ORIGINAL RESEARCH

High Morbidity of Preterm Neonates in Pregnancy with Preeclampsia: A Retrospective Study in Indonesia

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Abstract

Background: Preeclampsia is a leading cause of preterm birth, accompanied by compelling maternal and neonatal morbidities. This study aims to investigate preterm neonate outcomes in pregnancy with preeclampsia.

Materials and methods: A retrospective observational study was conducted in Indonesia's national referral hospital. Infants born <37 weeks from January 2015 to December 2018 were recruited, both from preeclamptic and non-preeclamptic mothers. The measured outcomes were necrotizing enterocolitis (NEC), hypoxic–ischemic encephalopathy (HIE), respiratory distress syndrome (RDS), as well as bronchopulmonary dysplasia (BPD).

Results: There were 2,750 preterm neonates enrolled in this study, with 455 neonates born from mothers with preeclampsia. Neonates in the preeclampsia group had a higher incidence of NEC (OR [odds ratio] 2.22; 95% CI [confidence interval] 1.5–3.17), HIE (OR 3.84; 95% CI 1.61–9.17), RDS (OR 5.51; 95% CI 4.35–6.98), and BPD (OR 1.87; 95% CI 1.03–3.42).

Conclusion: Neonatal morbidities, such as NEC, HIE, RDS, and BPD, were found higher in preterm neonates born from preeclamptic mothers compared to uncomplicated pregnant women.

Keywords: Perinatal outcome, Preeclampsia, Preterm labor.

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Introduction

Preeclampsia is one of the major causes of maternal and fetal morbidities.[1] This multisystem disorder is suspected to occur in 3–8% of all pregnancies globally.[2] Recent evidence estimates that the incidence of preeclampsia and eclampsia in Indonesia is 8.6 and 2.5%, respectively.[3] The incidence of preeclampsia in Cipto Mangunkusumo National Referral Hospital in 2013 was 20.9% of all deliveries and most patients were referred from midwives or other hospitals and did not do antenatal care in our hospital.[4]

The high rate of perinatal morbidity and mortality seen in pregnancies complicated by preeclampsia is primarily due to preterm delivery and uteroplacental insufficiency. Uteroplacental circulation disruption may cause disruption of fetal growth, hypoxemia, and even fetal death. Thus, termination of pregnancy is often necessary to minimize maternal–fetal health consequences. Nevertheless, an obstetrician must be able to balance the needs between an adequate fetal maturation and the risks of the mother and fetus when continuing pregnancy with preeclampsia.[1,5]

Problems with preterm neonates occur due to inadequate organ maturation. Neonatal preterm is more susceptible to infection and its various complications than neonates born at term. It possibly leads to disorders of the respiratory system (respiratory distress syndrome [RDS] and bronchopulmonary dysplasia [BPD]), central nervous system (cerebral palsy and hypoxic–ischemic encephalopathy [HIE]), cardiovascular, hematological (thrombocytopenia), and gastrointestinal system (necrotizing enterocolitis [NEC]).[1]

According to WHO, Indonesia has been listed as one of the countries with a high rate of preterm births, with 15.5% of all live births and 36% of all neonatal deaths.[6,7] In Cipto Mangunkusumo Hospital, a national referral hospital in Indonesia, the incidence of preterm birth in 2013 was 38.5%. This study aims to analyze the neonatal outcome in preterm birth complicated by preeclampsia in order to improve potential strategies for treatment options.

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Materials and Methods

A hospital-based retrospective observational study was conducted in the Obstetric and Gynecologic Department, Cipto Mangunkusumo General Hospital, National Tertiary Referral Hospital. Neonates born <37 weeks from January 1, 2015, to December 31, 2018, were included. Preterm neonates born from mothers with complications in pregnancy, such as cardiovascular, thyroid, autoimmune disease, diabetes mellitus, eclampsia, neonates with congenital anomalies, and stillbirths were excluded from the study.

Subjects were classified into control and preeclampsia groups.

The preeclampsia group was categorized based on preeclampsia or severe preeclampsia characteristics based on ACOG-13 criteria,[8] in which women above 20 weeks of gestational age should at least have blood pressure ≥140/≥90 mm Hg (on two occasions, at least 4 hours apart), blood pressure ≥160/≥110 mm Hg (within a short minute), and proteinuria (≥300 mg/24-hour urine collection or >2+ urinary dipstick). In addition, in case no proteinuria is found, the following diagnostic criteria can be applied: thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or headache.[8]

The subtype of preterm delivery based on gestational age was categorized as extremely preterm (24–27 weeks), very preterm (28–31 weeks), and moderate–late preterm (32–36 weeks). The measured outcomes were gestational age and neonatal morbidities, including NEC, HIE, RDS, and BPD. All data were collected from the neonatal medical records.

The data were then analyzed using SPSS 21.0. Bivariate analysis was performed using Chi-square test and Kruskal–Wallis test. The results were considered significant if p is <0.05. The Research Ethics Committee of Faculty of Medicine, Universitas Indonesia, has approved this study prior to any data collection.

Results

During the study period, there were 4,196 deliveries and 2,750 deliveries <37 weeks of gestation (65.5%). There were 455 (16.5%) neonates born to mothers with preeclampsia; 7.3% were extremely preterm and 27.9% and 64.8% were very preterm and moderate-to-late preterm. As much as 31.3% of neonates from the control group were extremely preterm and 19.7% and 49.1% were very preterm and moderate-to-late preterm (p <0.001). Among the neonates born preterm, it was found that 160 (5.82%) subjects were with NEC, 21 (0.76%) subjects with HIE, 1,246 (45.31%) subjects with RDS, and 56 subjects (2.04%) with BPD.

Preterm neonates born from mothers with preeclampsia had a higher incidence of NEC, RDS, HIE, and BPD (Table 1).

Bivariate analysis was done in order to determine the difference in the outcome of subtype preterm neonates with preeclampsia (Table 2).

Neonates in the preeclampsia group had a higher incidence of HIE and RDS in extremely preterm and higher incidence of RDS in very preterm, whereas a higher incidence of HIE, RDS, and BPD was in moderate-to-late preterm compared to the control group. Odds ratio (OR) could not be performed to compare the incidence of BPD in extremely preterm neonates because the number of survived neonates was very small.

Discussion

Our study found a higher incidence of preterm neonatal morbidities, such as NEC, HIE, RDS, and BPD from mothers with preeclampsia. One of the most common diseases found in neonatal intensive care units is NEC. The pathogenesis of the disease is associated with intestinal immaturity, reactive oxygen species (ROS), intestinal microbiome, inflammation, cytokines and local ischemia, or reperfusion injury. Pregnancy-induced hypertension (PIH) may reduce placental perfusion, which promotes fetal hypoxic–ischemic state in the intestine or in its mucosa, or production of inflammatory cytokines, leading to neonatal NEC.[9,10] Our study showed a similar result with a large study in Taiwan, where they found that an increased risk of subsequent neonatal NEC was related to PIH, with OR 1.86; 95% CI (confidence interval) 1.08–3.21.[9]

Neonatal HIE is an encephalopathy caused by hypoxic–ischemic damage leading to a low level of consciousness or seizures in neonates. According to population- and hospital-based studies in developed countries, the HIE incidence ranged 1.0–8.0 per live birth.[11] Our study found a lower incidence of HIE, 0.76% per 2,750 live births, but this might be due to a lower survival rate in extremely preterm neonates in our hospital compared to hospitals in developed countries. However, preterm neonates from the preeclampsia group in our study had a higher incidence of HIE (OR 3.84; 1.61–9.17). Evidence showed that maternal PIH has increased the risk of birth asphyxia, thus subsequently rising the risk of HIE. A cohort study in China showed an increased risk of HIE in women with hypertensive disorders, with a significantly higher risk found among preterm infants compared to full-term infants.[12]

Our study showed a higher incidence of RDS in any subtype of preterm in the preeclampsia group. Tagliaferro et al. showed infants born from preeclamptic mothers had a greater risk to develop severe RDS (OR 2.4; 95% CI 1.8–3.3) and BPD (OR 1.5; 95% CI 1.05–2.14) compared to infants without preeclampsia exposure.[13] The pathophysiological factors of RDS include an insufficient surfactant, overproduction of ROS, hyperoxygenation, and oxidative stress–promoting expression of cytokines.[10] Airway and alveolar progression in accordance with vascular growth are important parameters for normal lung development. Antiangiogenic intrauterine environment in preeclampsia will significantly disrupt fetal lung development, thus predisposing into severe respiratory failure.[13]

The pathogenesis of BPD is complex, including reduced alveolar volume, deficiency surfactant, immature extracellular matrix, inflammation, and oxidative stress.[10] Hypoxia and ischemia caused by preeclampsia may restrict fetal angiogenesis which is critical in alveolarization maintenance.[1] The incidence of BPD in preterm neonates from mothers with preeclampsia was 3.3%, significantly higher than preterm babies born to mothers without preeclampsia (OR 1.87; 1.03–3.42). A cohort study in the United States of Boston stated that the risk of having BPD is increased by the presence of preeclampsia with an OR 2.96 (CI 95% 1.17–7.51, p = 0.01).[14]

Based on our knowledge, this is the first study to analyze the outcomes of preterm neonates from mothers with preeclampsia in Indonesia. The limitations of our study include the absence of information on maternal characteristics and the presence of fetal growth restrictions.

In conclusion, our results support the data that preterm neonates born from preeclamptic mothers have a higher risk to develop NEC, HIE, RDS, and BPD compared to uncomplicated preterm birth.

Table 1: Clinical outcomes of preterm neonates

Variables	*Preeclampsia N = 455*	*Control group N = 2,295*	*p*	*OR; CI 95%*
NEC	47 (10.3%)	113 (4.9%)	<0.001	OR 2.22; 1.50–3.17
HIE	9 (2%)	12 (0.5%)	0.002	OR 3.84; 1.61–9.17
RDS	354 (77.8%)	892 (38.9%)	<0.001	OR 5.51; 4.35–6.98
BPD	15 (3.3%)	41 (1.8%)	0.04	OR 1.87; 1.03–3.42

Chi-square test

Table 2: Neonatal morbidity by subtype of preterm birth based in preeclampsia and control

Neonatal morbidity	*Preeclampsia*	*Control*	*p*	*OR; CI 95%*
Extremely preterm (*n* = 751)				
NEC				
Yes	2 (6.1%)	12 (1.7%)	0.09	3.79; 0.81–17.70
No	31 (93.9%)	706 (98.3%)		
HIE				
Yes	3 (9.1%)	1 (0.1%)	<0.001	71.7; 7.2–709.8
No	30 (90.9%)	717 (99.9%)		
RDS				
Yes	31 (93.9%)	76 (10.6%)	<0.001	130; 930.7–557.9
No	2 (6.1%)	642 (89.4%)		
BPD				
Yes	0	3 (0.4%)	0.40	NA
No	33 (100%)	65 (99.6%)		
Very preterm (*n* = 578)				
NEC				
Yes	29 (22.8%)	58 (12.9%)	0.06	2.00; 0.21–3.29
No	98 (77.2%)	393 (87.1%)		
HIE				
Yes	2 (1.6%)	9 (2%)	0.78	0.78; 0.16–3.68
No	125 (98.4%)	442 (98%)		
RDS				
Yes	119 (93.7%)	315 (69.9%)	<0.001	6.42; 3.05–13.51
No	8 (6.3%)	136 (30.1%)		
BPD				
Yes	8 (6.3%)	27 (5.9%)	0.46	0.73; 0.32–1.67
No	118 (93.7%)	293 (94.1%)		
Moderate-to-late preterm (*n* = 1,421)				
NEC				
Yes	16 (5.4%)	43 (3.8%)	0.22	1.44; 0.80–2.60
No	279 (94.6%)	1,083 (96.2%)		
HIE				
Yes	4 (1.4%)	2 (0.2%)	0.018	7.72; 1.41–42.38
No	291 (98.6%)	1,124 (99.8%)		
RDS				
Yes	204 (69.2%)	501 (42.3%)	<0.001	2.80; 2.13–3.68
No	91 (30.8%)	625 (57.7%)		
BPD				
Yes	7 (2.4%)	7 (0.06%)	0.011	3.88; 1.35–11.16
No	288 (97.6%)	1,119 (99.9%)		

Chi-square test

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