Effectiveness of Aspirin Dose in Preventing Preeclampsia in High-Risk Group: A Meta-Analysis

Tigor Peniel Simanjuntak, Elena, Batara Imanuel Sirait
Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Kristen Indonesia, Jakarta, Indonesia
Corresponding Author: Tigor Peniel Simanjuntak, Email: tigorpsimanjuntak@gmail.com

Abstract
Introduction: Preeclampsia is hypertension that occurs after 20 weeks of pregnancy and is accompanied by impaired function of the mother's organs or the uteroplacental unit.
Purpose: To evaluate the efficacy of aspirin doses in preventing preeclampsia in high-risk populations.
Method: This study follows the PRISMA protocol. The reviewers examined all the findings and selected studies that met the inclusion criteria and PICO analysis. Statistical analysis was performed using Review Manager 5.4 software. A total of 14 journals met the inclusion criteria with searches in four databases (PubMed, Science Direct, Google Scholar, and Plos One).
Result: Aspirin significantly reduced the incidence of preeclampsia in the high-risk group (RR 0.83 [95% CI: 0.78, 0.88], P<0.00001), reducing the incidence of preeclampsia by 50 mg/day (RR 0.56 [95% CI: 0.36, 0.86] P=0.008), 60 mg/day (RR 0.87 [95% CI: 0.81, 0.93] P <0.0001), 75 mg/day (RR 0.54 [95% CI: 0.40, 0.73] P<0.0001), 80-81 mg/day (RR 0.72 [95% CI: 0.56, 0.94] P=0.02), and 150 mg/day, reduced the incidence of PE (P<0.00001).
Conclusion: The results of the study show that the best dose of aspirin to prevent PE in high-risk groups is 75 mg/day.

Keywords: aspirin; dose; effectiveness; pre-eclampsia; prevention.

Efektivitas Dosis Aspirin untuk Mencegah Preeklamsia pada Kelompok Risiko Tinggi: Sebuah Metaanalisis

Abstrak
Pendahuluan: Preeklamsia adalah hipertensi yang terjadi setelah usia kehamilan 20 minggu dan disertai dengan gangguan fungsi organ ibu atau uteroplasenta.
Tujuan: Untuk mengetahui efektivitas dosis aspirin untuk mencegah preeklamsia pada kelompok risiko tinggi.
Metode: Penelitian ini mengikuti protokol PRISMA. Para peninjau memeriksa semua temuan dan memilih penelitian yang memenuhi kriteria inklusi dan analisis PICO. Analisis statistik dilakukan dengan menggunakan perangkat lunak Review Manager 5.4. Terdapat 14 jurnal yang memenuhi kriteria inklusi dengan pencarian di 4 database (PubMed, Science Direct, Google Scholar, dan Plos One).
Hasil: Aspirin secara signifikan menurunkan kejadian preeklampsia pada kelompok risiko tinggi (RR 0,83 [95% CI: 0,78, 0,88], P<0,00001), menurunkan kejadian preeklamsia sebesar 50 mg/hari (RR 0.56 [95% CI: 0.36, 0.86] P=0.008), 60 mg/hari (RR 0.87 [95% CI: 0,81, 0.93] P <0,0001), 75 mg/hari (RR 0,54 [95% CI: 0,40, 0,73] P<0,0001), 80-81 mg/hari (RR 0,72 [95% CI: 0,56, 0,94] P=0,02), dan 150 mg/hari, mengurangi kejadian PE (P<0,00001).
Kesimpulan: Hasil penelitian menunjukan bahwa dosis aspirin terbaik untuk mencegah PE pada kelompok risiko tinggi adalah 75 mg/hari.

Kata Kunci: aspirin; dosis; efektivitas; preeklampsia; pencegahan

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Introduction

Preeclampsia (PE) is a pregnancy-specific syndrome that can virtually affect every organ system. Preeclampsia is more than gestational hypertension with proteinuria; the appearance of proteinuria remains an important diagnostic criterion.[1] Referring to the International Society for the Study of Hypertension in Pregnancy (ISSHP) in 2018, PE is hypertension that occurs after 20 weeks of pregnancy, with or without the presence of proteinuria and maternal organ dysfunction or uteroplacental dysfunction.[2]

Preeclampsia or eclampsia is still a health problem in the world of obstetrics and gynecology. Particularly in developing nations, the mortality and morbidity rates due to PE remain high. The increasing rate of PE remains a concern in the world of health, necessitating prevention or treatment, especially in high-risk groups. There are more than 70,000 maternal deaths and 500,000 fetal deaths worldwide each year.[2] Hypertensive disorders during pregnancy were reported in 16% of maternal deaths, and those caused by preeclampsia were reported in 12.3%.[1]

Several medications and methods have been studied to reduce the risk of developing PE. Diets have been studied, including with low consumption of salt, vitamins, and minerals, as well as those that include the use of calcium, aspirin, and heparin.[1] Moreover, several studies have reported that various doses of aspirin can prevent PE. Therefore, the authors explored effective aspirin doses in preventing cardiovascular events in high-risk groups.

Methods

On October 4, 2023, a data search was carried out using four databases, namely PubMed, ScienceDirect, Google Scholar, and Plos One. The data search focused on the topic of using aspirin for the prevention of PE, as listed in Table 1.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were employed in conducting this systematic review and meta-analysis (Figure 1).[3] The inclusion criteria used include (1) international and national journals, (2) journals with a randomized controlled trial (RCT) study design, (3) no limitation on the year of publication of the study, (4) pregnant women at high risk of PE, and (5) therapy with aspirin only. Meanwhile, journal exclusion criteria include (1) review articles, (2) journals that do not report the results of consuming aspirin as a prevention of PE, and (3) journals that do not use RCT

Table 1. Keywords and searching strategy of this systematic review.

Databases	Keywords	Filters	Results
PubMed	(Aspirin OR Acetylsalicylic acid) AND Pre-eclampsia	Free full text. Full text. Clinical trial. Randomized clinical trial.	47
Plos One	Aspirin OR Acetylsalicylic Acid AND Pre-eclampsia	PLOS Medicine	4
Google Scholar	"Effectiveness" AND ("Aspirin" OR "Acetyl-salicylic Acid") AND "Prevent Preeclampsia" AND "RCT"	-	171
ScienceDirect	effectiveness AND aspirin AND prevent pre-eclampsia	Research articles	296

methods.

The selection of journals for quantitative meta-analysis studies employs a population, intervention, comparison, and outcome (PICO) analysis. This study analyzed the effectiveness of aspirin in preventing preeclampsia (PE) in high-risk pregnant women. The study subjects were divided into two groups: one received aspirin as an intervention, while the comparison group received a placebo or did not take aspirin. The primary outcome observed was the incidence of preeclampsia to assess whether aspirin had any benefit in reducing the risk of the condition.

The data is extracted in tabular form. Journal data collected include (1) author and year of publication, (2) research country, (3) research sample, and (4) outcome (dose, intervention, control). Table 2 shows the characteristics of the reviewed articles. Among the 14 studies included, six had a low risk of bias,[4-9] six had a high risk of bias,[10-15] while two exhibited some concerns,[16,17] primarily related to deviations from intended interventions (Figure 2).

After data extraction, a heterogeneity test was performed using the I^2 statistic. If $I^2 < 50\%$, the study was considered homogeneous, and a fixed-effects model was used; whereas if $I^2 > 50\%$, a random-effects model was used. Meta-analysis was performed to calculate the proportion of pooled data with a 95% confidence interval (CI) and $P<0.05$ as an indicator of statistical significance. Moreover, Relative Risk (RR) analysis was used to compare the probability of events between the intervention and control groups. Data processing for meta-analysis uses Review Manager 5.4 software and is presented using a forest plot (Figure 3).

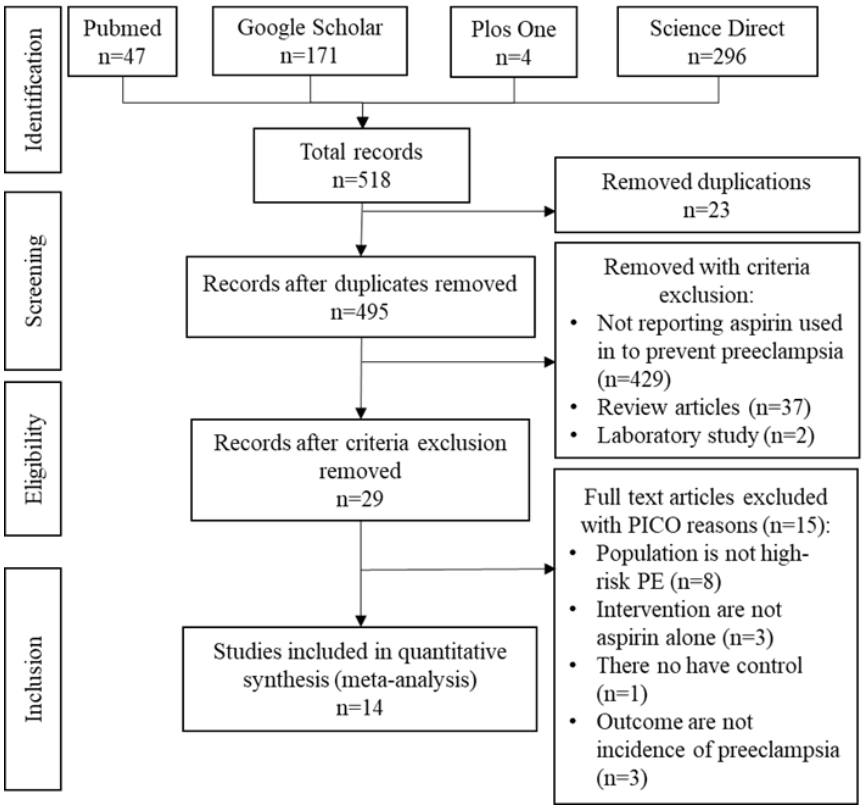

Figure 1 PRISMA Flow

Results

Table 2 Characteristics of the Studies

Author (Year)	Research Country	Characteristics	Results (Incidence of PE)		
			Aspirin Dose (mg/day)	Intervention	Control
Bar *et al*. (1997)[10]	Israel	RCT	60	6/41 (14.6%)	12/46 (26%)
Caritis *et al*. (1998)[4]	US	RCT	60	959/14247 (6.7%)	1082/14049 (7.7%)
Grab *et al*. (2000)[18]	German	RCT	100	3/22 (13.6%)	2/21 (9.5%)
Ebrashy *et al*. (2005)[18]	Mesir	RCT	75	25/74 (33.7%)	40/65 (61.5%)
Moore *et al*. (2014)[5]	US	RCT	60	59/265 (22.26%)	71/258 (27.52%)
Odibo *et al*. (2015)[12]	US	RCT	81	3/16 (18.7%)	3/14 (21.4%)
Liu *et al*. (2016)[13]	China	RCT	100	3/50 (6%)	10/48 (20.8%)
Rolnik *et al*. (2017)[6]	UK, Spain, Italy, Belgium, Greece, and Israel	RCT	150	69/789 (8.74%)	109/822 (13.2%)
Hauspurg *et al*. (2018)[17]	US	RCT	60	Normotension Group: 60/411 (14.5%)	63/416 (15.1%)
				Stage 1 Hypertension 24/101 (23.7%)	36/92 (39.1%)
Tolcher *et al*. (2020)[7]	Spanyol	RCT	60	231/1273 (18.1%)	254/1266 (20%)
Abdi *et al*. (2020)[8]	Iran	RCT	80	27/43 (62.7%)	38/43 (88.3%)
Gu et al (2020)[19]	China	RCT	25	37/272 (13.6%)	51/284 (17.9%)
			50	28/278 (10%)	
			75	26/271 (9.5%)	
Huai *et al*. (2021)[15]	China	RCT	100	Normotension group 4/95 (4.2%)	Normotension group 6/95 (6.3%)
			100	Stage 1 Hypertension 2/44 (4.5%)	Stage 1 Hypertension 10/49 (20.4%)
Lin *et al*. (2022)[20]	China	RCT	100	78/464 (16.8%)	74/434 (17.1%)

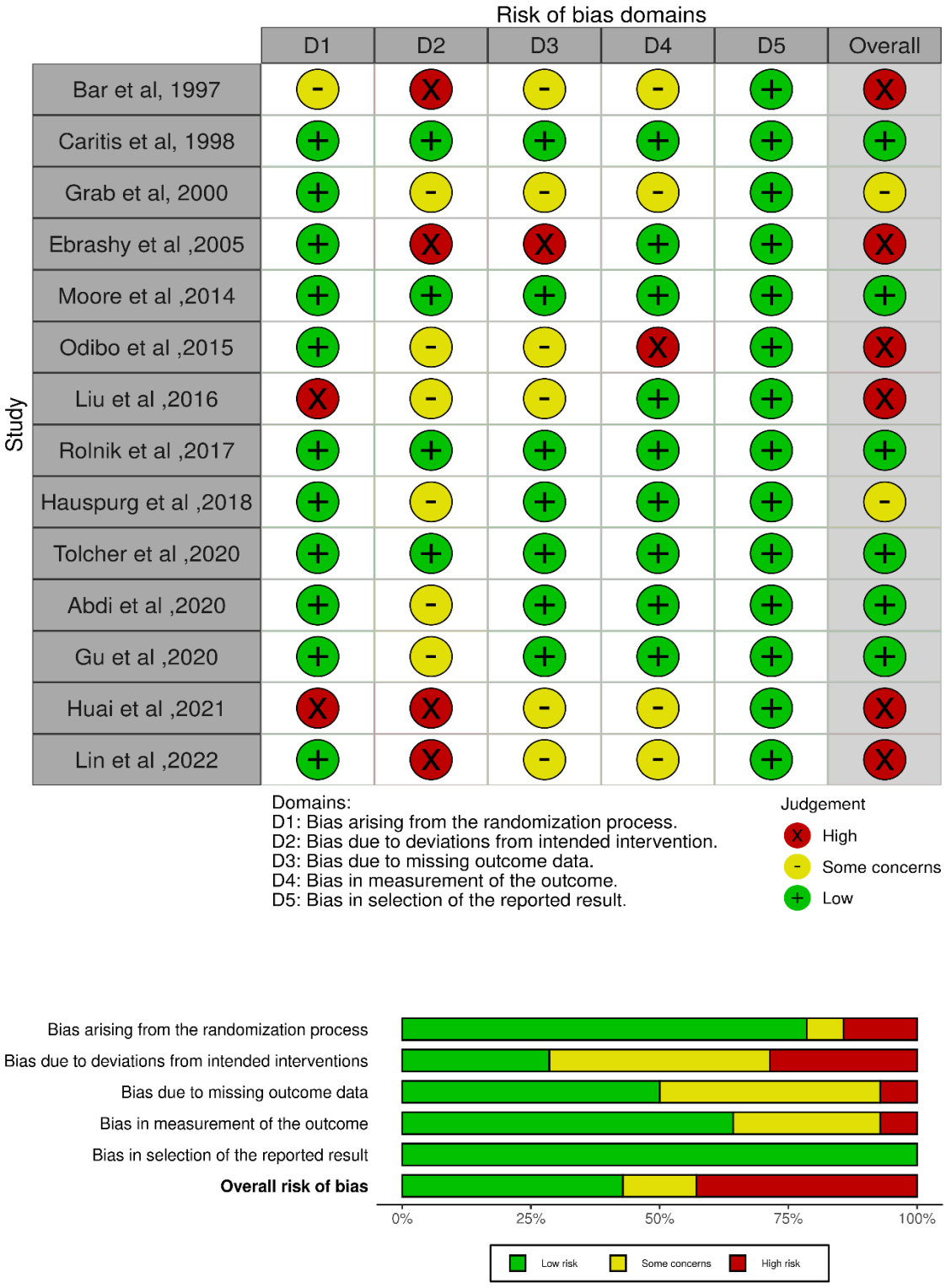

Figure 2 Traffic light plot of the risk of bias assessment.

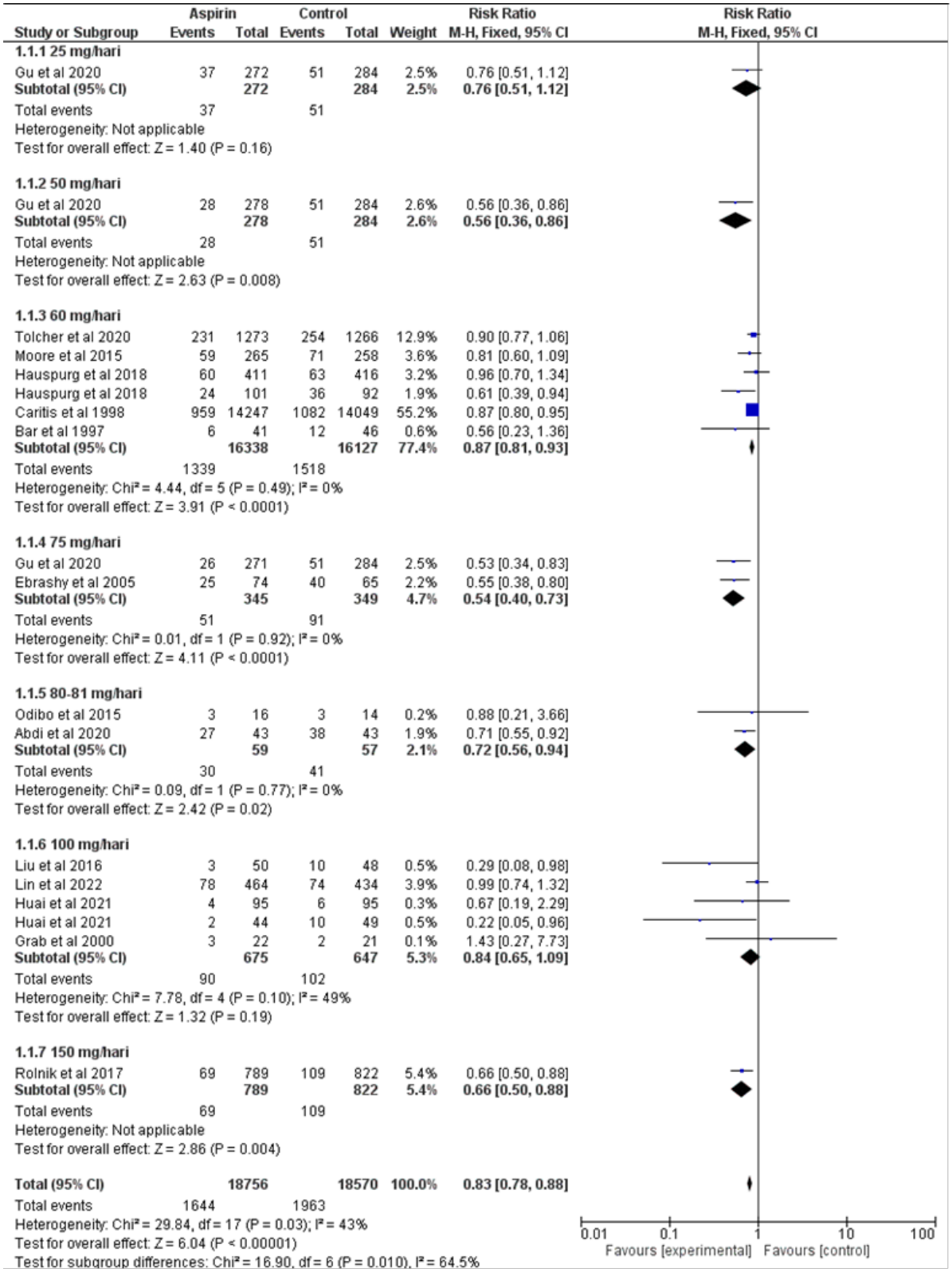

Figure 3 Forest Plot of Aspirin in Preventing Preeclampsia

The use of aspirin at a dose of 25 mg/day was not recommended to reduce the incidence of preeclampsia (PE) in high-risk mothers (RR 0.76 [95% CI: 0.51, 1.12], P=0.16). In contrast, a dose of 50 mg/day showed effectiveness in reducing the incidence of PE (RR 0.56 [95% CI 0.36, 0.86], P = 0.008).

Aspirin 60 mg/day is also recommended as the analysis showed homogeneity (I^2 = 0%, P = 0.49) with RR 0.87 [95% CI: 0.81, 0.93], P<0.0001. Similarly, the 75 mg/day dose yielded similar results (RR 0.54 [95% CI: 0.40, 0.73], P<0.0001; I^2 = 0%, P = 0.92).

Doses of 80-81 mg/day showed effectiveness in reducing the risk of PE with maintained homogeneity (I^2 = 0%, P = 0.77) and a relative risk (RR) of 0.72 [95% CI: 0.56, 0.94], P = 0.02. However, the use of 100 mg/day was not recommended because the results were not significant (RR 0.89 [95% CI: 0.76, 1.04], P = 0.14) and heterogeneity was observed (I^2 = 50%, P = 0.09).

In contrast, a dose of 150 mg/day can be recommended, as it has been shown to be effective in reducing the risk of PE (RR 0.66 [95% CI: 0.50, 0.88], P = 0.004). Overall, the meta-analysis revealed that aspirin use can help prevent PE in high-risk mothers (RR 0.83 [95% CI: 0.78, 0.88], P<0.00001) with good homogeneity (I^2 = 43%, P = 0.03).

Discussion

Preeclampsia causes death in 60,000 mothers and more than 500,000 premature births worldwide each year. The disease can cause proteinuria, acute kidney injury, liver dysfunction, hemolysis, thrombocytopenia, hepatic rupture, seizures, and stroke.[21]

This meta-analysis reviewed 14 experimental studies, involving 18,756 participants, to evaluate the efficacy of therapeutic doses of aspirin in preventing preeclampsia in high-risk groups. The results showed that aspirin doses of 50 mg/day (RR 0.56 [95% CI: 0.36, 0.86], P=0.008), 60 mg/day (RR 0.87 [95% CI: 0.81, 0.93], P<0.0001), 75 mg/day (RR 0.54 [95% CI: 0.40, 0.73], P<0.0001), 80-81mg/day (RR 0.72 [95% CI: 0.56, 0.94], P=0. 02), 150 mg/day (RR 0.66 [95% CI: 0.50, 0.88], P=0.004) can reduce the incidence of preeclampsia but aspirin at a dose of 25 mg/day (RR 0.76 [95% CI: 0.51, 1.12], P=0.16) and 100 mg/day (RR 0.89 [95% CI: 0.76, 1.04], P=0.14) cannot reduce the incidence of preeclampsia. These findings suggest that aspirin may be a helpful intervention in preventing preeclampsia.

This meta-analysis is in line with the study by Gu *et al*., which shows that aspirin at a dose of 25 mg/day significantly reduces the incidence of preeclampsia and early preeclampsia.[19] Moreover, this meta-analysis is in line with the meta-analysis of 39 research studies by Wang et al., which shows that aspirin at doses of 60 mg/day, 75 mg/day, and 80 mg/day has a beneficial effect on reducing the risk of preeclampsia in pregnant women.[22] However, this meta-analysis differs from the study by Wang *et al*., which showed that aspirin at 50 mg/day and 81 mg/day cannot reduce the risk of preeclampsia in pregnant women. This discrepancy may be due to differences in the type of population and the number of studies included.[22] This meta-analysis is in line with a previous meta-analysis, a study of 59 research studies by Komoróczy *et al*., showing that aspirin at a dose of 100 mg/day does not reduce the risk of preeclampsia in pregnant women.[23] In addition, this meta-analysis is in line with another meta-analysis of four research studies by Ghesquiere *et al*., showing that aspirin at a dose of 150 mg/day reduces the risk of preeclampsia in pregnant women.[24]

Women with high risk factors or moderate risk for preeclampsia should receive low-dose aspirin (81mg/day) for preeclampsia prophylaxis starting from 12 weeks to 28 weeks of gestation and continuing until delivery.[25] This recommendation is consistent with the findings of this study, the use of low-

dose aspirin 80-81mg/day (RR 0.72 [95% CI: 0.56, 0.94], P=0.02). Aspirin selectively and irreversibly inactivates the COX-1 enzyme, suppresses prostaglandin and thromboxane production, and inhibits platelet aggregation. The mechanism by which aspirin prevents preeclampsia remains unknown, and the proposed mechanisms are largely speculative, based on in vitro studies.[26]

This meta-analysis has several strengths. This is the most comprehensive review of aspirin use in the prevention of preeclampsia in women with high-risk factors. This study used seven aspirin dose samples and investigated the effects of all seven doses in women at high risk of preeclampsia. However, it remains to acknowledge some limitations, such as the relatively limited number of samples in each dose group, which may have affected the power of the statistical analysis performed. In addition, the variety of aspirin doses used in this study was limited, which restricted our ability to thoroughly evaluate the association between lower aspirin dose levels, such as 25 mg, and the prevention of preeclampsia. Finally, further studies with a larger sample size and a wider dose range are necessary to gain a more comprehensive understanding.

Disclosures

Funding

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Conflict of Interest

We declared that there was no conflict of interest.

Author Contribution

Tigor P. Simanjuntak, Elena, and Batara I. Sirait were involved in concepting. Tigor P. Simanjuntak and Elena were involved in designing and conducting the study. The manuscript was under the supervision of Tigor P. Simanjuntak. The data are analyzed by Tigor P. Simanjuntak. The final version of the paper is prepared by all Authors, who consent to its submission to this journal.

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