# Maternal Characteristics and the Effects of Early and Late-onset Types of Preeclampsia on Maternal and Perinatal Complications

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## ABSTRACT

**Background**: Preeclampsia is still the main cause of morbidity and mortality not only for mothers but also for fetal. The concept of early and late-onset preeclampsia is a more modern concept, and it is stated that these two entities have different etiologies and must be considered as different forms of the disease. This study aims to analyzing differences in maternal characteristics (age, number of parity, history of hypertension and diabetes mellitus) and laboratory results (platelet, ewitz, Lactic Acid Dehydrogenase/LDH) and to analyzing differences in maternal complications (maternal death, eclampsia, impending eclampsia, pulmonary edema, (hemolysis, elevated liver enzyme levels, and low platelet levels/HELLP syndrome) and perinatal complications (perinatal death, Intrauterine Growth Restriction/IUGR, fetal hypoxia and fetal distress) between early and late-onset preeclampsia. This study aimed to investigate the maternal characteristics and the effects of early and late-onset types of preeclampsia on maternal and perinatal complications.

**Subjects and Method**: This was a retrospective cohort study. The study was carried out at Dr. Moewardi Hospital, Surakarta, from January 1, 2016, to December 31, 2017. A total of 548 pregnant mothers with preeclampsia was selected for this study. The dependent variable was the incidence of preeclampsia. The independent variables were age, parity, hypertension, diabetes Mellitus, platelets, LDH, and proteinuria. The data were obtained from the medical record and analyzed by a multiple linear regression.

**Results:** The number of patients with early-onset (162) was less than late-onset (386). More patients have multiparity in early and late-onset. In early-onset preeclampsia, thrombocytopenia and LDH increase tend to be present, and ewitz >+1. Early-onset preeclampsia tends to result in more maternal and perinatal complications.

**Conclusion**: The incidence of early-onset is less than late-onset, but early-onset provides worse complications for both maternal and perinatal.

**Keywords**: Early-onset preeclampsia, late-onset preeclampsia, characteristics, maternal and perinatal complications

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## BACKGROUND

Preeclampsia is still the main cause of morbidity and mortality not only for mothers but also for fetal (Ananth and Wapner, 2013). In the world, the prevalence of preeclampsia is around 5% -15% of all pregnancies (Srinivas et al., 2009).In Indonesia, 30%-40% ofcases of preeclampsia are the cause of death in pregnant women and 30%-50% are the cause of perinatal death. Specifically for hypertension in pregnancy, including preeclampsia, is found in persistent numbers and tends to increase in 5%-7% of pregnancies and is the most frequent medical complication in pregnancy. About 70% of women diagnosed

with hypertension in pregnancy are pre-eclampsia. At the Dr. Moewardi Hospital, Surakarta, the mortality rate of pregnant women in 2012 caused by preeclampsia was 63.30% in which 19 women died from the total of 30 pregnant women and in 2013 was 57.14% in which 12 women died from the total of 21 pregnant women (Sulistyowati et al., 2016).

Preeclampsia is diagnosed when a normotensive pregnant woman at first, after 20 weeks of pregnancy her blood pressure is higher than 140/90mmHg, with or without proteinuria, followed by thrombocytopenia, pulmonary edema and organ lesions that affect the end organs such as kidneys, brain or liver (ACOG, 2013).The mother and fetus are at high risk of getting complications that will be very detrimental if the right action is not implemented earlier.

The exact etiology of preeclampsia is still unclear, suspected endothelial dysfunction plays an important role in the development of preeclampsia (Mateus et al., 2011). Until now there is no effective treatment that has been found to prevent preeclampsia, other than giving birth to a fetus and placenta (Woods et al., 2011).

The complications arising from pre-eclampsia are including eclampsia, hemolytic-elevated liver enzymes and low platelets (HELLP syndrome), Disseminated Intravascular Coagulopathy (DIC), emergency hypertension, encephalopathy hypertension and blindness of the cerebral cortical region (Cunningham et al., 2013).

Preeclampsia is divided into gestational age <34 weeks (early-onset) and gestational age ≥ 34 weeks of (late-onset). The concept of early and late-onset preeclampsia is a more modern concept, and it is stated that these two entities have different etiologies and must be considered as different forms of the disease. Early-onset pre-

eclampsia is caused by placentation disorders in which there is a disturbance of spiral arterial remodeling in myometrial and also trophoblast invasion in the spiral arteriolar wall. In late-onset preeclampsia, a hypothesis is found regarding the maternal constitution which causes maternal endothelial damage which has nothing to do with damage due to trophoblastic invasion.

## SUBJECTS AND METHOD
### 1. Study Design
This was a retrospective cohort study conducted at the Dr. Meowardi Hospital, Surakarta, Central Java from January 1, 2016, to December 31, 2017.
### 2. Population and Sampling
The population in this study was all pregnant mothers with preeclampsia. The patient's data were collected from medical records of Dr. Moewardi Hospital, Surakarta by holding on to the code of severe preeclampsia, namely O14.1 within a period of two years, January 1, 2016, until December 31, 2017. A total of 548 pregnant mothers was selected for this study. With inclusion criteria are all data on preeclampsia patients who gave birth at the Dr. Moewardi Hospital, Surakarta with the ICD 10 code number is O14.1 and exclusion criteria are all patient data from Dr. Moewardi Hospital, Surakarta which is not with ICD 10 code number O14.1 and incomplete data.
### 3. Study Variable
The dependent variable was the incidence of preeclampsia. The independent variables were age, parity, hypertension, diabetes mellitus, platelets, LDH, and ewitz (proteinuria).
### 4. Data Analysis
The analysis used univariate, bivariate (Chisquare), and multiple linear regression with 95% confidence intervals and $p < 0.05$, and processed using SPSS (Software Package

for Social Science) software. The study was approved by the ethics committee Dr. Moewardi Hospital on April 24, 2018, with the number of 521 / IV / HREC / 2018.

## RESULTS

From the data obtained it was found that there were 1845 deliveries over a period of two years, patients with the preeclampsia code O14.1 obtained 548 patient data. From these data, the number of patients with early-onset preeclampsia was 162 patients (29.60%) and 386 patients (70.40%) with late-onset preeclampsia.

**Table 1. Sample Characteristics**

| Variables | Preeclampsia | | | | OR | 95% CI | p |
|---|---|---|---|---|---|---|---|
| | Early-onset (n=162) | | Late-onset (n=386) | | | | |
| | N | % | N | % | | | |
| **Age** | | | | | | | |
| <20 years old | 4 | 2.5 | 13 | 3.4 | | | 0.714 |
| 20-34 years old | 99 | 61.1 | 236 | 61.1 | | | |
| >34 years | 59 | 36.4 | 137 | 35.5 | | | |
| **Parity** | | | | | | | |
| 1 | 38 | 23.5 | 125 | 32.4 | 1.13 | 1.01 to 1.26 | 0.037 |
| >1 | 124 | 76.5 | 261 | 6.6 | | | |
| **History of Hypertension** | | | | | | | |
| No | 105 | 64.8 | 257 | 66.6 | 1.05 | 0.81 to 1.35 | 0.691 |
| Yes | 57 | 35.2 | 129 | 33.4 | | | |
| **History of DM** | | | | | | | |
| No | 146 | 90.1 | 364 | 93.1 | 1.73 | 0.93 to 3.21 | 0.079 |
| Yes | 6 | 9.9 | 22 | 6.9 | | | |
| **Thrombocytopenia** | | | | | | | |
| No(≥100,000) | 120 | 74.1 | 351 | 90.9 | 2.85 | 1.89 to 4.30 | < 0.001 |
| Yes( <100,000) | 42 | 25.9 | 35 | 9.1 | | | |
| **LDH** | | | | | | | |
| No (< 600U/l) | 90 | 55.6 | 346 | 89.6 | 4.28 | 3.05 to 6.02 | <0.001 |
| Yes (>600 U/l) | 72 | 44.4 | 40 | 10.4 | | | |
| **Ewitz** | | | | | | | |
| +1 | 47 | 29.0 | 233 | 60.4 | 1.79 | 1.53 to 2.09 | <0.001 |
| >+1 | 115 | 71.0 | 153 | 39.6 | | | |

Table 1 showed there was no significant difference in maternal age characteristics between early-onset preeclampsia and late-onset preeclampsia (p= 0.850). There was a significant difference between parity of early and late-onset preeclampsia mothers (OR= 1.13; p= 0.037), where early-onset preeclampsia was 76.5% with parity >1, while late-onset preeclampsia was 67.6% with parity >1 time. There was no signify-cant difference in the incidence of hyper-tension between early-onset preeclampsia and late-onset preeclampsia (p= 0.690). There was no significant difference in the incidence of diabetes mellitus between early-onset preeclampsia and late-onset preeclampsia (p=0.079). There was a signi-ficant difference in the incidence of throm-bocytopenia between early and late-onset preeclampsia (OR= 2.85; p<0.001), where early-onset preeclampsia was 25.9% with platelets <100,000, while late-onset pre-eclampsia 9.1% with platelets <100.000. There was a significant difference in the incidence of LDH> 600 between early-onset preeclampsia and late-onset pre-eclampsia (OR= 4.28; p <0.001), where early-onset preeclampsia patients were 44.4% with LDH> 600, whereas late-onset preeclampsia patients were 10.4% with

LDH> 600. There was a significant differrence in the incidence of quality proteinuria > +1 between early-onset preeclampsia and late-onset preeclampsia (OR= 1.79; p <0.001), where early-onset preeclampsia patients were 71.0% with proteinuria > +1, whereas preeclampsia patients late-onset 39.6% with proteinuria > +1. In this study the distribution for proteinuria > +1, which means +2, +3 and +4, the distribution obtained is +2 by 53%, +3 by 39%, and +4 by 8%.

**Table 2. Maternal Complication**

| Variables | Early-onset (n=162) | | Late-onset (n=386) | | OR | 95% CI | p |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | | | |
| **Maternal death** | | | | | | | |
| No | 151 | 93.2 | 384 | 99.5 | 13.10 | 2.93 to 58.46 | <0.001 |
| Yes | 11 | 6.8 | 2 | 0.5 | | | |
| **Eclampsia** | | | | | | | |
| No | 145 | 89.5 | 371 | 96.1 | 2.70 | 1.38 to 5.27 | 0.003 |
| Yes | 17 | 10.5 | 15 | 3.9 | | | |
| **Impending Eclampsia** | | | | | | | |
| No | 134 | 82.7 | 330 | 85.5 | 1.19 | 0.78 to 1.80 | 0.436 |
| Yes | 28 | 17.3 | 56 | 14.5 | | | |
| **Pulmonary edema** | | | | | | | |
| No | 128 | 79.0 | 363 | 94.0 | 3.52 | 2.14 to 5.78 | <0.001 |
| Yes | 34 | 21.0 | 23 | 6.0 | | | |
| **HELLP syndrome** | | | | | | | |
| No | 81 | 50.0 | 351 | 90.9 | 5.51 | 3.88 to 7.83 | <0.001 |
| Yes | 81 | 50.0 | 35 | 9.1 | | | |

Table 2 showed that there was a significant difference in the incidence of maternal mortality between early-onset preeclampsia and late-onset preeclampsia (OR= 13.10; p<0.001), where early-onset preeclampsia patients were 6.8% and late-onset 0.5%. There was a significant differrence in eclampsia between early and late-onset preeclampsia (OR= 2.70; p=0.003), where early-onset preeclampsia patients were 10.50% while late-onset 3.90%. There was no significant difference in the incidence of impending eclampsia between early and late-onset preeclampsia (p= 0.410). There was a significant difference in the incidence of pulmonary edema between early and late-onset preeclampsia (OR= 3.52; p<0.001), where early-onset preeclampsia patients were 21% and 6% late-onset patients with pulmonary edema. There was a significant difference in HELLP syndrome incidence between early and late-onset preeclampsia (OR= 5.51;

p<0.001), where early-onset preeclampsia patients were 50% while late-onset 9.1% with HELLP syndrome.

Table 3 showed that there was a significant difference in the incidence of perinatal mortality between early and late-onset preeclampsia (OR= 8.45; p<0.001) in which early-onset preeclampsia patients were 43.8% while 5.2% of late-onset preeclampsia with perinatal mortality. There was a significant difference in the incidence of IUGR between early and late-onset preeclampsia (OR= 6.18; p<0.001), where early-onset preeclampsia patients were 51.2%, while late-onset was 8.3% with IUGR. There was a significant difference in the incidence of fetal distress/hypoxia between early and late-onset preeclampsia (OR= 2.88; p<0.001), where early-onset preeclampsia patients were 56.8% while late-onset 19.7% with fetal distress/ hypoxia.

**Table 3. Perinatal Complication**

| Variables | Early-onset (n=162) | | Late-onset (n=386) | | OR | 95% CI | p |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | | | |
| **Perinatal death** | | | | | | | |
| No | 91 | 56.2 | 366 | 94.8 | 8.45 | 5.33 to 13.41 | <0.001 |
| Yes | 71 | 43.8 | 20 | 5.2 | | | |
| **IUGR** | | | | | | | |
| No | 79 | 48.8 | 354 | 91.7 | 6.18 | 4.29 to 8.89 | <0.001 |
| Yes | 83 | 51.2 | 32 | 8.3 | | | |
| **Fetal Hypoxia/Fetal Distress** | | | | | | | |
| No | 70 | 43.2 | 310 | 80.3 | 2.88 | 2.26 to 3.67 | <0.001 |
| Yes | 92 | 56.8 | 76 | 19.7 | | | |

**Table 4. Multivariate Analysis Effect of Maternal Characteristics on the Incidence of Preeclampsia**

| Variables | OR | 95% CI | | p |
|---|---|---|---|---|
| | | Lower limit | Upper limit | |
| **Age** | | | | |
| 20-34 years | 0.91 | 0.270 | 3.090 | 0.815 |
| >34 years | 0.85 | 0.240 | 3.076 | 0.791 |
| **Parity (>1)** | 1.40 | 0.853 | 2.308 | 0.183 |
| **Hypertension (Yes)** | 0.84 | 0.541 | 1.332 | 0.476 |
| **Diabetes Mellitus (Yes)** | 1.62 | 0.752 | 3.530 | 0.216 |
| **Platelets (<100.000)** | 1.81 | 1.033 | 3.175 | 0.038 |
| **LDH (>600)** | 4.37 | 2.668 | 7.185 | <0.001 |
| **Proteinuria (>+1)** | 2.14 | 1.369 | 3.345 | <0.001 |

Table 4 showed that greatly influence the incidence of late-onset preeclampsia are LDH variables, with<0.001 and OR= 4.37 (2.66 to 7.18), where patients with LDH > 600 are at risk for early-onset preeclampsia 4.37 (2.66 to 7.18). Other variables that affected were proteinuria (p= 0.001 and OR= 2.14 (1.36 to 3.34) and platelets p= 0.038 and OR= 1.81 (1.03 to 3.17).

### DISCUSSION

#### 1. The effect of maternal age towards preeclampsia

There was no significant difference in maternal age characteristics between early-onset preeclampsia and late-onset preeclampsia (p= 0.850). In this study both show that the age range of 20 to 34 years is the age at which preeclampsia is more common both early and late-onset. This research is in accordance with the theory which states that nutrition in pregnant women plays a role in the incidence of preeclampsia, where women aged > 30 years the level of micronutrients in the blood during pregnancy is lower when compared to young age (Danielle et al., 2014).

#### 2. The effect of parity towards preeclampsia

There was a significant difference between parity of early and late-onset preeclampsia mothers where early-onset preeclampsia was 76.5% with parity > 1, while late-onset preeclampsia was 67.6% with parity> 1 time. The results of this study indicate that the characteristics of preeclampsia women are more directed at parity > 1, which is related to maternal stress factors. A large

number of children (multiparous) is one of the causes of maternal stress. Psychological events such as high-stress levels, anxiety or depression can directly or indirectly affect pregnancy because it causes preeclampsia. Psychological stress can affect up to 18% in pregnant women, where there is a change in the functioning of the neuroendocrine system and the immune system. Dangerous conditions can directly change the hypothalamic-pituitary-adrenal (HPA) axis, which leads to increased cortisol levels and related changes in cellular immunity. High cortisol levels are associated with hypertension and endothelial dysfunction (Priscila et al., 2011).

### 3. The effect of hypertension towards preeclampsia

This study shows no significant difference in the incidence of hypertension between early-onset preeclampsia and late-onset preeclampsia. This is in line with research in Washington, which states that hypertension can be at risk for mothers with early and late-onset preeclampsia (Lisonkova and Joseph, 2013).

### 4. The effect of diabetes mellitus towards preeclampsia

This study shows no significant difference in the incidence of diabetes mellitus between early-onset preeclampsia and late-onset preeclampsia. This is in line with research in Washington, which states that a history of Diabetes mellitus can be at risk in mothers with early and late-onset preeclampsia (Lisonkova and Joseph, 2013).

### 5. The effect of thrombocytopenia towards preeclampsia

This study shows a significant difference in the incidence of thrombocytopenia between early and late-onset preeclampsia where early-onset preeclampsia was 25.9% with platelets <100.000, while late-onset preeclampsia 9.1% with platelets <100.000.

### 6. The effect of LDH towards preeclampsia

This study shows a significant difference in the incidence of LDH> 600 between early-onset preeclampsia and late-onset preeclampsia where early-onset preeclampsia patients were 44.4% with LDH> 600, whereas late-onset preeclampsia patients were 10.4% with LDH> 600 This is in line with research conducted in women in America with results in early-onset of lesions in the placenta that cause abnormalities in the umbilical arteries and uterine arteries, resulting in lysis, thrombocytopenia, IUGR, HELLP syndrome. Whereas, for late-onset, there is no significant disturbance in the placenta, commonly seen in patients with obesity and cardiovascular disease (Mifsud and Sebire, 2014).

### 7. The effect of quality proteinuria towards preeclampsia

This study shows a significant difference in the incidence of quality proteinuria >+1 between early-onset preeclampsia and late-onset preeclampsia where early-onset preeclampsia patients were 71.0% with proteinuria >+1, whereas preeclampsia patients late-onset 39.6% with proteinuria >+1. In this study the distribution for proteinuria > +1, which means +2, +3 and +4, the distribution obtained is +2 by 53%, +3 by 39%, and +4 by 8%. This is related to the basic theory of early-onset preeclampsia that results from trophoblast invasion which causes endothelial damage to blood vessels throughout the maternal body (Mifsud and Sebire, 2014).

### 8. The effect of maternal mortality towards preeclampsia

This study shows a significant difference in the incidence of maternal mortality between early-onset preeclampsia and late-onset preeclampsia where early-onset preeclampsia patients were 6.8% and late-onset 0.5%. Research in women in the

Netherlands concluded that early-onset preeclampsia causes more maternal and infant morbidity and mortality (Boundewijn, 2008).

## 9. The effect of eclampsia towards preeclampsia

This study shows a significant difference in eclampsia between early and late-onset preeclampsia where early-onset preeclampsia patients were 10.50% while late-onset 3.90%. This is consistent with research in Turkish women, concluding that early-onset preeclampsia increases the risk of maternal mortality by twenty times compared with late-onset preeclampsia (Halenur et al., 2015).

## 10. The effect of impending eclampsia towards preeclampsia

This study shows no significant difference in the incidence of impending eclampsia between early and late-onset preeclampsia. Where early-onset preeclampsia patients were 17.30% and late-onset were 14.50% with impending eclampsia.

## 11. The effect of pulmonary edema towards preeclampsia

This study shows a significant difference in the incidence of pulmonary edema between early and late-onset preeclampsia where early-onset preeclampsia patients were 21% and 6% late-onset patients with pulmonary edema. It is stated that early-onset preeclampsia is preeclampsia that has occurred at < 34 weeks gestation and is more due to trophoblast invasion that has occurred at a young gestational age, resulting in long enough endothelial damage in the maternal body which can cause disturbances in the body's circulation increased pulmonary capillary permeability that causes pulmonary edema (Peter et al., 2003).

## 12. The effect of HELLP syndrome towards preeclampsia

This study shows a significant difference in HELLP syndrome incidence between early and late-onset preeclampsia where early-onset preeclampsia patients were 50% while late-onset 9.1% with HELLP syndrome. This is consistent with studies that mention early-onset preeclampsia is associated with higher maternal, perinatal morbidity and mortality, especially in cases such as eclampsia and HELLP syndrome (Hutcheon et al., 2011).

## 13. The effect of perinatal mortality towards preeclampsia

This study shows a significant difference in the incidence of perinatal mortality between early and late-onset preeclampsia in which early-onset preeclampsia patients were 43.8% while 5.2% of late-onset preeclampsia with perinatal mortality. It was stated that in early-onset outcomes of neonatal deaths were higher than late-onset (Simsek et al., 2016).

## 14. The effect of IUGR towards preeclampsia

This study shows a significant difference in the incidence of IUGR between early and late-onset preeclampsia where early-onset preeclampsia patients were 51.2%, while late-onset was 8.3% with IUGR. This study is in accordance with studies in African women, found that fetuses with IUGR output were found in early-onset patients, and were not found in late-onset (Gathiram and Moodley, 2016).

## 15. The effect of fetal distress/ hypoxia towards preeclampsia

This study shows a significant difference in the incidence of fetal distress/hypoxia between early and late-onset preeclampsia where early-onset preeclampsia patients were 56.8% while late-onset 19.7% with fetal distress/hypoxia. This is in line with the results of research in Bandung, Indonesia. It was concluded that the incidence of early-onset was less than late-onset, perinatal complications in the form of IUGR and fetal asphyxia were obtained in

early-onset preeclampsia (Aziz and Johanes, 2016).

From this study, it is known that maternal characteristics that greatly influence the incidence of late-onset preeclampsia are LDH variables where patients with LDH > 600 are at risk for early-onset preeclampsia 4.37 (2.66 to 7.18). Other variables that affected were proteinuria and platelets. These results prove that the theory of the causes of preeclampsia is not only due to trophoblast invasion causes the failure of spiral artery remodeling, but is also influenced by the maternal constitution (Creasy, 2014).

The most common complication in early and late-onset preeclampsia is to look at the OR values for each maternal and perinatal complication. The results showed that maternal mortality was the most common complication, followed by complications of perinatal death and complications of IUGR. This is in accordance with previous studies which stated that maternal and perinatal mortality increased 16 times in early-onset preeclampsia (Lisonkova and Joseph, 2013).

Characteristics of patients with early and late-onset are more likely to lead to multiparity groups, this is related to maternal stress factors that have an impact on the incidence of preeclampsia. A large number of children (multiparity) is one of the causes of maternal stress. Psychological events such as high-stress levels, anxiety or depression can directly or indirectly affect pregnancy because it causes preeclampsia. Psychological stress can affect up to 18% in pregnant women, where there is a change in the functioning of the neuroendocrine system and the immune system. Dangerous conditions can directly change the hypothalamic-pituitary-adrenal (HPA) axis, which leads to increased cortisol levels and related changes in cellular immunity. High

cortisol levels are associated with hypertension and endothelial dysfunction. Early-onset preeclampsia tends to cause maternal complications (maternal death, eclampsia, pulmonary edema, HELLP syndrome) and perinatal complications (perinatal death, IUGR, and fetal distress/ fetal hypoxia).

## AUTHOR CONTRIBUTION

Sintia Damayanti collected the data and wrote the manuscript. Sri Sulistyowati examined data and analyze the data. Ari Natalia Probandari suggested the discussion.

## FUNDING AND SPONSORSHIP

## ACKNOWLEDGMENT

## CONFLICT OF INTEREST

There was no conflict of interest in this study.

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