy. Preeclampsia can worsen kidney function, which can lead to kidney failure in more severe cases. The prevalence of preeclampsia in women with chronic kidney disease is very high, especially if the disease was already severe before pregnancy.[21] Some autoimmune diseases, such as systemic lupus erythematosus (SLE) and Sjögren's syndrome, can increase the risk of preeclampsia. Autoimmune diseases cause systemic inflammation and endothelial dysfunction, which are key mechanisms in the development of preeclampsia. Women with SLE, for example, have a 2-3 times higher risk of preeclampsia compared to the general population. Strict management of autoimmune conditions during pregnancy is very important to reduce the risk of preeclampsia.[22] In this study, it was found that out of 302 research samples, only 13 subjects had a history of autoimmune diseases obtained through anamnesis, which may be one of the factors that autoimmune diseases in this study are not significantly related to the incidence of preeclampsia. Some studies show that not all autoimmune diseases are directly correlated with preeclampsia. Although autoimmune diseases such as systemic lupus erythematosus (SLE) and antiphospholipid syndrome are often associated with an increased risk of preeclampsia, not all autoimmune conditions have a significant relationship. Some studies emphasize that certain autoimmune conditions do not universally cause preeclampsia, depending on clinical variables and the population being studied.[23]

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by the presence of antibodies that increase the risk of blood clotting. APS significantly increases the risk of preeclampsia because microthrombosis occurring in the placenta can disrupt blood flow to the fetus, causing hypertension and organ dysfunction. Women with APS have a higher risk of experiencing severe preeclampsia and premature birth.[24] Several other studies reported a significant relationship, particularly in cases of early-onset preeclampsia, while other studies did not find a statistically significant relationship between APS and PE. Clark et al conducted an analysis aimed at determining the relationship between APS and preeclampsia without other clinical criteria for APS.[25] This study could not find a relationship between preeclampsia and APS in the general population as well as in women at risk of developing preeclampsia; however, women who met the criteria (clinical and laboratory) for APS were at high risk of developing preeclampsia. Marchetti et al analyzed plasma samples from 199 women with "mild" preeclampsia and from 143 women with severe preeclampsia, as well as from 195 control women. This study aims to determine the incidence of APS in women with "mild" and severe preeclampsia. Only in women who experience severe preeclampsia is a connection with APS detected.[26] A systematic review study found that three studies showed a relationship while three other studies showed no relationship.[27-30] The conclusion from several studies above is that the prevalence of APS in preeclampsia has not been definitively identified.[31]

CONCLUSION

There are five independent variables that significantly affect preeclampsia in this study, namely parity, multipara with preeclampsia, multiple pregnancies, diabetes in pregnancy, and chronic hypertension.

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