

## Comparison of Neonates Outcome in Patients with Early and Late Onset of Preeclampsia at Margono Hospital Purwokerto in the Period June-December 2022

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### Abstract

**Introduction:** Preeclampsia affects 5% to 7% of pregnant women globally and is responsible for more than 70,000 maternal deaths and 500,000 fetal deaths worldwide each year. Preeclampsia has the highest morbidity and mortality rate. There are two subtypes of preeclampsia based on the onset: early-onset preeclampsia (<34 weeks of gestation) and late-onset preeclampsia ( $\geq$ 34 weeks of gestation). The difference in preeclampsia onset may result in different neonatal outcomes. This study aims to evaluate the neonate outcomes in patients with early-onset and late-onset preeclampsia and see whether there is a significant difference between those variables.

**Methods:** The research was conducted at Margono Hospital in Purwokerto, Indonesia. The research design used is observational analytic with a cross-sectional method. The research subjects are 106 pregnant women with preeclampsia who gave birth at Margono Hospital from June to December 2022. Data analysis used is the Mann-Whitney and Chi-square statistical test with a 95% confidence level.

**Results:** The study subjects, consisting of 38 subjects with early onset preeclampsia and 68 subjects with late-onset preeclampsia, showed a significant difference between the onset of preeclampsia and neonatal outcomes, as indicated by birth weight, birth length, APGAR scores, NICU admission, and status of the neonate at discharge, with p-values <0.05.

**Conclusion:** The onset of preeclampsia affects the outcome of neonates.

**Key words:** Neonatal outcome, onset of preeclampsia, preeclampsia.

## Perbandingan Luaran Neonatus pada Pasien dengan Preeklampsia Awitan Dini dan Awitan Lambat di Rumah Sakit Margono Purwokerto pada Periode Juni-Desember 2022

### Abstrak

**Pendahuluan:** Preeklampsia terjadi pada 5% hingga 7% wanita hamil di seluruh dunia dan bertanggung jawab atas lebih dari 70.000 kematian ibu dan 500.000 kematian janin di seluruh dunia setiap tahunnya. Preeklampsia menempati penyakit dengan angka morbiditas dan mortalitas tertinggi, Terdapat dua sub tipe preeklampsia berdasarkan awitannya: preeklampsia awitan dini (usia kehamilan <34 minggu) dan preeklampsia awitan lambat ( $\geq$ 34 minggu kehamilan). Perbedaan awitan preeklampsia dapat mengakibatkan luaran neonatus yang berbeda. Penelitian ini bertujuan untuk mengkaji perbandingan luaran neonatus pada pasien dengan preeklampsia awitan dini dan preeklampsia awitan lambat serta menganalisis perbedaan yang bermakna antara variabel tersebut.

**Metode:** Penelitian dilakukan di RS Margono Purwokerto, Indonesia. Desain penelitian yang digunakan adalah analitik observasional dengan metode cross-sectional. Subjek penelitian ini adalah 106 wanita yang melahirkan di RS Margono Purwokerto dengan diagnosis preeklampsia pada bulan Juni – Desember 2022. Analisis data menggunakan uji statistik Mann Whitney dan Chi-square dengan tingkat kepercayaan 95%.

**Hasil:** Subjek penelitian terdiri atas 38 subjek dengan preeklampsia awitan dini dan 68 subjek dengan preeklampsia awitan lambat. Hasil penelitian menunjukkan adanya perbedaan yang bermakna antara awitan preeklampsia dan luaran neonatus digambarkan dari berat badan lahir, panjang badan lahir, skor APGAR, perawatan NICU, dan kondisi neonatus saat pulang dari rumah sakit dengan nilai  $p < 0.05$ .

**Kesimpulan:** Awitan preeklampsia berpengaruh terhadap luaran neonatus.

**Kata kunci:** Awitan preeklampsia, luaran neonatus, preeklampsia

## Introduction

Epidemiological data show that preeclampsia is the common condition with an incidence of 2–8% of pregnancies worldwide. Preeclampsia is one of the main causes of maternal and perinatal death. The incidence of preeclampsia was found to be higher in nulliparous women (3–7%) than in multiparous women (1–3%).<sup>1</sup> Hypertension in pregnancy occurs in 10% of pregnant women worldwide. These conditions can include preeclampsia, eclampsia, gestational hypertension, and chronic hypertension.<sup>1,2</sup> The incidence of preeclampsia varies widely in each country. The World Health Organization (WHO) estimates preeclampsia is more common in developing countries. The prevalence of preeclampsia in developing countries ranges from 1.8–16.7%.<sup>3</sup>

Preeclampsia is one of the highest causes of maternal mortality in Indonesia. The incidence of preeclampsia in Indonesia is 128,273 cases per year, or about 5.3% of all pregnant women. In the last two decades, there has been no significant reduction in the incidence of preeclampsia in Indonesia.<sup>4</sup> Epidemiological data on preeclampsia in Indonesia are also widely known through research at major hospitals throughout Indonesia. A retrospective cohort study in 2016 at seven referral hospitals in Medan, Bandung, Semarang, Solo, Surabaya, Bali and Manado found 1,232 cases of preeclampsia in one year. Of all these cases, several risk factors were found, such as anemia (26%), obesity (10%), and chronic hypertension (8%). Furthermore, maternal death was reported in 2.2% of cases, while the perinatal mortality rate reached 12%.<sup>5</sup>

Preeclampsia causes significant morbidity and mortality from both maternal and neonatal perspectives. Morbidity and mortality caused by preeclampsia are related to systemic endothelial dysfunction, microvascular thrombosis that causes

ischemia, central nervous system disorders such as seizures or strokes, acute tubular necrosis, coagulopathy, and abruptio placentae.<sup>8</sup>

Moreover, preeclampsia is a complication of pregnancy defined as the new onset of persistent high blood pressure during pregnancy (i.e., systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg and protein in the urine (proteinuria), both occurring after 20 to 20 weeks of gestation.<sup>9</sup> Preeclampsia is divided into two subtypes based on the time of onset of the disease: early-onset preeclampsia, which occurs before 34 weeks of gestation and late-onset preeclampsia, which occurs at 34 weeks of gestation or more.<sup>10</sup>

Preeclampsia, with the highest morbidity and mortality rate, affects 5% to 7% of pregnant women globally and is responsible for more than 70,000 maternal deaths and 500,000 fetal deaths worldwide each year. In the United States, preeclampsia is a leading cause of maternal death, severe maternal morbidity, maternal intensive care, cesarean section, and prematurity.<sup>11</sup> Therefore, this research aims to see how early-onset preeclampsia and late-onset preeclampsia affect neonatal outcomes and see whether there is a significant difference between the onset of preeclampsia and neonatal outcomes.

## Methods

This research uses secondary data obtained from the medical records at Margono Hospital Purwokerto in the period June to December 2022. The research subjects are women who had given birth at Margono Hospital Purwokerto with a diagnosis of preeclampsia. All pregnant women who gave birth from June to December 2022, with a gestational age above 20 weeks, and diagnosed with preeclampsia were included in this study. The research samples were collected from secondary data obtained from

the medical records in accordance with the research variables, consisting of 106 subjects. The samples were selected using the total sampling method. This research is an analytic observational study with a cross-sectional approach because the data concerning the independent and dependent variables are measured in a certain period simultaneously. The population in this study were all women who had given birth at Margono Hospital Purwokerto with a diagnosis of preeclampsia.

The dependent variables of this research include neonatal outcomes, including birth weight, birth length, APGAR score at 1, 5, and 10 minutes, NICU admission, and status of neonate at discharge. Meanwhile, the independent variables include the onset of preeclampsia, divided into early-onset preeclampsia and late-onset preeclampsia. The research was conducted by taking secondary data using the following steps. First, the research determined the source of data/information obtained from the medical records in accordance with the research variables; then, the data was collected and presented in a table. The data was processed by categorizing it according to the group and then analyzed statistically.

Univariate data analysis was carried out to describe the characteristics of each independent variable (the onset of preeclampsia) and the dependent variable (neonatal outcome). Bivariate analysis was used to determine the relationship between the independent variable and the dependent variable. Data analysis using unpaired T-test statistics is performed if the data is normally distributed, and the Mann-Whitney statistical test is used if the data is not normally distributed, with a 95% confidence level. Proportions were compared using the Chi-square test or Fisher's exact test depending on their applicability for the two groups. If the results of  $p < 0.05$ , there is a significant relationship between the independent variable and the dependent variable. If the results of

$p > 0.05$ , there is no significant relationship between the independent and dependent variables.

## Results

This study compares the neonatal outcomes in patients with early-onset and late-onset preeclampsia at Margono Purwokerto Hospital in the period June-December 2022 through secondary data obtained from the results of recording medical records, with a total of 106 research subjects. The characteristics of the research subjects are shown in the following table.

Table 1 shows that most of the subjects were between 21-34-years-old (65 subjects), and most of them experienced late-onset preeclampsia. Moreover, the research subjects showed the median of gestational age is around 36 weeks, with a median of 32 weeks in the early-onset group and a median of 37 weeks in the late-onset group. Most of the subjects were multiparous, with the majority in the late-onset preeclampsia group. According to the BMI before pregnancy, higher proportions were seen in the obese group (38 subjects), and only 33 subjects had a normal BMI. All of the mothers underwent antenatal care at least once, and most of them have visited for antenatal care more than six times. The antenatal care observed in this study included antenatal care performed by midwives, primary health care or obstetrician-gynecologists. In addition, most of the subjects (89 subjects) had a vaginal delivery performed. Out of 106 neonates, 103 neonates were live-born, and 3 neonates were still-born. All live-born neonates will be observed further in this study.

Table 2 describes the outcomes of the neonates observed in this study. The outcome of neonates include birth weight, birth length, APGAR scores at 1, 5 and 10 minutes, and neonate status at discharge. The median birth weight is 2.760 gr, and the median birth

**Table 1 Characteristics of Research Subjects**

Characteristics	Total (n = 106)	Early Onset (n = 38)	Late Onset (n = 68)
<b>Maternal Age (years)</b>			
< 20	4	3	1
21-34	65	23	42
≥ 35	37	12	25
<b>Gestational Age at Delivery (weeks)</b>	36 (26-42)	32 (26-33)	37 (34-42)
<b>Parity</b>			
Primiparous	17	3	14
Multiparous (2-4)	82	32	50
Grand Multiparity (>5)	7	3	4
<b>Prepregnancy BMI (kg/m<sup>2</sup>)</b>			
Underweight (<18.5)	11	0	11
Normoweight (18.5-24.9)	33	11	22
Overweight (24.9 – 29.9)	24	12	12
Obese (≥30)	38	15	23
<b>Antenatal Care</b>			
0	0	0	0
1-2	6	2	4
3-5	17	9	8
≥6	83	27	56
<b>Delivery Method</b>			
Vaginal Delivery	17	6	11
Caesarean Section	89	32	57
<b>Outcome of Delivery</b>			
Live birth	103	36	67
Stillbirth	3	2	1

**Table 2 Neonatal Outcome**

Characteristics	Total (n = 106)	Early Onset (n = 38)	Late Onset (n = 68)	p-value
<b>Birth Weight (gr)</b>	2760 (700-4180)	1970 (700-3645)	3000 (2500-4180)	<0.001
<b>Birth Length (cm)</b>	47 (32-52)	42 (33-49)	46 (32-52)	<0.001
<b>APGAR score</b>				
1'	7 (0-9)	6 (0-9)	7 (0-8)	0.001
5'	8 (0-9)	7 (0-9)	8 (0-9)	0.001
10'	9 (0-10)	8 (0-10)	9 (0-10)	0.001
<b>NICU Admission*</b>				
Yes	26	23	3	<0.001
No	77	13	64	
<b>Status of Neonate at Discharge*</b>				
Alive	88	22	66	<0.001
Dead	15	14	1	

\*= Among live-born neonates (n= 103)

length is 47 cm. Both birth weight and birth length are found to be higher in the late-onset group compared to the early-onset group. The median of the APGAR Score varies in both observed groups, ranging from 6 to 9.

Based on the results of the normality test, the Kolmogorov Smirnov normality test showed  $p < 0.05$ , meaning that the data were not normally distributed, so the Mann-Whitney statistical test was used. The results of the Mann-Whitney statistical test on the onset of preeclampsia on neonatal outcomes showed that there is a significant difference between early-onset preeclampsia and late-onset preeclampsia for the neonatal parameters, including birth weight and birth length ( $p < 0.001$ ) as well as APGAR scores at 1, 5, and 10 minutes ( $p = 0.001$ ).

NICU admission and neonates status at discharge were also observed in this study, and the results were compared among live-born neonates. A chi-square test was performed to analyze the categorical data, showing there is a significant difference between the number of NICU admissions in the early-onset and late-onset preeclampsia groups ( $p < 0.001$ ). Out of 26 neonates admitted to the NICU, 23 neonates were born from mothers in the early-onset preeclampsia group. In addition, the neonates status at discharge shows a significant difference between the two groups ( $p < 0.001$ ). A total of 15 neonates died at discharge; 14 of them were from the early-onset preeclampsia group.

## Discussion

The research results show that there is a statistically significant difference between the onset of preeclampsia and neonatal outcomes, based on birth weight, birth length, and APGAR scores (Table 2). Neonates born from mothers with early-onset preeclampsia tend to be born prematurely (Table 1). Therefore, the median of birth weight and birth length were lower in this group. Intrauterine fetal growth

retardation is reported to tend to occur in babies conceived by mothers with early-onset preeclampsia. In early-onset preeclampsia, placental dysfunction occurs, and it leads to the insufficient nutritional intake of the fetus in the womb, causing the baby to be born with a lower weight and considered small for the gestational age. Babies of mothers with late-onset preeclampsia will not experience growth retardation because the placenta is normal or does not experience functional disorders, so the babies born will have normal birth weight or greater for that gestational age.<sup>12,13</sup> Previous studies have suggested that the pathophysiology of early-onset preeclampsia differs from that of late-onset preeclampsia, even though the causes of preeclampsia are unclear. Early-onset disease appears to be mediated by the placenta, while late-onset disease is mediated by maternal factors and a maternal overreaction to pregnancy.<sup>14</sup>

A study aiming to determine the predictive performance of placental growth factor (PLGF) and FMS-like kinase 1 (SFLT-1) as markers of neonates with low birth weight in a large population-based cohort found that the SFLT-1/PLGF ratio was a potential predictor of birth weight. In a population-based screening, the birth weight of neonates is found to be lower in patients with preeclampsia.<sup>15</sup> A previous research conducted by Lisnawati et al. stated that there were differences in the birth weight of infants between patients with early-onset preeclampsia and late-onset preeclampsia. Babies with low birth weight for gestational age tend to be born from patients with early-onset preeclampsia, whereas babies with birth weight appropriate for gestational age tend to be born from a patient with late-onset preeclampsia. However, there was no significant difference in infant birth weight between patients with severe preeclampsia/early and late-onset eclampsia.<sup>16</sup>

Preeclampsia is a multi-system disorder in pregnant women that can affect the

condition of the fetus through the mechanism of placental insufficiency, putting their children at risk of experiencing intrauterine growth retardation.<sup>17</sup> In addition, Lindheimer et al. stated that patients with preeclampsia have an abnormal placenta, resulting in restriction of placental blood flow, leading to relative hypoxia in the uteroplacental environment. Hypoxic conditions will stimulate the release of factors that can constrict the blood vessels of the placenta, resulting in placental insufficiency and a reduced supply of nutrients to the fetus. This mechanism causes fetal growth retardation in preeclampsia patients.<sup>15</sup>

Regarding the newborn complications, women with preeclampsia had newborns with low birth weight and low APGAR scores at the fifth minute.<sup>18</sup> In this study, there is a significant difference between APGAR scores in the early-onset and late-onset groups (Table 2). The exact mechanism relating the onset of preeclampsia to APGAR scores is still unknown. However, the most likely cause is that the placental dysfunction condition disrupts the adequate intrauterine environment for fetal growth and development.<sup>19</sup> Growth-restricted fetuses have an increased risk of perinatal outcomes and neonatal complications. A study in Ethiopia by Teka et al. reported that women with early onset disease had increased unfavorable perinatal outcomes, including the APGAR score at the 5th minute (AOR = 13.79, 95% CI: 1.16, 163.78), low birth weight (AOR = 10.14, 95% CI 4.29, 23.91), and neonatal death (AOR = 6.82, 95% CI: 1.89, 24.58).<sup>20</sup> In the long term period, newborns are also at greater risk of developmental delays and behavioral problems in childhood and of metabolic hypertension and diabetes in adulthood.<sup>21</sup>

The severity of preeclampsia may also play a significant role in determining the neonatal outcome. A study by Raras et al. concluded that patients with severe

preeclampsia have a large prevalence of adverse side effects with high morbidity and mortality rates that can affect maternal and perinatal outcomes.<sup>22</sup> Mothers with preeclampsia are at risk of giving birth to a baby with low birth weight. In preeclampsia, abnormalities of the placenta and vasospasm, and endothelial injury will occur. In preeclampsia, there is a failure of spiral artery remodeling due to a failed invasion of trophoblasts in the spiral arteries, resulting in decreased uteroplacental blood flow. Reduced blood flow to the uteroplacental could cause hypoxia and placental ischemia, leading to stunted fetal growth. Previous research stated that pregnant women with preeclampsia were four times at risk of giving birth to babies with low birth weight. Moreover, 117 mothers did not have preeclampsia, and as many as 117 mothers gave birth to babies with low birth weights. Another cause of low birth weight from maternal factors was the short interval of birth (less than one year) and low socioeconomic conditions.<sup>23</sup>

Although it is clear that mothers with severe preeclampsia tend to deliver at earlier gestations, the higher birth weight deficit at earlier gestations still persists even after controlling the severity of preeclampsia using matching. Thus, the evidence is insufficient to conclude that the higher incidence of growth restriction in pregnancies delivered at lower gestational ages is related to the preeclampsia severity. Preeclampsia severity is defined clinically in terms of maternal symptoms but may also be considered in terms of direct placental impact.<sup>24</sup> These results are in line with those found in Faiza et al. study, which indicated that mothers with severe preeclampsia had a risk of 3.303 times and 4.5 times for preterm childbirth compared to women without severe preeclampsia. It has been recognized that in severe preeclampsia, preterm birth can occur due to vasospasm of blood vessels, which will reduce blood flow to the placenta and impair the function of the

placental. If vasospasm lasts for a long time, it will interfere with fetal growth. If there is an increase in uterine tone and sensitivity to stimulation, it can result in preterm birth.<sup>25</sup>

Table 2 shows that the rate of NICU admission is higher in neonates born from mothers with early-onset preeclampsia. As discussed before, early-onset preeclampsia is associated with the risk of preterm birth and its complications, therefore resulting in poorer neonatal outcomes. Neonates with birth weight below 2000 gr will be more likely to be admitted to the NICU. A study in Istanbul, Turkey, found that early onset preeclampsia significantly increased the risks of IUGR (OR 2.96; 95% CL: 1.12–7.81), being small for gestational age (OR 2.5; 95% CL: 1.05–5.95), respiratory distress syndrome (OR 15.35; 95% CL: 3.06–76.99), patent ductus arteriosus (OR 11.43; 95% CL: 1.36–96.16) and hospitalization in the NICU (OR 2.48; 95% CL: 1.06–5.77).<sup>26</sup> Furthermore, a study by Weitzner et al. concluded that neonates from mothers in the early onset preeclampsia group were hospitalized longer than those in the late-onset preeclampsia group (9.8 days vs. 4.5 days, respectively;  $P=0.003$ ).<sup>27</sup> In addition, a study from the Netherlands by Joris et al. reported a higher perinatal mortality rate in early-onset preeclampsia associated with an almost twofold increase in perinatal death as compared to pregnancy without preeclampsia.<sup>28</sup> Compared to the late-onset preeclampsia group, this study found that neonates who were discharged dead from the hospital come mainly from the early-onset preeclampsia group (14 out of 15 neonates). It is significantly related, considering that common causes of neonatal death include complications of preterm birth.

This study concludes that the onset of preeclampsia may affect neonatal outcomes. It is associated with the risk of preterm birth and neonatal complications. There is a significant difference in neonatal outcome illustrated by birth weight, birth length,

APGAR score, NICU admission, and neonate status at discharge between early-onset preeclampsia and late-onset preeclampsia ( $p<0.05$ ). The neonatal outcome is found to be poorer in neonates born from mothers with early-onset preeclampsia.

### **Study Limitation**

This research still has limitations in terms of considering other factors that affect the birth weight of the baby, such as the nutritional status of the mother. The nutritional status of pregnant women can usually be measured by anthropometric measurements, namely by assessing the mother's weight gain during pregnancy and measuring the circumference of the pregnant woman's upper arm. The measurement of upper arm circumference is not completely listed in the medical record data, so this variable cannot be included in this study. However, it is expected that in the future, efforts can be made for early detection and management of severe preeclampsia and eclampsia to reduce the risk of fetal growth retardation in pregnant women, one of which can be seen from the birth weight of the baby.

### **Conflict Of Interest**

The authors have no conflicts of interest to declare. We certify that the submission is original work and is not under review at any other publication.

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