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Meta-Analysis

The Effect of Low Dose of Aspirin on the Preeclampsia in Pregnant Women: A Meta-Analysis

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ABSTRACT

Background: In 2020 there were 4,627 maternal deaths in Indonesia. Preeclampsia is a complication in pregnancy that occurs 2-8% of all pregnancies and is a major cause of maternal morbidity. Low-dose aspirin has been shown to be a safe and effective primary prevention for the incidence of preeclampsia. With preventive measures can reduce both moral and material losses for patients at high risk for the incidence of preeclampsia. The purpose of this study was to estimate the magnitude of the effect of low-dose aspirin on the incidence of preeclampsia in pregnant women based on previous research.
Subjects and Method: This study is a systematic review and meta-analysis. Article searches were conducted using electronic databases such as Google Scholar, PubMed, Cochrane, Science Direct. The articles used are published articles from 2012-2022. The keywords used to search the article were "Aspirin OR Acetylsalicylic Acid AND Prevention AND Pre-Eclampsia OR Toxemia AND Randomized Controlled Trials". The inclusion criteria used are articles with randomized control trial studies, full text articles are available, the results of the analysis used are Risk Ratio. The population of the study was high-risk pregnant women, the research intervention was the administration of low-dose aspirin, the study comparison was a placebo, and the outcome of the study was preeclampsia, the articles were in English or Indonesian. The article search results are listed in the PRISMA diagram and analyzed using the Review Manager 5.3 application.
Results: A total of 7 articles from China, America, India, Congo, Guatemala, Pakistan, and Finland showed that aspirin had an effect of 0.87 times in reducing the incidence of preeclampsia when compared with placebo or no administration (RR = 0.87; 95% CI 0.72 to 1.05). although not statistically significant (p=0.160).
Conclusion: Low-dose aspirin affects the incidence of preeclampsia in pregnant women.

Keywords: low-dose aspirin, preeclampsia, pregnant women.

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BACKGROUND

The number of maternal deaths compiled from the recording of family health programs at the ministry of health in 2020 shows 4,627 deaths in Indonesia (Ministry of Health, 2021). Hypertension in pregnancy is a health problem that contributes to high mortality and morbidity rates and pre-eclampsia is a complication in pregnancy that occurs 2-8% of all pregnancies and is a major cause of maternal morbidity (Scazzocchio et al., 2017). Efforts that can be made

to accelerate the decline in MMR are to ensure that every mother is able to access quality health services and prevent and manage pregnancy complications and improve care for pregnant women (Ministry of Health, 2021). Efforts to improve prenatal care are an important step towards achieving sustainable development health targets (SDGs). WHO (2011) issued a recommendation as a preventive measure to prevent preeclampsia, namely the administration of low-dose aspirin (75 mg) in high-risk women and starting before 20 weeks of gestation. The US Preventive Services Task Force (USPSTF) also recommends the use of aspirin to prevent morbidity and mortality due to preeclampsia and recommends low-dose aspirin 81 mg/day at >12 weeks' gestation in pregnant women at high risk for preeclampsia (Espinoza, 2021). This therapy inhibits thromboxane-mediated vasoconstriction and prevents failure of the physiologic transformation of the spiral arteries. Its use is not associated with significant complications (Iskandar et al., 2017). By finding preventive measures for the incidence of preeclampsia, it is expected to reduce both moral and material losses for patients at high risk for the incidence of preeclampsia. On this basis, researchers are interested in conducting a study using a systematic review and meta-analysis approach to investigate relevant clinical studies regarding the effect of low-dose aspirin on the incidence of preeclampsia.

SUBJECTS AND METHOD

1.Study Design

This study uses a systematic review and meta-analysis. Article searches were conducted using electronic databases such as Google Scholar, PubMed, Cochrane, Science Direct. The articles used are published articles from 2012-2022. The keywords used to search the article were “Aspirin OR Acetylsalicylic Acid AND Prevention AND Pre-Eclampsia OR Toxemia AND Randomized Controlled Trials”. The article search results are listed in the PRISMA diagram and analyzed using the Review Manager 5.3 application.

2.Inclusion Criteria

The inclusion criteria used were articles with randomized control trial studies, full text articles were available, the results of the analysis used were Risk Ratio (RR), research outcomes were preeclampsia, articles used English or Indonesian.

3. Exclusion Criteria

The outcome measures in the study were incomplete/did not describe the results clearly. Year of publication > 10 years. Interventions and populations that are carried out are different. Paid/locked articles.

4. Variable Operational Definition

In formulating research problems PICO is used. The population is pregnant women with high risk. The intervention was administration of low-dose aspirin, and the comparison was placebo or no administration, the final outcome was the incidence of preeclampsia.

Preeclampsia is a difficult condition in pregnant women and generally occurs at gestational age of more than 20 weeks and is characterized by hypertension and proteinuria.

Low-dose aspirin is the trade name for acetylsalicylic acid. Low-dose aspirin is the single most cost-effective drug for the prevention of secondary thrombosis. Low-dose aspirin is widely used in the prevention of pregnancy disorders such as preeclampsia.

5.Instrument

Quality assessment in this study using the CASP Randomized Controlled Trials Checklist.

6. Data Analysis

Articles were collected using PRISMA diagrams and analyzed using the Review Manager 5.3 application by calculating effect sizes and heterogeneity to determine the combined research model and form the final results of the meta-analysis..

RESULTS

Research from a clinical trial of a primary study of low-dose aspirin related to the incidence of preeclampsia in pregnant women consisted of 7 articles from China, America, India, Congo, Guatemala, Pakistan, and Finland.

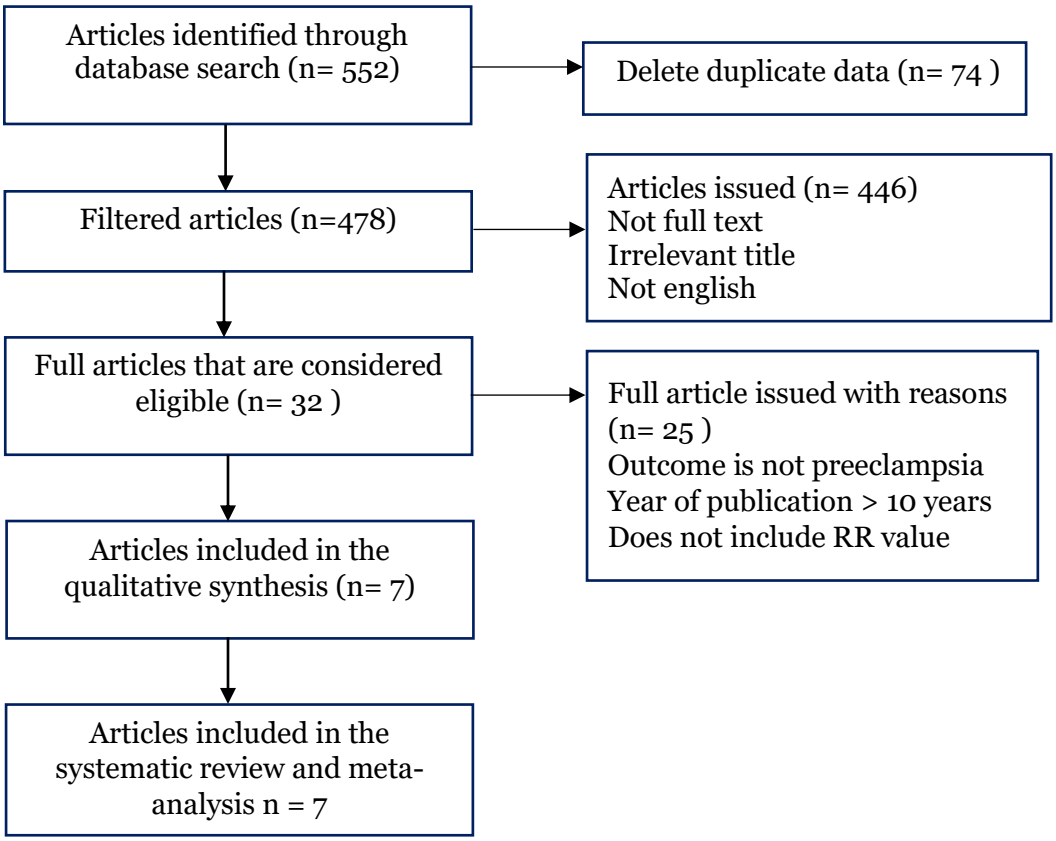

Figure 1. PRISMA Flowchart

A total of 552 articles were identified through an electronic database search. After removing 74 duplication articles, 478 articles were filtered and 446 of them were excluded because they were not appropriate. A total of 32 articles were eligible and could be assessed for eligibility, 25 of which were excluded on grounds. The following reasons are given for full-text articles that meet the exclusion criteria:

1. Articles reporting outcomes other than preeclampsia
2. The effect size used is not RR
3. Year of publication > 10 years

A total of 7 articles that met the quality assessment were included in the quantitative synthesis using meta-analysis.

Table 1. Assessment of the quality of studies published by CASP ((Critical Appraisal Skills Program)

No	Indicator	Publication (Author and Year)						
		Li Lin et al. (2018)	Hoffman et al. (2020)	Abramovici et al. (2015)	Villa et al. (2012)	Odibo et al. (2015)	Tolcher et al. (2020)	Amin et al. (2020)
1	Does the experiment clearly address the clinical problem?	2	2	2	2	2	2	2
2	Was the intervention given to participants at random?	2	2	2	2	2	2	2
3	Were all patients included in the study properly accounted for in the conclusions? Were all patients analyzed according to the randomized study groups?	2	2	2	2	2	2	2
4	Are patients, health workers, and researchers blinded?	2	2	2	2	2	2	2
5	Were the study groups similar at the start of the study?	2	2	2	2	2	2	2
6	Outside of the intervention studied, were the study groups treated equally?	2	2	2	2	2	2	2
7	Is the effect of the intervention large enough?	2	2	2	2	2	2	2
8	How precise is the estimation of the effect of the intervention?	2	2	2	2	2	2	2
9	Do the benefits provided by the intervention outweigh the costs and disadvantages?	2	2	2	2	2	2	2
10	Are the results applicable to the context of practice or local populations?	2	2	2	2	2	2	2
11	Are all other clinically important outcomes considered in this article?	2	2	2	2	2	2	2
	Total	22	22	22	22	22	22	22

Note: 2: Yes; 1: Hesitant; 0: No

Table 2. Description of the main studies included in the meta-analysis primary study

No	Author (year)	Country	Study design	Sample		P (Population)	I (Intervention)	C (Comparison)	O (Outcome)	RR (CI 95%)
				Aspirin	Placebo					
1	Lin et al (2018)	China	RCT	464	434	Pregnant women at high risk	Administration of aspirin 100 mg/day at 12-20 weeks' gestation until 34 weeks' gestation	placebo	Preeclampsia	RR= 0.99 (0.74 to 1.317)
2	Hoffman et al (2020)	Congo, India, Zambia, etc.	RCT	5990	5986	Pregnant Women (Nuliparous) with singleton pregnancies	Administration of aspirin 81 mg/day at 6-13 weeks' gestation until 36 weeks' gestation	placebo	Preeclampsia	RR=1.08 (0.94 to 1.25)
3	Abramo Vici et al (2015)	America	RCT	1483	1495	High risk and low risk pregnant women with smoking status	Administration of aspirin 60 mg/day at gestational age between 13-26 weeks of gestation until delivery	placebo	Preeclampsia	RR=0.4 (0.1 to 1.4)
4	Villa et al (2012)	Finland	RCT	61	60	Pregnant women at high risk	Administration of 100 mg/day at 12 weeks-13 weeks of gestation during pregnancy	placebo	Preeclampsia	0.7 (0.3 to 1.7)
5	Odibo et al. (2015)	USA	RCT	26	25	Pregnant women at high risk with singleton pregnancies	Administration of aspirin 81 mg/day at 11-13 weeks of gestation until delivery	placebo	Preeclampsia	0.88 (0.21 to 3.66)
6	Tolcher et al. (2020)	America	RCT	1273	1266	Pregnant women with high risk and low risk by race	Administration of aspirin 60 mg/day at gestational age between 13 and 26 weeks of gestation	placebo	Preeclampsia	0.91 (0.77 to 1.06)
7	Amin et al. (2020)	Pakistan	RCT	78	78	Primigravida pregnant women without risk factors for PE	Administration of 75 mg of aspirin starting from 8 to 16 weeks of gestation until 36 weeks	placebo	Preeclampsia	0.22 (0.05 to 0.99)

Research quality assessment

Quality assessment in this study used a randomized controlled trial checklist published by CASP (Critical Appraisal Skills Program). This assessment criteria consists of eleven criteria, with each measure given a score of 2= if you answer yes, 1= if you answer in doubt, and 0= if you answer no. The following are the assessment criteria by CASP (Critical Appraisal Skills Program) including:

1. Does the experiment answer the research clearly?
2. Was the intervention given to the participants randomly?
3. Were all patients included in the study properly accounted for in the conclusions? Were all analyzed according to the randomized study groups?
4. Are patients, health workers, and researchers blinded?
5. Were the study groups similar at the start of the study?
6. Outside of the intervention studied, were the study groups treated equally?
7. Is the effect of the intervention large enough?
8. What is the precision of the estimated effect of the intervention?
9. Do the benefits provided by the intervention outweigh the costs and disadvantages?
10. Are the results applicable to the context of practice or local populations?
11. Were all other clinically important outcomes considered in this article?

The next step is to calculate the overall effect of combining the data. Data analysis was performed using Review Manager (RevMan) 5.3 released by the Cochrane Collaboration. In data analysis using RevMan 5.3 the research results will be described in the form of forest plot and funnel plot images, then the results of the research will be analyzed based on variations between studies with fixed effects model analysis models and random effects models.

Table 1 shows the assessment of study quality using a randomized controlled trial checklist published by CASP (Critical Appraisal Skills Program) as follows:

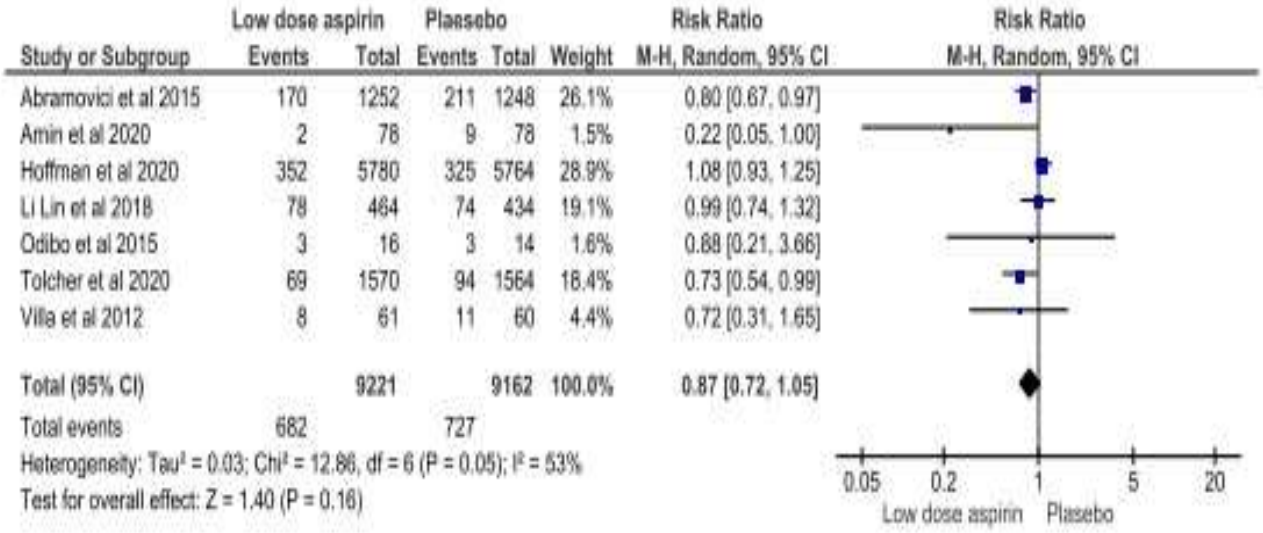

Figure 2 . Forest plot effect of low-dose aspirin to the incidence of preeclampsia

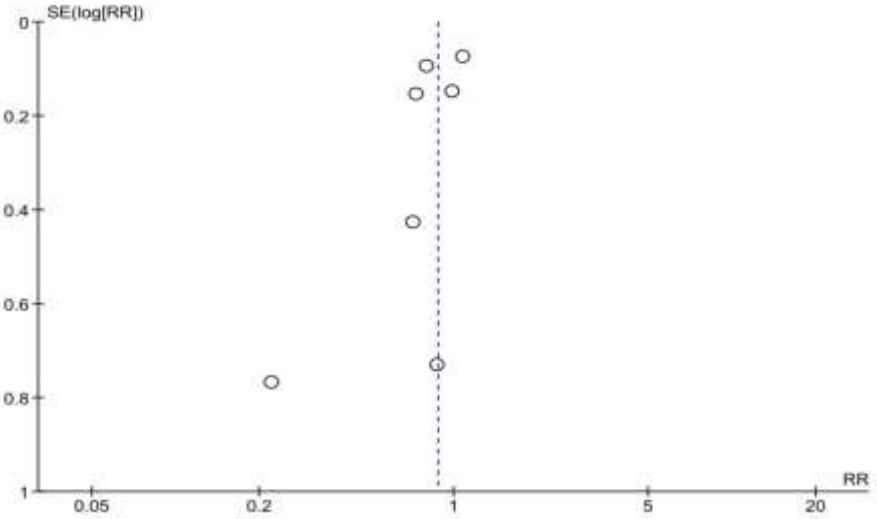

Figure 3. Funnel Plot Effect of low-dose aspirin to the incidence of preeclampsia

The Forest Plot in Figure 2 shows that low-dose aspirin can prevent preeclampsia better than placebo with a 0.87 times lower probability of occurrence of preeclampsia compared to placebo therapy, although not statistically significant. This study uses random effects because the level of diversity is 53% (heterogeneous).

The funnel plot in Figure 3 shows the asymmetry between the right and left plots, which means that there is publication bias in this study and an overestimate. on the right plot there is a distribution with a total of two plots and on the left there are five plots and one plot that touches the vertical line. The plot on the right has a standard error between 0 and 0.2 and the plot on the left has a standard error between 0 and 0.8 .

DISCUSSION

Based on research, developing countries have a high trend in terms of maternal mortality due to preeclampsia/eclampsia compared to developed countries which tend to decrease in mortality due to preeclampsia. Preeclampsia is characterized by hypertension after 20 weeks of gestation with other complications in pregnant women. In 2013 the American College of Obstetrics and Gynecology (ACOG) task force revised the criteria for preeclampsia, which is characterized by hypertensive disorders even without proteinuria to make the diagnosis. However, it can be followed by other complications such as impaired liver function, pulmonary edema, renal insufficiency, etc. (Ferry, 2022).

Under certain circumstances preeclampsia can progress to an obstetric emergency of eclampsia, which refers to the onset of seizures in patients with preeclampsia. Eclampsia is an obstetric emergency characterized by the onset of seizures, coma, in patients with preeclampsia before and after delivery. When preeclampsia occurs in pregnant women, preeclampsia can affect the platelets in a woman's blood so that it is more ready to clot and cause blood to clot, antiplatelet drugs such as aspirin function to prevent blood clots and play a role in preventing preeclampsia and complications (Duley et al, 2018).

Low-dose aspirin can be started early in the second trimester to reduce the risk of preeclampsia, preterm delivery, and intrauterine growth retardation in women at high

risk for developing preeclampsia. The American College of Obstetricians and Gynecologists (ACOG) and the US Preventive Services Task Force (USPTSF) recommend low-dose aspirin as a preventive measure that can be started after 12 weeks of age and ideally before 16 weeks of gestation (Ferri, 2022).

This meta-analysis as an effort to examine the effect of low-dose aspirin on the incidence of preeclampsia involving a total sample of 18,383 people with 7 primary studies with randomized controlled trials originating from several countries including China, India, Finland, Congo, Pakistan, America. . The findings of this study are to assess the effect of low-dose aspirin on the incidence of preeclampsia and based on the meta-analysis presented in the forest plot, the forest plot is a graphical representation of the results of the meta-analysis that includes several important information including the average score, standard deviation, risk ratio and the number of research samples. In addition to the forest plot, the meta analysis also provides a funnel plot. A funnel plot is a plot that describes the estimated effect of each study, which if the graph depicts asymmetry between the right and left plots, it indicates the occurrence of publication bias. Based on the results of this meta-analysis, it can be seen that aspirin is quite influential in reducing the incidence of preeclampsia when compared with placebo or without any administration with a value (RR = 0.87; 95% CI 0.72 to 1.05) although it is not statistically significant with p= 0.160.

These results are supported by Duley et al. (2018) which states that low-dose aspirin slightly reduces the risk of preeclampsia and its complications, but assurances about the safety of higher-dose aspirin or other antiplatelet agents need further research. Low-dose aspirin prophylactically initiated in high-risk patients before 16 weeks of gestation is considered more effective in preventing preeclampsia, severe preeclampsia, and IUGR. However, the investigators added that they would conduct a large sample RCT with the aim of comparing low-dose aspirin started at or after 16 weeks of gestation. (Xu, 2015).

An RCT study in China by Gu (2020) stated that low-dose aspirin significantly reduced the incidence of preeclampsia. The results of the Mantel-Haenszel trend test showed that there was a linear relationship between dose and the incidence of preeclampsia and early preeclampsia. Pearson's results showed that the incidence of preeclampsia and early preeclampsia was negatively correlated with aspirin dose.

Researchers concluded that low-dose aspirin can prevent preeclampsia and early preeclampsia. Its efficacy is dose dependent. It can reduce the rate of postpartum hemorrhage, fetal growth restriction, premature birth and cesarean section. The limitations of the research in this study are search bias because the researcher only uses 3 databases and ignores articles that are not published online, publication bias seen in the results of the funnel plot that is not symmetrical to the right and left, language bias because the researcher only uses English and Indonesian.

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AUTHORS' CONTRIBUTION

Meike Arianty as the main researcher who chooses the topic, conducts searches and collects data in this study. Bhisma Murti and

Uki Retno Budihastuti conducted data analysis and reviewed research documents.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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