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Indian Journal of Obstetrics and Gynecology Research

Journal homepage: www.ijogr.org

Original Research Article

Risk factors associated with early and late onset preeclampsia in national referral centre hospital

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Abstract

Background: To investigate what conditions or risk factors can cause early onset preeclampsia and late onset preeclampsia.
Materials and Methods: This was an retrospective analysis with a cross sectional design. The data was collected using medical records, which include maternal data, medical history, and obstetric history. Risk factors associated with preeclampsia were studied between early onset preeclampsia and late onset preeclampsia. Risk factors were analyzed by logistic regression analysis.
Results: The data obtained showed that all samples in the early onset preeclampsia group had a previous history of hypertension, gestational diabetes and diabetes mellitus. Risk factors associated with early onset preeclampsia were maternal age (Odd ratio [OR] 1.61, 95% Confident Interval [CI] 1.24-5.12), chronic hypertension (OR 5.97, 95% CI 3.10-8.37), history of preeclampsia with incident (OR 2.53, 95% CI 1.46-6.36). Risk factors associated with late onset preeclampsia were maternal age (OR 1.25, 95% CI 2.12-6.31), chronic hypertension (OR 2.06, 95% CI 1.41-3.92), BMI (OR 3.27, 95% CI 1.95-7.11).
Conclusion: Although they share some etiological features, they also differ with respect to other risk factors. The two preeclampsia types should be treated as distinct entities from an etiological standpoint.

Keywords: Risk factor, Preeclampsia, Early onset, Late onset.

Received: 11-05-2024; **Accepted:** 04-11-2024; **Available Online**: 13-08-2025

1. Introduction

Preeclampsia is a multi-organ disorder that occurs during pregnancy and the postpartum period which is characterized by blood pressure ≥ 140/90 mmHg that appears after 20 weeks of gestation in patients who previously had no history of hypertension. According to WHO (World Health Organization) in 2017, preeclampsia is one of the highest causes of death in pregnant women worldwide. The incidence of preeclampsia occurs in 10-17% of pregnancies. The disease causes more than 50,000 maternal deaths and more than 500,000 fetal deaths worldwide.[1-4]

Preeclampsia is classified as either early onset preeclampsia or late onset preeclampsia, depending on the gestational age at which the condition was initially identified. When identified at less than 34 weeks of gestation, the condition is referred to as Early onset preeclampsia (EOP). It is referred to as Late onset preeclampsia (LOP) if the gestational age is 34 weeks or more. While late-onset preeclampsia may show less severe clinical signs, early-onset preeclampsia is regarded to be quite dangerous for both the mother and the fetus.[3]

Preeclampsia can cause abortion, prematurity, intrauterine growth retardation and even stillbirth. Therefore, early detection (antenatal care) is needed to prevent this disease. Examination of risk factors, early diagnosis and intervention in every pregnant woman can be taken as one of the steps to reduce mortality due to preeclampsia.[5]

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https://doi.org/10.18231/j.ijogr.v.12.i.3.13

Pregestational diabetes, thrombophilia, nulliparity, multifetal gestations, chronic hypertension, pregestational diabetes, gestational diabetes, systemic lupus erythematosus, prepregnancy Body Mass Index (BMI) > 30, maternal age ≥ 35 years, kidney disease, assisted reproductive technology, and obstructive sleep apnea are among the risk factors that have been linked to the incidence of preeclampsia. Preeclampsia is associated with risk factors in Indonesia, including obesity, history of hypertension, history of preeclampsia in prior pregnancies, maternal age ≥ 35 years, BMI, nullipara, and active or passive smoker.[6,7]

This study aims to determine the characteristics and whether there are differences in risk factors in the occurrence of early onset and late onset preeclampsia. These risk factors can help clinician to predict and identify cases that may develop into early onset and late onset preeclampsia. This study included maternal age, active or passive smoking, BMI, multifetal pregnancy, gestational diabetes, diabetes mellitus, chronic hypertension, history of preeclampsia, family history of hypertension, preeclampsia, and diabetes mellitus.

2. Materials and Methods

This type of study is a retrospective analytic with a cross sectional design. This study used a total sampling of all preeclampsia patients at Gatot Soebroto Army Central Hospital in 2015-2017. The data was collected using medical records, which include maternal data, medical history, and obstetric history. Inclusion criteria in this study were all treatment patients diagnosed with preeclampsia. Exclusion criteria were patients who had incomplete medical record data. Preeclampsia was diagnosed based on the blood pressure ≥ 140/90 mmHg with proteinuria, which occur after 20 weeks gestational age. The independent variables in this study were maternal age, active or passive smoking, BMI, multifetal pregnancy, gestational diabetes, diabetes mellitus, chronic hypertension, history of preeclampsia, family history of preeclampsia, family history of hypertension, family history of diabetes mellitus. The dependent variable in this study is the incidence of early onset and late onset preeclampsia.

In a univariate analysis, risk factors were examined between each preeclampsia group and the controls. The relationship between risk factors and each preeclampsia category was then assessed using multivariate logistic regression analysis. A multivariate regression analysis was performed using the risk factors that showed significant results in the univariate study. Adjusted odds ratio (OR) with 95% confidence interval (CI) was calculated. A *P*-value < 0.05 was considered statistically significant. Collected data was statistically analyzed using Stata 12.

3. Results

There were 212 samples divided into three groups, which consisted 172 samples no preeclampsia, 8 samples in early onset preeclampsia, and 32 samples in late onset preeclampsia. Demographic and obstetrical characteristics data is shown in **Table 1**, most of study population was in the age group < 40 years old. In contrast to the late onset preeclampsia group, which was more common in patients with BMI ≥ 25. Early onset preeclampsia group was more common in patients with BMI < 25. The medical and obstetric history in early onset preeclampsia, this group had history of hypertension (100%) and history of gestational diabetes (100%) which is much higher than that of late onset preeclampsia.

The relationship between maternal age and chronic hypertension with the incidence of preeclampsia and the strength of the relationship expressed by the OR is 1.38 and 2.17 (**Table 2**). This indicates a 2.17 times higher risk of preeclampsia in women with chronic hypertension (95% CI: 1.36-8.29). The strongest relationship with the incidence of EOP is chronic hypertension (95% CI: 1.36-8.29) (**Table 3**). Different from the incidence of preeclampsia and EOP where the strongest relationship is in the factor of chronic hypertension, but in the late onset of preeclampsia the strongest relationship with the incidence of LOP is the BMI factor (**Table 4**).

Table 1: Demographic and obstetrical characteristics data of study population

Variables		**No Preeclampsia**	**EOP**	**LOP**	***p-value***		
					Preeclampsia	**EOP**	**LOP**
Maternal Age (y.o.)	< 40	169(98.3%)	6(75%)	23(71.9%)	0.04	0.03	0.04
	≥ 40	3(1.7%)	2(25%)	9(28.1%)			
BMI (Kg/m^2)	< 25	94(72.7%)	5(62.5%)	9(53.1%)	ns	ns	0.02
	≥ 25	78(27.3%)	3(17.5%)	23(46.9%)			
Smoker	No	183(86.3%)	7(87.5%)	28(87.5%)	ns	ns	ns
	Yes	29(13.7%)	1(12.5%)	4(12.5%)			
Multifetal Pregnancy	No	170(98.8%)	3(17.5%)	31(98.9%)	ns	ns	ns
	Yes	2(1.2%)	5(62.5%)	1(3.1%)			
Chronic Hypertension	No	170(98.8%)	2(25%)	14(43.8%)	0.01	0.01	0.04
	Yes	2(1.2%)	6(75%)	18(56.2%)			

Table 1 Continued…							
Diabetes Mellitus	No	167(97.1%)	8(100%)	27(84.3%)	ns	ns	ns
	Yes	5(2.9%)	0(0%)	5(15.7%)			
Gestational Diabetes	No	168(97.7%)	8(100%)	29(90.6%)	ns	ns	ns
	Yes	4(2.3%)	0(0%)	3(9.4%)			
History of Preeclampsia	No	168(97.7%)	8(100%)	27(84.3%)	ns	0.03	ns
	Yes	4(2.3%)	0(0%)	5(15.7%)			
Preeclampsia in Family	No	164(95.3%)	7(87.5%)	28(87.5%)	ns	ns	ns
	Yes	8(4.7%)	1(12.5%)	4(87.5%)			
Hypertension in Family	No	166(96.5%)	7(87.5%)	29(90.6%)	ns	ns	ns
	Yes	6(3.5%)	1(12.5%)	3(9.4%)			
DM in Family	No	167(97.1%)	8(100%)	28(87.5%)	ns	ns	ns
	Yes	5(2.9%)	0(0%)	4(87.5%)			

EOP, Early onset preeclampsia; LOP, Late onset preeclampsia; NS, Nonstatistically significant.

Table 2: Relationship between maternal age and chronic hypertension with the incidence of preeclampsia

	Preeclampsia	
	p-value	**OR (95% CI)**
Maternal Age	0.04	1.38 (1.24-7.10)
Chronic Hypertension	0.01	2.17 (1.36-8.29)

Table 3: Relationship between maternal age, chronic hypertension, history of preeclampsia with the incidence of EOP

Early Onset Preeclampsia		
	p-value	**OR (95% CI)**
Maternal Age	0.03	1.61 (1.24-5.12)
Chronic Hypertension	0.01	5.97 (3.10-8.37)
History of Preeclampsia	0.03	2.53 (1.46-6.36)

Table 4: Relationship between maternal age, chronic hypertension, BMI with the incidence of LOP

Late Onset Preeclampsia		
	p-value	**OR (95% CI)**
Maternal Age	0.04	1.25 (2.12-6.31)
Chronic Hypertension	0.04	2.06 (1.41-3.92)
BMI	0.02	3.27 (1.95-7.11)

4. Discussion

The study indicate that there are similarities and differences in the risk factors for EOP and LOP. The risk factors that both show an association with preeclampsia are maternal age and chronic hypertension. Tyas et al., confirms that advanced maternal age (>35 years) is an important risk factor for poor maternal outcome in cases of preeclampsia. Preeclamptic women complicated by advanced maternal age are at high risk for poor pregnancy outcomes, cesarean delivery, and postpartum hemorrhage, even though the risk of the complications of preeclampsia itself (HELLP syndrome,

eclampsia, pulmonary edema, and visual impairment) is not increased.[8]

This study confirms that the major risk factors for EOP are maternal age, chronic hypertension, and history of preeclampsia. Li X et al., suggest women with a history of preeclampsia have an increased risk of developing recurrent preeclampsia in future pregnancies. 93.7% women with history of preeclampsia (EOP) developed EOP in second pregnancy and 56.5% women with previous LOP developed EOP in second pregnancy. The baby weight in recurrent preeclampsia was significantly decreased compared to that in first pregnancy with preeclampsia.[9]

Chronic hypertension is the risk factor most closely linked to EOP (OR = 5.97). According to this study, the history of hypertension is typically higher in those with early onset preeclampsia (75% vs 56.2%). This result is consistent with another study that discovered a history of persistent hypertension as one of the risk factors for early onset preeclampsia. The relationship between early onset preeclampsia and chronic hypertension may be due to the end-organ damage and vascular complications that chronic hypertension can produce. Although a family history of hypertension is typically linked to late onset preeclampsia, there may also be a genetic component. This may be occurring because to the distinct pathophysiology of EOP and LOP.[10]

Major risk factors for LOP are maternal age, chronic hypertension, and BMI. The risk factor most associated with EOP is BMI ≥ 25 kg/m2 (OR = 3.27). Robillard et al., late onset preeclampsia (>34 weeks' gestation) is by far the most common phenotype of preeclampsia. In LOP, the main triggers appear to be increased maternal BMI, increased gestational weight, and other clinical characteristics consisting of metabolic syndrome and maternal age.[11]

The current study finding which were consistent with earlier research, demonstrated a significant direct relationship between an increase in BMI and the chance of preeclampsia and pregnancy-related hypertension. For women who were overweight and had a BMI of 26 kg/m2, the adjusted risk of having preeclampsia was twice as high as it was for mothers who were obese and had a BMI of 30 kg/m2.[12,13]

Mechanisms linking obesity with preeclampsia. Pregnancy induced insulin resistance. Reduced cytotrophoblast migration and uterine spiral artery remodeling are linked to obesity or excessive weight gain during pregnancy, which can result in hypoxia and placental ischemia. Under these circumstances, endothelial dysfunction—which is characterized by decreased endothelial nitric oxide production and increased oxidative stress is brought on by the release of soluble anti-angiogenic factor and placental inflammatory factor into the mother circulation. This leads to the typical preeclampsia symptoms of hypertension, proteinuria, and edema.[12-14]

Preeclampsia has uncertain causes, however maternal and placental factors have a role in the disease's etiology. There is increasing evidence to suggest that the pathophysiological features of early onset preeclampsia are different from those of late onset preeclampsia. While late-onset preeclampsia is more closely linked to predisposing maternal variables than to placental involvement, early-onset preeclampsia is more closely linked to intrinsic placental factors.[15,16]

As a limitation of the study, we have to consider the retrospective nature of the study. Even if a lot of data is captured, some details, such the duration of the sexual relationship and/or primipaternity, might not be included. Besides that, the small number of multifetal pregnancies and smokers means that the effect of these factors cannot be assessed. This study has a small study population. It is hoped that future studies can involve a larger study population.

5. Conclusion

The risk factors that differ between early and late onset of preeclampsia were history of preeclampsia and BMI ≥ 25 kg/m2. Maternal age and chronic hypertension were risk factors for both early and late onset preeclampsia. Although they share some etiological features, they also differ with respect to other risk factors. The two preeclampsia types should be treated as distinct entities from an etiological standpoint.

6. Source of Funding

None.

7. Conflict of Interest

None.

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Cite this article: Johnny, Endjun JJ, Nathalia J. Risk factors associated with early and late onset preeclampsia in national referral centre hospital. *Indian J Obstet Gynecol Res*. 2025;12(3):432–436.