RESEARCH ARTICLE

Maternal and Perinatal Outcomes of Early-onset and Late-onset Preeclampsia at a Tertiary Center Hospital

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Abstract

Aim: Preeclampsia is still a major health problem in Indonesia, that causes maternal and perinatal morbidity and mortality. This study compares the maternal and perinatal outcomes between early-onset preeclampsia (EO-PE) and late-onset preeclampsia (LO-PE) at a tertiary care center in Indonesia during 2016.

Materials and methods: This cross-sectional study includes 102 patients with preeclampsia. Preeclampsia was divided based on the gestational age: <34 weeks as EO-PE and ≥34 weeks as LO-PE. The primary outcomes were maternal and perinatal outcomes.

Results: The incidence of all preeclampsia in this study was 12.5% during 2016. EO-PE is associated with a longer length of stay compared to LO-PE [8 (5) vs 6 (3); p <0.0001]. Other maternal outcomes, such as mode of delivery, maternal death, eclampsia, HELLP syndrome, gestational diabetes mellitus, and lung edema, were not significantly different. EO-PE was also correlated with worse perinatal outcomes, such as preterm birth (97.6 vs 38%; p <0.001; OR 66.9; 95% CI: 8.49–527.1), baby birth weight [1,525 (763) vs 2,650 (650); p <0.001], baby birth length [41 (6) vs 47 (4); p <0.001], lower Apgar score at first minute [5 (5) vs 7 (2); p <0.0001], and lower Apgar score at fifth minute [7 (5) vs 8 (2); p <0.0001].

Conclusion: EO-PE is associated with worse maternal and perinatal outcomes compared to LO-PE. The presence of EO-PE should be responded to with tight monitoring and early intervention to reduce the risk of maternal and perinatal complications

Keywords: Cross-sectional study, Early-onset preeclampsia, Late-onset preeclampsia, Maternal outcome, Perinatal outcome.

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Introduction

Hypertension in pregnancy is one of the main health problems that causes maternal and perinatal morbidity and mortality worldwide. The prevalence ranged from 1 to 8%.[1,2] Hypertension in pregnancy is an umbrella term of six categories, including preeclampsia–eclampsia, chronic hypertension, chronic hypertension with superimposed preeclampsia, gestational hypertension, white coat hypertension, and masked hypertension.[1–4] Preeclampsia is the most common type of hypertension in pregnancy.[3]

Preeclampsia is defined as new onset of hypertension (≥140/90 mm Hg) that is present above 20 weeks of gestation along with new onset of proteinuria and other systemic multiorgan disorders.[3,5] Indonesia is a huge developing country that is still struggling with maternal neonatal mortality caused by preeclampsia. In Dr Soetomo Hospital, 30% of maternal death was due to preeclampsia during 2013.[6] Based on *Survei Demografi dan Kesehatan Indonesia* 2012, the maternal mortality ratio (MMR) was 359 per 100,000 live births. Preeclampsia was the second highest cause of maternal mortality from 2007 to 2012.[7] In the past 3 years, the incidence of preeclampsia significantly increases in Indonesia.[8] MMR is one of the indicators of women's health development. Millennium Development Goals' target is to reduce three-fourths of MMR in 2015.[9] The MMR due to preeclampsia was 4.91%.[10] The exact cause of preeclampsia is still unknown, and it was agreed as a multifactorial disease. Nowadays, researchers have accepted a new concept to approach preeclampsia. It was divided into early-onset preeclampsia (EO-PE) and late-onset preeclampsia (LO-PE) based on the gestational ages.[5]

EO-PE is preeclampsia that occurs <34 weeks of gestation, and LO-PE occurs ≥34 weeks of gestation. EO-PE and LO-PE have different pathophysiology, clinical manifestations, and clinical outcomes and are therefore considered two different forms of disease.[11–13] EO-PE is characterized by a primary uteroplacental involvement. On the other hand, LO-PE is associated with a maternal factor with normal placentation and uteroplacental perfusion.[12–15] EO-PE is associated with worse maternal and perinatal outcomes; otherwise, LO-PE is usually less severe.[14] The placental factor in EO-PE is caused by poor placentation and shallow remodeling of spiral arteries that happen during the first half of the pregnancy. This placental malformation will cause hypersecretion of pro-inflammatory and antiangiogenic factors to the maternal circulation and lead to the development of the maternal syndrome of preeclampsia. While in the fetus, this pathology will cause uteroplacental circulatory problems and end up in intrauterine fetal growth restriction (IUGR) or intrauterine fetal death (IUFD).[15]

This new concept gives a better knowledge of the etiology and the pathogenesis of this medical riddle.[13] Understanding this new concept will increase awareness of disease severity and maternal

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and perinatal outcomes. Early detection in high-risk women having EO-PE with appropriate intervention could have a significant impact on maternal and perinatal outcomes.[13] This study is aimed to present characteristics of maternal and perinatal outcomes of EO-PE and LO-PE in the Indonesian population.

Materials and Methods

The inclusion criteria of this cross-sectional study involve all pregnant women with preeclampsia in Dr Soetomo General Hospital, a tertiary care center in East Java, Indonesia, from January 2016 to December 2016. This study began after the approval from the Ethics Committee of Dr Soetomo General Hospital (No. 2375/UN3.1.1/PPd.10/2017). One hundred two data were collected from patient medical records. Patients with grossly incomplete data were excluded from this study. Some of the data did not have gestational age and some other data were incomplete due to the lack of information from the referral hospital. Preeclampsia was diagnosed based on the new onset of hypertension (blood pressure ≥140/90 mm Hg), proteinuria in gestational age >20 weeks, and the presence of multiorgan involvement.[3–5] Patients were divided into two groups: EO-PE when preeclampsia occurred at gestational age <34 weeks, while LO-PE when preeclampsia occurred at gestational age ≥34 weeks.[12–14] The maternal and perinatal outcomes were analyzed and compared between both groups. The primary outcome of this study was the maternal outcomes [length of hospital stay , mode of delivery, maternal death, eclampsia, HELLP syndrome, gestational diabetes mellitus (GDM), and lung edema] and perinatal outcomes (perinatal death, IUFD, neonatal death, prematurity, IUGR, baby birth weight, baby birth length, and Apgar score).

Pulmonary edema was diagnosed based on the clinical presentation (severe respiratory distress) and imaging (butterfly appearance on chest X-rays).[8] GDM was diagnosed based on the abnormal 100-g oral glucose tolerance test (minimal two items). Eclampsia was defined as occurrence of new-onset grand mal seizures in women with preeclampsia that can occur before, during, or after delivery.[3] HELLP syndrome was diagnosed with presentation of hemolysis, elevated liver enzymes (AST/ALT >50 U/L), thrombocytopenia (<100.000/μL), and LDH >600 U/L that may occur antepartum or postpartum.[3,6] IUGR was diagnosed during pregnancy using serial ultrasonography and Doppler examination. In ultrasonography, we observed IUGR through fetal biometry femur length/abdominal circumference ratio (FL/AC ratio × 100, >23.5 used as the cutoff), estimated fetal weight <10th percentile, abnormal Doppler examination of the middle cerebral artery and umbilical artery, and cerebroplacental ratio <1. After delivery, it was confirmed by Ballard and Lubchenco score measurement (LS <10%).[2,6,8] Apgar score was measured immediately after birth in the first and fifth minutes. It was assessed by the clinical status of the newborn, consisting of five components: color, heart rate, reflexes, muscle tone, and respiration.[16]

Data were analyzed using SPSS® 23. Test selection was based on evaluating normal distribution variables, employing the Kolmogorov–Smirnov test. Statistics for continuous variables were presented as mean ± standard deviation, while categorical variables were presented as frequencies (*n*%). Testing for the differences of continuous variables between EO-PE and LO-PE groups with normal distribution was accomplished by an unpaired *t*-test. Continuous variables with abnormal distribution were analyzed using the Mann–Whitney test. Testing for the differences of categorical nominal variables was done by the Chi-square (χ^2)-test and used Fisher's exact test when data were not eligible for Chi-square. Categorical ordinal variables were analyzed using a Mann–Whitney test. Differences were considered statistically significant at $p < 0.05$.

Results

There were 143 (12.5%) women admitted with preeclampsia from a total of 1,144 deliveries in Dr Soetomo General Hospital from January to December 2016. Fifty-one data were excluded because of incomplete significant data. Regarding the maternal outcomes, there was a significant difference between EO-PE and LO-PE in-hospital length of stay. EO-PE had a longer length of stay than LO-PE [8 (3–24) vs 6 (2–27), $p = 0.00$]. Other maternal complications (eclampsia, HELLP syndrome, GDM, and lung edema) were not significantly different between both groups, but EO-PE tends to have a higher prevalence except lung edema (Table 1).

The result demonstrated a significant association between the perinatal outcomes and the onset of preeclampsia. Patients with EO-PE had a higher preterm birth [41 (97.6%) vs 19 (38%), $p = 0.00$, OR = 66.9 (CI 95% 8.49–527.1)], smaller baby birth weight [1,525 (520–3,400) vs 2,650 (1,300–2,700), $p = 0.00$], shorter baby birth length [41 (30–51) vs 47 (35–52), $p = 0.00$], and lower Apgar score in the first and fifth minutes (Table 2).

Discussion

The incidence of preeclampsia in this study was 12.5%. This number does not represent the real condition of preeclampsia cases in Indonesia because our hospital is a tertiary referral hospital, which managed only selected patients with complicated conditions. In this study, we found that EO-PE is associated with a significantly longer hospital length of stay compared to LO-PE. EO-PE also had a higher incidence of preeclampsia complications, such as eclampsia, HELLP syndrome, and GDM, although not statistically significant.

A prospective comparative study confirmed that EO-PE had a longer duration of stay in hospital ($p < 0.0001$) and also a higher frequency of HELLP syndrome ($p < 0.0001$).[13] Another cross-sectional study held in Guwahati also states that EO-PE had statistically significant, worse maternal complications than LO-PE.[17] EO-PE needs a longer duration length of stay due to high blood pressure and the occurrence of severe complications.[18] In this study, EO-PE

Table 1: Maternal outcomes in early- and late-onset preeclampsia

Characteristics	*EO-PE (n = 47)*	*LO-PE (n = 55)*	*p value*
Length of stay in hospital (days)[1]	8 (5)	6 (3)	0.000*
Mode of delivery[2]			
Vaginal delivery	17 (39.5%)	17 (33.3%)	0.533
Cesarean section	26 (60.5%)	34 (66.7%)	
Maternal outcomes[3]			
Live	42 (97.7%)	48 (94.1%)	0.622
Death	1 (2.3%)	3 (5.9%)	
Eclampsia[2]	7 (16.3%)	5 (9.8%)	0.349
HELLP syndrome[2]	13 (30.2%)	8 (15.7%)	0.092
Gestational diabetes mellitus[3]	4 (9.3%)	3 (5.9%)	0.699
Lung edema[2]	6 (14%)	12 (23.5%)	0.240

*$p < 0.05$, indicates significant value. [1]Mann–Whitney; [2]Chi-square (χ^2) test; [3]Fisher's exact test

Table 2: Perinatal outcomes in early- and late-onset preeclampsia

Characteristics	*EO-PE (n = 42)*	*LO-PE (n = 50)*	*p value*	*Odds ratio (OR)*
Alive[2]	36 (85.7%)	45 (90%)	0.528	—
IUFD[2]	6 (14.3%)	5 (10%)	0.528	—
Neonatal death[3]	1 (2.4%)	0 (0%)	0.457	—
Gestational age at delivery[2]				
Preterm	41 (97.6%)	19 (38%)	0.000*	66.9 (8.49–527.1)
Term	1 (2.4%)	31 (62%)		
IUGR[3]	5 (11.9%)	4 (8%)	0.727	—
Birth weight[1]	1,525 (763)	2,650 (650)	0.000*	—
Birth length[1]	41 (6)	47 (4)	0.000*	—
Apgar score-1[1]	5 (5)	7 (2)	0.000*	—
Apgar score-5[1]	7 (5)	8 (2)	0.000*	—

*p <0.05, indicates significant value. [1]Mann–Whitney; [2]Chi-square (χ^2) test; [3]Fisher's exact test

had a higher prevalence of maternal complications, such as HELLP syndrome (30.2 vs 15.7%) and eclampsia (16.3 vs 9.8%). These two complications are life-threatening and usually need intensive care treatment that prolongs the length of treatment in the hospital. Also, in our hospital, we still managed EO-PE without any complications conservatively. The patients were monitored tightly and treated in the hospital until the gestational age reached 34 weeks or severe complications developed. When one of these two conditions appears, the pregnancy will be terminated immediately. This conservative treatment was performed to reduce the perinatal mortality and morbidity since the availability of neonatal intensive care unit bed in our hospital is very limited.[6] A longer duration of preeclampsia will lead to the development of a worse maternal complication, related to abundant cytotoxic factors released into the maternal circulation.[3,14,18]

EO-PE that occurred during the second trimester caused poor placentation and subsequent hypoxic placenta. Hypoxic placenta activates pathological cascade including proangiogenic and antiangiogenic imbalance, maternal oxidative stress, endothelial dysfunction, and immunological dysfunction. Angiogenic and antiangiogenic factor imbalance induced placental ischemia and released abundant pro-inflammatory cytokines which result in maternal endothelial dysfunction and increase inflammatory responses.[19,20] These mechanisms lead to the clinical manifestation and complications of preeclampsia, such as hypertension, proteinuria, HELLP syndrome, pulmonary cerebral edema, and eclampsia.[20]

In this study, HELLP syndrome occurrence was higher in EO-PE (30.2 vs 15.7%), although not statistically significant. This finding is in accordance with the previous studies.[21,22] HELLP syndrome incidence was 10% in all severe preeclampsia. Both preeclampsia and HELLP syndrome have their origin in the placenta. Impaired extravillous trophoblast invasion in the decidua layer and insufficient remodeling spiral artery reduced placental perfusion. It liberates bioactive factors that cause maternal generalized endothelial cell dysfunction and induce systemic inflammatory reaction.[22,23] Varkonyi et al. conducted a microarray study of women with EO-PE and HELLP syndrome and concluded that there were similar placental transcriptomes between EO-PE and HELLP syndrome. This similar pathophysiology may lead to shared placental and clinical manifestation between EO-PE and HELLP syndrome.[22] Another explanation is that HELLP syndrome is characterized by an increased sFlt-1/P1GF ratio, an antiangiogenic state. sFlt-1 was found significantly increased in EO-PE, a lot higher than LO-PE.[24] Excess antiangiogenic factors produced by the placenta circulate to the distal organ and cause vascular and peripheral organ damage that will cause widespread organ damage.[24]

The incidence of eclampsia was also higher in EO-PE, although not statistically significant. A prospective study observed that eclampsia is significantly higher in patients with EO-PE compared to the LO-PE group (11.2 vs 4.6%; p <0.007).[25] EO-PE is currently associated with generalized endothelial dysfunction.[26] Because of endothelium involvement, preeclampsia is a global systemic syndrome affecting many maternal organs including the central nervous system. The change in the maternal brain is consistent with the decrease in organ perfusion.[27] This might be the reason why in this study we found that the incidence of eclampsia was higher in the EO-PE group.

EO-PE had earlier gestational age at birth, smaller baby birth weight, baby birth length, and also lower Apgar score at first and fifth minutes. This finding supports the concept that EO-PE is responsible for most of fetal morbidity and mortality.[20] EO-PE is 66.9 times more likely to experience preterm birth than LO-PE. Worse maternal conditions might be the reason for more early iatrogenic termination in EO-PE and lead to a higher preterm birth rate. Other conditions that lead to early termination include uncontrolled blood pressure, abnormal laboratory values, oligohydramnios, and severe IUGR that endanger fetal survival.[13,21,28] These results may show that a pregnancy would not be expected to reach term delivery with a chronically impaired placental implantation, as found in EO-PE.[29] This finding is in line with a prospective comparative study of 158 samples. EO-PE had early termination with a mean gestational age at delivery of 33.57 ± 3.61 vs 36.90 ± 37. The gestational age at delivery had a huge impact on perinatal morbidity and mortality.[13,16,30] In this study, we observed that EO-PE had worse maternal complications, such as eclampsia and HELLP syndrome, that might be the reason for early iatrogenic termination.

This study supports findings of lower baby birth weight and baby birth length in EO-PE like another study.[5] Gomathy et al. state that EO-PE had a birth weight less than 2000 g compared to LO-PE (91.6 vs 15.2%; p <0.0001).[5] Even not significantly different, EO-PE had a higher occurrence of IUGR compared to LO-PE (11.9 vs 8%; p = 0.727). The main pathological feature of EO-PE is the incomplete remodeling of the spiral artery, resulting in hypoperfusion of the placenta and reduced nutrient supply to the fetus and causing IUGR/low baby birth weight. Meanwhile,

LO-PE is associated with normal placental development, placental vessel diameter, uteroplacental perfusion, and placental volume, leading to better perinatal outcomes.[11] The other explanation is related to the timing and duration of the disease. Since EO-PE occurred early in the second trimester compared to LO-PE, this will provide a longer chronic in utero hypoxic environment, while most LO-PEs occurred at the end of the third trimester, leading to a shorter-time uteroplacental perfusion impairment. The finding of LO-PE is usually managed with immediate delivery, providing earlier management for the baby and shorter pathological conditions in utero.[15,31]

Lower Apgar scores at first and fifth minutes were more often found in EO-PE (p <0.05). Apgar score is used for reporting a newborn's status immediately after birth and response during resuscitation.[16] Preterm termination of pregnancy will affect baby birth length, baby birth weight, and Apgar score.[5,13] Adverse perinatal outcomes might be caused by prematurity itself rather than the severity of preeclampsia.[30] Prematurity is associated with low baby birth weight and lower Apgar score.[32–34] There was a higher incidence of lower Apgar scores at lower gestational ages.[35] Another study observed that preterm birth is the most evident risk factor for a low Apgar score. An infant born at 32 weeks of gestation had an Apgar score at fifth minute <7 higher in preterm birth (34 vs 1.1%; p <0.001).[33] That might be the reason that the preterm baby had an unstable condition during the perinatal period.

Conclusion

Preeclampsia stands out as a huge maternal health problem in Indonesia and most low-middle income countries, that caused maternal and perinatal morbidity and mortality. EO-PE is associated with worse maternal and perinatal outcomes. EO-PE should be managed with early intervention, tight observation, and early referral to reduce maternal and perinatal complications. However, optimal management of LO-PE is also important since it forms most PE cases, although having a better prognosis.

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