

Risk of small for gestational age babies in preterm delivery due to pregnancy-induced hypertension

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ABSTRACT

BACKGROUND Pregnancy-induced hypertension (PIH) causes high maternal morbidity and mortality worldwide. This study aims to assess the impact of PIH on fetal growth according to gestational age in preterm deliveries.

METHODS A prospective cohort study using secondary data was undertaken in Ende District, East Nusa Tenggara, Indonesia from September 2014 to August 2015. The t-test was performed to compare mean birth weight based on gestational week between normotensive and PIH women, continued by linear regression. The chi-square or Fisher exact test was also conducted to determine the probability of birthing small for the gestational age (SGA) and large for gestational age (LGA) babies between normotensive and PIH women.

RESULTS A total of 1,673 deliveries were recorded in Ende Hospital over the 1-year study period, among which 182 cases involved preterm births. The PIH group had lower birth weight than normotensive women at each gestational age starting from 32–35 weeks ($p=0.004$; 95% CI 150.84–771.36). Normotensive women at gestational ages of 32 ($p=0.05$; 95% CI 0.01–0.83), 34 ($p=0.37$; 95% CI 0.01–4.12), and 36 ($p=0.31$; 95% CI 0.02–2.95) weeks had a lower risk of birthing SGA babies than PIH women; LGA babies were recorded at gestational ages of 33 ($p=1.00$; 95% CI 0.07–37.73) and 35 ($p=0.31$; 95% CI 0.34–63.07) weeks.

CONCLUSIONS Poor perfusion of the uteroplacental is one of the reasons behind intrauterine growth restriction, which results in SGA babies born to PIH women.

KEYWORDS fetal growth, pregnancy-induced hypertension, preterm delivery, small for gestational age

Pregnancy-induced hypertension (PIH), a complication occurring in approximately 2–8% of all pregnancies, causes high maternal morbidity and mortality worldwide.¹ In low- and middle-income countries, 10–15% of all direct maternal deaths are related to PIH.^{1,2} According to Riset Kesehatan Dasar 2007 in Indonesia, PIH is one of three main causes of maternal morbidity and mortality with a prevalence of around 12.7%.³ Unfortunately, the causes of preeclampsia remain unknown; however, some scholars believe that disruption of placental function

in early pregnancy contributes to the condition.¹ PIH is associated with higher risks of adverse perinatal outcomes, including low birth weight and preterm birth, compared with normotension.⁴

Birth weight is influenced by both duration of gestation and rate of fetal growth. PIH, especially preeclampsia, increases the risk of preterm delivery as a maternal indication.⁵ Preterm deliveries occur at <37 weeks of gestational age as a cut-off.⁶ A total of 14.9 million babies (around 11.1%) were born preterm in 2010. The prevalence of preterm births in South

East Asia is approximately 13.6% (1.5 million babies).⁷ According to World Health Organization (WHO) data in 2012, Indonesia reported the 9th highest rates of preterm birth, whereas the rate was 15.5 per 100 live births.⁸ One of the risk factors of preterm labor is uteroplacental ischemia as the hypothesis of PIH. Advanced maternal age, low body mass index (BMI), and multiple pregnancies are also associated with the incidence of preterm birth. Preterm birth is the second largest direct cause of child deaths under 5 years old. While preterm babies can survive, they are at increased risk of developing neurodevelopmental, respiratory, and gastrointestinal complications.⁶

To date, no studies examining the impact of PIH, especially in preterm deliveries, are available in Indonesia. To the best of our knowledge, no studies have yet been conducted on the effect of PIH on the mean birth weight and fetal growth among preterm births in PIH and normotensive women. PIH is known to contribute to preterm birth and low birth weight; preterm births, in turn, increase the risk of perinatal morbidity and mortality. Therefore, this study aims to assess the impact of PIH on fetal growth according to gestational age, especially in preterm deliveries.

METHODS

A prospective cohort study was conducted using data from the registry book of delivery in the emergency room of Ende Hospital, the only hospital in Ende District, East Nusa Tenggara, Indonesia. Data from September 2014 to August 2015 were obtained, and patient confidentiality was guaranteed. All women with singleton pregnancies on preterm labor (<37 weeks of gestation) were recruited and gave informed consent as participants this study without considering signs of life. The exclusion criteria were women with pre-existing (chronic) hypertension, multiple pregnancies, history of diabetes, and cardiovascular disease. These criteria are considered confounding variables that can impact the pathogenesis of PIH and its outcomes.

PIH in this study consisted of gestational hypertension and preeclampsia. An office (or in-hospital) systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg based on the average of at least two measurements, taken at least 15 min apart, using the same arm without proteinuria after the 20th week of gestation was considered gestational hypertension. Preeclampsia was diagnosed

as gestational hypertension with proteinuria or one or more adverse conditions or one or more severe complications. Significant proteinuria was defined as ≥ 0.3 g/d in a complete 24-hour urine collection or ≥ 30 mg/mmol urinary protein/creatinine ratio in a random urine sample or urinary dipstick proteinuria $\geq 1+$. Adverse conditions included maternal symptoms, signs, and abnormal laboratory results, and abnormal fetal monitoring results impacts to the maternal and also the fetal condition.⁹

We defined gestational age through the last menstrual period date according to "Buku Kesehatan Ibu dan Anak" (Mother and Child Health Book), physical examination, and, if available, the results of first- or early second-trimester ultrasonography. Birth weight was classified into two categories, namely for a specific gestational age (GA) and independent of GA. Birth weight based on a specific GA was divided into small for gestational age (SGA), appropriate for gestational age (AGA), and large for gestational age (LGA). SGA was defined as body weight (BW) <10th percentile of the expected weight for GA, AGA was defined as BW between the 10th and 90th percentile of the expected weight for GA, and LGA was defined as BW >90th percentile of the expected weight for GA.

Several potential confounding variables that could influence the outcomes include maternal age and parity. The t-test was performed to compare mean birth weight based on gestational week between normotensive and PIH women. To adjust for potential confounding effects, we applied linear regression using birth weight as the dependent variable and complication (normal=0, PIH=1), parity, and maternal age as independent variables. The regression (β) coefficient was estimated by the method of backward. We also performed chi-square or Fisher exact tests and determined odds ratios to determine the probability of birthing SGA or LGA babies between normotensive and PIH women. All p-values were 2-tailed, and the significance level was set to <0.05. Statistical package for the social sciences (SPSS) 23.0 for Windows was used for all analyses. This article has been accepted for ethical clearance by the Faculty of Medicine Universitas Indonesia (No. 0323/UN2.F1/ETIK/2018).

RESULTS

A total of 1,673 deliveries were recorded in Ende Hospital over the 1-year study period. Of these

Table 1. Characteristics of preterm labor patients

| Characteristics | NBP, n (%) (n=133) | PIH, n (%) (n=39) |
|---------------------------|---------------------|---------------------|
| Age (years) | | |
| <20 | 11 (8.3) | 1 (2.6) |
| 20–35 | 101 (75.9) | 21 (53.8) |
| >35 | 21 (15.8) | 17 (43.6) |
| Gestational age (weeks)* | 34 (23–36) | 33 (24–36) |
| Parity | | |
| Nulliparity | 60 (45.1) | 17 (43.6) |
| Primiparity | 36 (27.1) | 5 (12.8) |
| Multiparity | 37 (27.8) | 17 (43.6) |
| Referral status | | |
| Primary health care | 84 (62.3) | 23 (59.0) |
| General clinic | 5 (3.8) | 5 (12.8) |
| Hospital | 0 (0) | 2 (5.1) |
| Polyclinic | 5 (3.8) | 8 (20.5) |
| Without reference | 39 (29.3) | 1 (2.6) |
| Method of delivery | | |
| Normal | 89 (66.9) | 18 (46.2) |
| Cesarean section | 36 (27.1) | 20 (51.3) |
| Birth weight (g) | | |
| Median (min–max) | 2,450 (500.0–4,100) | 1,875 (500.0–4,000) |
| Mean (SD) | 2,342.9 (655.7) | 1,842.3 (864.7) |
| Sex | | |
| Male | 71 (53.4) | 18 (46.2) |
| Female | 50 (37.6) | 16 (41.0) |

*median (min–max). SD=standard deviation; NBP=normal blood pressure; PIH=pregnancy-induced hypertension

deliveries, 182 cases were preterm births. Seven cases involved multiple pregnancies, two cases involved a history of diabetes mellitus, and one case included chronic hypertension; thus, based on the inclusion criteria, only 172 cases were included in this study. Of these 172 preterm births, 133 women (77.3%) had normal blood pressure while the rest (22.7%) had PIH. Both normotensive and PIH groups were aged 20–35 years old and they were still nulliparity. Most of the women (62.3% of normotensive women; 59.0% of PIH women) were referred from primary health care centers. Overall, the PIH group revealed lower birth weight than the normotensive group (Table 1).

Figure 1 and Table 2 show the impact of PIH on birth weight by gestational age. Babies born at gestational ages <32 weeks were pooled to increase the sample size and enable meaningful comparisons. The minimum gestational age in this study was 23 weeks, and the birth weight recorded at this age was only 650 g. To increase the number of samples,

we combined cases of gestational hypertension and preeclampsia into the PIH group. Overall, the mean birth weight of preterm babies in the normotensive group were higher than those of women in the PIH group at each gestational age starting from 32–35 weeks. Only PIH women at 36 weeks of gestation showed higher mean birth weight than normotensive women (2,756.3 g versus 2,622.7 g). Babies born at gestational ages ≤32 weeks revealed mean birth weight that were statistically different between the normotensive and PIH groups. After adjusting for potential confounding variables, births at all gestational ages from ≤32 weeks showed statistically significant differences between groups, even at 36 weeks. Specifically, the PIH group delivered babies with higher mean birth weight than the normotensive group.

Normotensive women at gestational ages of ≤32 (p=0.05; 95% CI 0.01–0.83), 34 (p=0.37; 95% CI 0.01–4.12), and 36 (p=0.31; 95% CI 0.02–2.95) weeks had a lower

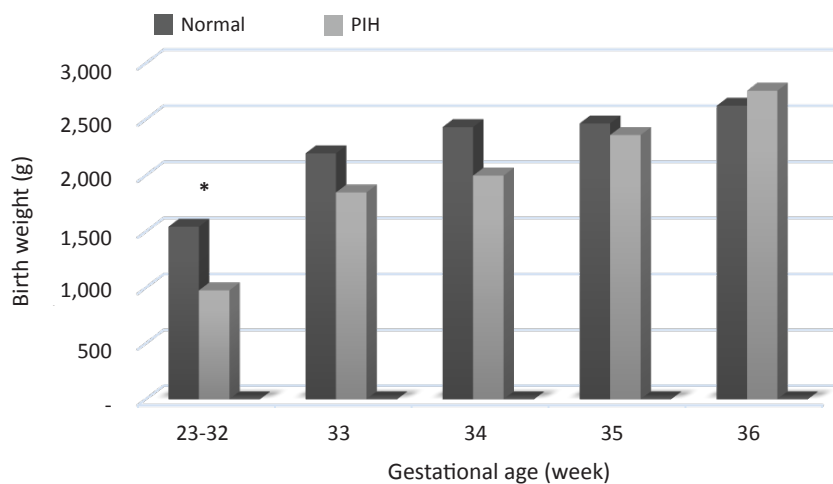


Figure 1. Impact of pregnancy-induced hypertension on mean birth weight by gestational age

*p<0.05. PIH=pregnancy-induced hypertension

risk of birthing SGA babies than PIH women; however, differences found were not statistically significant. LGA babies were observed at gestational ages of 33 (p=1.00; 95% CI 0.07–37.73) and 36 (p=0.31; 95% CI 0.34–63.07) weeks.

Table 3 depicts the impact of PIH on birth weight according to the WHO classification of preterm births. Using this classification, the group including extremely preterm births could not be analyzed due to a lack of samples. The PIH group showed a higher risk of birthing SGA babies (OR 27.00; 95% CI 1.26–578.35; p=0.04) than the normotensive group in the very preterm period, and differences found were statistically significant. In the moderate and late preterm periods, PIH women tended to have a lower risk of birthing LGA babies than the normotensive group; however, differences found were not statistically significant.

DISCUSSION

The prevalence of preterm births in Ende Hospital over the course of a year was 10.9%. This result was not different from the data published by WHO in 1995, which found the prevalence rate in Indonesia to be around 14.2%. In fact, this rate was lower than that in the USA (12.7%), a high-income country, in 2005.¹⁰ The contribution of preterm birth describes the preterm delivery due to maternal and fetal indication. One of the maternal indications of preterm births is PIH. Hauth et al¹¹ revealed that 19.5% of the preterm deliveries they studied were due to PIH. By comparison, our study showed a higher prevalence (28.1%) of preterm deliveries. Baha and Society of Obstetricians and Gynecologists of Canada (SOGC) recommend that all women with severe preeclampsia deliver immediately without considering gestational

Table 2. Univariate and multivariate analyses of the impact of PIH on mean of birth weight by gestational age and the risk of birthing small or large gestational age babies between groups

| Weeks of gestation | Study sample | | BWD mean (g) | SE | β | SGA OR (95% CI) | AGA | LGA OR (95% CI) |
|--------------------|----------------------|------------|--------------|-------|---------|-------------------|------|-------------------|
| | Normotensive (n=133) | PIH (n=39) | | | | | | |
| ≤32 | 21 | 10 | 566.8* | 255.1 | 566.8* | 0.08 (0.01–0.83)* | 1.00 | – |
| 33 | 6 | 6 | 348.3 | 369.1 | 506.9* | – | 1.00 | 1.67 (0.07–37.73) |
| 34 | 28 | 5 | 431.8 | 240.5 | 547.4* | 0.21 (0.01–4.12) | 1.00 | – |
| 35 | 21 | 8 | 103.3 | 214.5 | – | – | 1.00 | 0.81 (0.07–9.18) |
| 36 | 45 | 4 | –133.6 | 477.3 | –134.3* | 0.22 (0.02–2.95) | 1.00 | 4.63 (0.34–63.07) |
| NA | 12 | 6 | | | | | | |

*p<0.05. PIH=pregnancy-induced hypertension; BWD=birth weight difference; SE=standard error of the mean; β=adjustment for maternal age and parity; SGA=small for gestational age; AGA=appropriate for gestational age; LGA=large for gestational age; NA=not applicable

Table 3. Univariate and multivariate analyses of the impact of PIH on mean of birth weight according to the WHO classification and the risk of birthing small or large gestational age babies between groups

| Weeks of gestation | Study sample | | BWD mean (g) | SE | β | SGA OR (95% CI) | AGA | LGA OR (95% CI) |
|--------------------|----------------------|------------|--------------|--------|---------|----------------------|------|------------------|
| | Normotensive (n=133) | PIH (n=39) | | | | | | |
| <28 | 4 | 2 | 450.0 | 422.0 | – | – | 1.00 | – |
| 28–<32 | 13 | 4 | 635.6 | 336.5 | 635.6 | 27.00 (1.26–578.35)* | 1.00 | – |
| 32–33 | 10 | 10 | 605.0 | 274.5* | 605.0* | – | 1.00 | 0.25 (0.02–2.95) |
| 34–<37 | 94 | 17 | 182.5 | 138.3 | 221.0 | 1.87 (0.34–10.30) | 1.00 | 0.75 (0.15–3.67) |
| NA | 12 | 6 | | | | | | |

* $p < 0.05$. PIH=pregnancy-induced hypertension; BWD=birth weight difference; SE=standard error of the mean; β =adjustment for maternal age and parity; SGA=small for gestational age; AGA=appropriate for gestational age; LGA=large for gestational age; NA=not applicable

age.¹² In addition, for preterm deliveries, the SOGC states that women with non-severe preeclampsia at 24 + 0 to 33 + 6 weeks of gestation may consider expectant management only if the very preterm infants' facilities are supported; at gestational ages of 34 + 0 to 36 + 6 weeks, insufficient evidence supporting the merits of expectant management is available.⁹ Therefore, the high rate of preterm deliveries may be attributed to PIH.

Most organizations agree to classified preterm births into extremely preterm (<28 weeks), very preterm (28–<32 weeks), moderate preterm (32–33 weeks), and late preterm (34–<37 weeks). In our study, 18.6% of the cases were extremely to very preterm births, 15.7% were moderate preterm births, and 65.7% were late preterm births. This result was in accordance with Goldenberg et al⁶ who showed preterm birth rates of 20% extremely to very preterm, 20% moderate preterm, and 60–70% late preterm.

This study showed the effect of PIH on birth weight according to gestational age in preterm births. The birth weight of babies in the PIH group was lower than that of babies in the normotensive group by 103.3–566.8 g ($p=0.004$; 95% CI 150.84–771.36); however, at a gestational age of 36 weeks, the birth weight of babies in the PIH group was 133.6 g higher than that of babies in the normotensive group ($p=0.94$). Xiong et al⁵ showed that the effect of decreased birth weight in preeclampsia and gestational hypertension was observed mostly among preterm births and revealed that the overall effect on birth weight depends on the proportion of full-term and preterm deliveries among PIH patients. In an earlier study by Xiong et al,¹³ no difference in mean birth weight between the preeclampsia and normotensive groups was found

due to the small proportion of preeclamptic patients delivering preterm.

This study showed that normotensive women have a lower risk of birthing SGA babies at 32, 34, and 36 weeks of gestation than PIH women. Risks for LGA babies were inconsistent and statistically differed between normotensive and PIH women based on gestational age. In some gestational ages, the risk of birthing SGA and LGA babies could not be determined due to a lack of samples. Maternal hypertension reduces uteroplacental perfusion that contributes to impaired fetal growth and results in SGA babies due to intrauterine growth restriction (IUGR). Ferrazzani et al¹⁴ found that pregnancies complicated by preeclampsia are related to SGA babies due to the influence of maternal proteinuria on fetal outcomes. Proteinuria promotes higher rates of placental insufficiency. Lisonkova et al¹⁵ stated that early-onset preeclampsia increases the risk of birthing an SGA baby (OR 7.19; 95% CI 6.49–7.96) compared with late-onset preeclampsia (OR 2.94; 95% CI 2.80–3.09). Early-onset is preeclampsia occurring at 20–34 weeks of gestation, while late-onset preeclampsia occurs beyond this period. Early-onset preeclampsia presents a higher risk of birthing an SGA baby than late-onset preeclampsia because the profound effects of poor placental perfusion occur during early gestation. At 36 weeks of gestation, the PIH group showed higher mean birth weight and birthed more LGA babies than normotensive women, probably due to the growth-enhancing effects of increased uteroplacental blood flow due to high blood pressure early in the pregnancy.¹⁶ Preeclampsia, which causes preterm deliveries, is more likely to exert a detrimental effect than a beneficial one on fetal growth; however, uteroplacental

hypoperfusion was too short duration to impact the fetal size so that they delivered LGA babies.⁵

This work presents some limitations that had to be noted. We did not know when preeclampsia developed in the women admitted to the hospital, so we assumed that preeclampsia occurred only recently. In addition, the data of PIH in preterm deliveries over the study period, which included only 39 cases, were scarce. Therefore, we merged the data of gestational hypertension and preeclampsia to represent the data of PIH. We also could not provide information about antenatal screening because this procedure was not recorded in the registry book. However, as only one local hospital has been established in Ende District, all PIH cases referred to the hospital within the study year were documented. Finally, we excluded all cases missing birthweight data (10.5% of the cases) from the analysis.

Future epidemiologic and basic molecular studies should be conducted to determine the effect of preeclampsia on birth weight in preterm deliveries. In particular, the onset of preeclampsia must be carefully recorded to evaluate the effect of severity and length of preeclampsia on birthweight.

In conclusion, PIH contributes to preterm deliveries. The earlier the gestational age of PIH, the higher the risk of birthing an SGA baby and the lower the mean birth weight. Poor perfusion of the uteroplacental is one of the reasons behind IUGR, which results in SGA babies born to PIH women.

Conflict of Interest

The authors affirm no conflicts of interest in this study.

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