Preeclampsia Incidences and Adverse Drug

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Preeclampsia Incidences and Adverse Drug Reactions in Relation to Aspirin Administration: A Comparative Study of Doses 80 mg and 125 mg/day in Indonesian Population

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Abstract

This study examined the occurrence of preeclampsia (PE) and the side effects of low-dose Aspirin therapy (80mg versus 125mg) in high-risk pregnant women. Participants were randomly assigned to receive either 80mg or 125mg of Aspirin until 36 weeks of gestation, and outcomes were assessed post-delivery. Of the 93 women involved, 47 received 80mg and 46 received 125mg of Aspirin. While three women in the 80mg group developed PE compared to one in the 125mg group, the difference was not statistically significant (p>0.05). Maternal outcomes and Aspirin side effects were also similar between the groups (p>0.05). Fetal outcomes showed no significant difference in Apgar scores (p=0.054), but a better systolic decrease was associated with the 125mg dose (p=0.015). In conclusion, administration of either 80mg and 125mg Aspirin doses from 12-16 weeks gestation demonstrated comparable effectiveness in preventing PE, with similar maternal outcomes, PE incidence, and drug side effects in Indonesian population.

Keywords: *low dose aspirin, preeclampsia, prevention, maternal outcome, adverse event.*

INTRODUCTION

Preeclampsia (PE) is recognized as the leading cause of perinatal morbidity and mortality, and it is associated with long-term organ damage in women who can overcome these challenges. A prior meta-analysis by Nicolaides et al. demonstrated the efficacy of prophylactic aspirin in reducing the incidence of PE among high-risk mothers (Roberge et al., 2017, p.2). Nevertheless, there persists a prolonged debate regarding the optimal dosage necessary to attain the desired outcome.

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Nicolaides et al. conducted an in-depth meta-analysis, reviewing 45 clinical studies that involved a total of 20,909 pregnant women receiving daily Aspirin doses ranging from 50 to 150 mg. The administration of Aspirin at or before 16 weeks of gestation demonstrated a significant reduction in the risk of PE. This observation suggests a correlation between the dosage of Aspirin and the decrease in risk. The study findings indicated a positive association between the augmentation of Aspirin dosage during the early months of pregnancy and a subsequent decrease in the probability of developing PE. However, the administration of Aspirin after the 16th week of gestation resulted in a less pronounced reduction in the incidence of preeclampsia, showing a moderate to minimal preventive effect. Moreover, there was no apparent trend indicating a dose-dependent relationship (Roberge et al., 2017, p.3).

The administration of low-dose Aspirin therapy has become a standard practice for preventing preeclampsia among individuals at high risk, particularly in developing countries such as Indonesia (Indonesian Preeclampsia Guidelines). There are several dose variations and brand names. The often-utilized preparation is a proprietary formulation containing an 80mg dosage. It is typically more costly than its generic counterparts and may not always be readily accessible at primary healthcare facilities.

The aspirin formulation provided in primary health centers, typically prescribed for pain relief, is of high dosage. In light of this rationale, researchers propose investigating the application of a 125mg Aspirin dosage, falling within the recommended range for low-dose Aspirin administration. Given the geographical challenges faced by primary health centers located in remote and difficult-to-reach areas of Indonesia, this study employs a low-dose Aspirin regimen using a readily available formulation found in these centers. Specifically, this approach involves administering a quarter of the standard 500mg Aspirin tablet dose. Through the adoption of this cost-effective method, patients encounter no difficulty in accessing low-dose Aspirin therapy.

The objective of the current investigation is to assess the most efficient dose regimen, taking into consideration factors such as the accessibility of preparations, cost-effectiveness, safety in both short and long-term usage, and the potential to alleviate preeclampsia while reducing uterine artery resistance. This study's primary goal is to examine the incidence of preeclampsia in high-risk patients receiving low-dose aspirin at two distinct doses: 80 mg/day and 125 mg/day. The secondary aim is to evaluate the impact of both dosage regimens on uterine artery resistance as well as the occurrence of short-term and long-term side effects.

MATERIALS AND METHODS

Study design

This was a randomized, double-blind clinical trial investigation at Dr. Soetomo Hospital Surabaya, the Indonesian tertiary care facility. The study population consisted of pregnant women with a gestational age ranging from 12 to 16 weeks who were enrolled during the designated study period. They were selected from the outpatient obstetric clinics and monitored through delivery. A clearance for ethics was acquired from the Institutional Ethics Committee (No.125/KEH/2019).

The samples were pregnant women (age 18–40 years, singleton or multifetal gestation, and live fetus at 12–16 weeks) with a high risk of preeclampsia (PE). High-risk preeclampsia determined as follows: (a) at least one high-risk factor, including history of PE in a previous pregnancy, diabetes mellitus, chronic hypertension (systolic blood pressure (SBP) 140 mmHg or diastolic blood pressure (DBP) 90 mmHg, which is diagnosed before pregnancy or before 20 weeks gestation), autoimmune disease, (b) at least two intermediate-risk factors, including body-mass index (BMI) ≥28 kg/m^2, advanced maternal age of ≥35 years, family history of PE, or nulliparity. Pregnant women

with known aspirin allergies, histories of asthma, peptic ulcers, liver disease, renal disease, and bleeding disorders were excluded from the study. Written information regarding the trial and an explanation of every part of the study was provided to the eligible study population.

Pregnant participants were subjected to a random allocation procedure, segregating them into two groups. The first group, designated as Group A, was administered a daily dose of 80 mg Aspirin, while Group B received a daily dose of 125 mg of Aspirin. The randomization process was carried out employing block randomization. An online platform (http://www.sealedenvelope.com) was employed to facilitate the block randomization process.

Hospital pharmacists will provide the drugs used in this study. Aspirin 125mg is obtained by dividing a 500 mg dose of salicylic acid into four and then packaging it into capsules; an 80 mg dose of aspirin is also repackaged in the same capsule form. Aspirin is given according to the clinical practice guidelines for preeclampsia which applied at Dr. Soetomo General Academic Hospital. The Aspirin therapy was administered among pregnant women with high-risk of PE from 12-16 weeks until 36 weeks of gestation and evaluated monthly during antenatal care examination.

The primary outcome observed was the development of PE. Secondary objectives were fetal outcome (Birth weight, Apgars score, and NICU admission) and maternal outcome (gestational age at delivery and adverse outcome). PE was diagnosed by the development of new hypertension (BP ≥140/90 mmHg) with abnormal organ involvement during the second half of pregnancy (≥20 weeks of pregnancy) (ISSHP 2014)

A Chi-square test and Fisher's exact test, both descriptive statistics, were used to compare the difference in categorical variables (the number of PE cases and drug side effects). An independent t-test was used to examine the continuous variables with normal distributions. The Mann-Whitney U test was used to look at the variables that were not normally distributed. All statistical analyses were performed using SPSS version 25 (IBM et al., New York, USA), with significance set to $p<0.05$.

RESULTS

Ninety-three pregnant women within the gestational age range of 12-16 weeks met the inclusion criteria and were included in the present study. Among these 93 pregnant women, a randomization protocol was enacted to establish the allocation of low-dose Aspirin therapy 80mg and 125mg. Out of 93 pregnant women, 11 women dropped out and were excluded from the study analysis. The reasons for these dropouts included one instance of patient abortion, another case of patient non-compliance with medication, and nine instances where patients were unable to attend follow-up visits in the hospital. Thus, 82 pregnant women were enrolled; 41 pregnant women were given Aspirin at a dose of 80mg, and the rest were given at 125mg for PE prevention.

Table 1 presents a summary of the participants' demographic and obstetrical characteristics. The mean age of pregnant women in group 80mg was 31.27 ± 5.41 years, and in group 125mg was 30.63 ± 5.33 years. The mean BMI of pregnant women in group 80mg was 26.94 ± 6.29 kg/m^2, and in group 125mg was 26.90 ± 5.82 kg/m^2. The mean gestational age of pregnant women during initial Aspirin therapy given in group 80mg was 14.70 ± 1.64 weeks, and in group 125mg was 14.80 ± 1.79 weeks. No significant differences were found in blood pressure or mean arterial pressure (MAP) at admission across both treatment groups ($p>0.05$).

Table 1. Demographic characteristic of included pregnant women in the study (n = 82)

Variables	80 mg (n = 41)	125 mg (n = 41)	p-value
Maternal age, year	31.27 ± 5.41	30.63 ± 5.33	
<20	1 (2.4%)	0	0.595
20 - 35	31 (75.6%)	33 (80.5%)	
>35	9 (22%)	8 (19.5%)	
Gravida, n (%)			
Primigravida	8 (19.5%)	11 (26.8%)	0.601
Multigravida	33 (80.5%)	30 (73.2%)	
BMI (km/m^2), mean ± SD	26.94 ± 6.29	26.90 ± 5.82	
Non-obese	27 (65.8%)	23 (56.1%)	0.756
Obese	14 (34.2%)	18 (43.9%)	
Gestational age of initial Aspirin therapy, weeks, mean ± SD	14.70 ± 1.64	14.80 ± 1.79	0.429
PE screening category, n (%)			
History taking and physical examination (MAP >90 & ROT >15)	36 (87.9%)	34 (85.2%)	0.616
History of PE or SLE	3 (7.3%)	6 (14.6%)	0.482
Doppler velocimetry (resistive index of uterine artery ≥ 0.58)	2 (4.8%)	1 (0.2%)	1.000
Blood pressure at admission, mmHg, mean ± SD			
SBP	121.8 ± 3.0	123.1 ± 3.0	0.057
DBP	80.6 ± 11.97	80.87 ± 1.48	0.751
MAP at admission, mmHg, mean ± SD	93.92 ± 1.95	94.75 ± 1.65	0.063

Following the administration of low-dose Aspirin treatment from the 12-16 weeks of gestation up until the 36th week, ongoing monitoring was conducted on the pregnant participants throughout their pregnancies until delivery. The findings revealed a total of four incidences of PE, consisting of three cases within the 80mg group and one case within the 125 mg group, with no statistically significant difference between groups ($p>0.05$). This result indicates that administration of 80mg and 125mg for PE prevention in high-risk pregnant women demonstrates considerable outcomes in terms of PE incidence. Regarding the decrease in blood pressure following therapy, it was found that better systolic decrease was associated with administering 125mg of Aspirin ($p=0.015$). However, no significant differences were observed among other variables in terms of maternal outcomes, as presented in Table 2.

Table 2. Comparison of maternal and fetal outcomes between groups (n = 82)

Variables	80 mg (n = 41)	125 mg (n = 41)	p-value
Gestational age at delivery, weeks, mean ± SD	38.04 ± 0.97	38.29 ± 0.55	0.190
Outcome following therapy, n (%)			
Normal	38 (92.7%)	40 (97.6%)	0.616
PE	3 (7.3%)	1 (2.4%)	
BP at delivery, mmHg, mean ± SD			
SBP	115.63 ± 9.27	112.21 ± 5.55	0.065
DBP	74.75 ± 7.0	72.17 ± 4.34	0.483
MAP	88.29 ± 7.65	85.62 ± 4.56	0.381
BP differences (compared to admission), mmHg, mean ± SD			
ΔSBP	6.19 ± 9.48	10.60 ± 6.07	0.015
ΔDBP	5.85 ± 6.71	8.71 ± 4.52	0.081
ΔMAP	5.63 ± 7.63	9.13 ± 4.66	0.053
Delivery methods, n (%)			
Pervaginam	22 (53.6%)	27 (65.9%)	0.513
Cesarean section	19 (46.4%)	14 (34.1%)	
Labor induction, n (%)			
Yes	17 (41.5%)	20 (48.7%)	0.654
No	24 (58.5%)	21 (51.3%)	
Cesarean section indication, n (%)			
Obstetric	16 (84.3%)	13 (92.4%)	
Non-obstetric (HIV)	3 (15.7%)	1 (7.6%)	
Adverse effects, n (%)			
Nausea	-	2 (4.8%)	
Vomiting	-	-	0.241
Gastric bleeding	-	-	
Birthweight, gram, mean ± SD	2,917.93 ± 498.60	2,963.17 ± 109.53	0.611
Apgar score, n (%)			
<7	2 (4.8%)	0	0.054
≥7	39 (95.2%)	41 (100%)	
NICU admission, n (%)	-	-	

DISCUSSION

The administration of low-dose Aspirin appears to be the most promising prevention method for PE, but it is also fraught with controversy regarding its efficacy, dosage, and safety. Thus, this study aimed to evaluate the incidence of PE and drug side effects among pregnant women at high risk of PE who received different daily low-dose Aspirin therapy, which is 80mg or 125mg.

The results of the current study found that there was no significant difference in the incidence of PE between both groups, indicating comparable effectiveness of therapy for PE prevention. During the follow-up period, the incidence of PE in the present study was relatively low in both groups. This finding follows the results of previous research that low-dose aspirin 60-150 can be used to prevent preeclampsia in cases with a high risk of preeclampsia.

The administration of low-dose Aspirin ranging from 60-150 mg in pregnant women 12-16 weeks gestation with positive PE screening or high-risk factors for PE provides an improved response to the incidence of PE so that the administration of low-dose aspirin in this gestational age period provides a protective effect against poor pregnancy outcomes such as PE (Coomarasamy et al., 2001, p.3). A previous study found that administering low-dose aspirin in women with high-risk PE recommended starting this prevention therapy from 12-16 weeks of gestation, as the initial process of spiral artery transformation begins at eight weeks of pregnancy and is completed at 24 weeks of gestation (Espinoza wt al., 2006, p.2). Thus, pregnancy complications such as PE can be prevented.

Increasing the dose of Aspirin may affect the outcome of PE, but both 80 mg and 125mg doses in the present study did not show a statistically significant difference. Notably, the administration of 125mg of Aspirin tended to reduce the incidence of PE compared to 80mg of Aspirin. These findings align with previous studies where bigger doses of Aspirin (100-150 mg) had a more significant effect on improving uterine artery resistance and reducing adverse maternal and neonatal outcomes compared to Aspirin doses of 60-80mg (Roberge et al., 2017, p.3, Devore, 2014).

In the present study, one out of three patients in the 80mg group who developed PE was reported to have advanced maternal age (41 y.o), whereas two patients were found to have a history of PE in prior pregnancy and extreme obesity (BMI 48.4); thus, 80mg dose of Aspirin may be insufficient in preventing PE among these women. This finding agrees with previous research by Adibrata et al., which reported that increasing the daily dose from 80mg to 125mg may significantly reduce uterine arterial resistance, which is a hallmark of the development of PE (Adibrata, 2018).

The maternal age group of 20-35 y.o in the present study dominated the frequency of subjects in both groups compared to other age groups. Despite this age group being deemed not a high-risk factor for developing PE, several other risk factors might contribute to the development of PE, including MAP > 90, ROT > 15, previous history of PE, BMI obesity class I, and extreme obesity. Several characteristics that are the main risk factors for PE have been identified in the earlier study, including maternal age, parity, and BMI (Hypertension in pregnancy, 2013, p. 4). Another previous study found that age is one of the crucial factors for the development of PE, as advanced maternal age (>40 years) might double the risk of developing PE (OR=1.96; 95%CI 1.34-2.87) (Carty et al., 2012). It is noteworthy that the majority of pregnant women who participated in the present study were multigravida with positive PE screening. Even though PE was mainly reported to be a disease of primigravida (Dekker and Sibai, 1993, p.5), the positive PE screening in these women might be due to other risk factors. Similarly, although the majority of pregnant women in the present study were not obese, other factors still can contribute to the development of PE among this population. This finding aligns with a previous study conducted by Ernawati et al., which reported the incidence of PE in patients who were not obese in Indonesia. It was reported that obesity, a definitive risk

factor for PE, almost doubled the risk of developing PE among pregnant women (Carty et al., 2012). Two patients with class I obesity and one with extreme obesity were reported to develop PE in the present study during the follow-up period. In highly obese pregnant women, it can be associated with the dose-response effect of Aspirin in preventing PE by considering the mother's weight (Roberge et al., 2017, p.2, Poon et al., 2019, p.2). From the results of PE outcomes, the 125mg dose of Aspirin tends to be superior to 80mg, as evidenced by the lower incidence of PE.

The decrease in blood pressure and MAP in the present study was not found to be significantly different between the two groups. However, better systolic decrease was significantly associated with administering 125mg of Aspirin. This finding might be attributed to the dose-response effect, as explained in prior studies (Roberge et al., 2017, p.2, Poon et al., 2019, p.2). In normal pregnancy, hemodynamic modifications cause a decrease in blood pressure despite an increase in cardiac output and blood volume (factors that would typically cause an increase in blood pressure). The decrease in blood pressure can be explained by the decrease in peripheral vascular resistance. This is a physiological adaptation of the pregnant woman's body to meet the adequacy of blood flow to the uterus (Cunningham, 2014, p.3; Wareing, 2004, p.2; Roberts, 2014, p.4). The remodeling process of the spiral artery, which has primarily occurred in 12-16 weeks of pregnancy, causes the uteroplacental blood vessels to be relatively vasodilated and unable to respond to vasoactive substances. Consequently, uteroplacental vascular resistance will also be reduced. Thus, it is not surprising if there is adequate uteroplacental blood flow to ensure good fetal growth.

A total of three patients were found at initial PE screening with abnormalities of uterine artery from Doppler velocimetry examination—however, the outcomes of these three patients were reported to be improved following receiving Aspirin therapy. One of the features of PE screening is characterized by decreased uteroplacental circulation, which can be determined from physical examination and ultrasound Doppler velocimetry of the uterine arteries. The principle of this examination is the ability to identify reduced diastolic blood flow in the uterine arteries as a hallmark of impaired placentation (Guzman et al., 2005, p.5). From ultrasound examination, the disruption of placentation among women with PE is characterized by high resistance values in the uterine arteries, which is caused by impaired trophoblast migration in the myometrium and inadequate physiological changes in the spiral artery, as evidenced by histopathological examination (Rolnik et al., 2017, p.6).

The administration of Aspirin may lead to reduced vascular resistance by interfering with platelet aggregation with irreversible inactivation of platelet cyclooxygenase (COX) enzymes, while the dose-dependent effects of Aspirin on endothelial cells quickly restore COX activity so that it is less significant when compared to antiplatelet effects in platelets. Thus, administering low-dose Aspirin can improve the ratio of PGI2 and TXA2, reduce vascular resistance, and improve uteroplacental circulation. This has been proven by administering low doses of Aspirin (60-150 mg/day), preferentially inhibiting thromboxane production without significantly affecting prostacyclin production (Roberge et al., 2017, p.4; Floyd and Ferro, 2014, p.3). Analysis of thromboxane (TBX2) and prostacyclin (6-keto-PGF-1a) metabolites in maternal urine found that low-dose Aspirin reduced thromboxane metabolites by 61-87%, while prostacyclin metabolites had no effect (Walsh et al., 2011, p.4).

There was no significant difference in the comparison of side effects of the drug between groups, although there were two women in the 125mg group experienced nausea. These findings align with Nicolaides' study, which states that there is no difference in side effects following administration of Aspirin therapy (Roberge et al., 2017, p.5; Devore, 2014).

This study represents the first investigation conducted in Asia that aims to examine the efficacy of delivering 80 mg and 125 mg doses of Aspirin. Additionally, it intends to evaluate the effectiveness of administering a 125 mg dose derived from a 500 mg dosage divided into four equal parts. Unfortunately, it solely assessed the clinical outcomes of patients without evaluating the levels of PE biomolecular parameters such as PlGF, sFlt-1, and TNF-α. Consequently, additional research is suggested to investigate the impact of administering aspirin at doses of 80 and 125 in the Asian population, particularly in Indonesia. Furthermore, the effectiveness of administering divided doses concerning alterations in preeclampsia biomarkers necessitates further investigation.

CONCLUSION

The study concludes that among women with high-risk pregnancies, the administration of daily Aspirin 125mg starting between 12 and 16 weeks of gestation until 36 weeks demonstrated a comparable effect in reducing the development of preeclampsia compared to a dose of 80mg. This study also showed a similar fetomaternal outcome (maternal outcomes, the incidence of PE, and drug side effects) in both groups, comparing 80mg and 125mg of Aspirin for the prevention of preeclampsia.

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