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PREVENTION OF SUPERIMPOSED PREECLAMPSIA WITH LOW-DOSE ASPIRIN: A SYSTEMATIC REVIEW

Mayla Azkiya*
*Sentra Medika Langut Hospital, Indramayu, West Java, Indonesia

Corresponding Author:
maylaazkiyaz1993@gmail.com

ABSTRACT

Background: *Aspirin is currently the most widely prescribed treatment in the prevention of cardiovascular complications. At low doses, aspirin is also widely used to prevent pregnancy-related vascular disorders, such as preeclampsia and intrauterine growth restriction, and maternal disorders like antiphospholipid syndrome. The indications for the use of aspirin during pregnancy are, however, the subject of much controversy.*

The aim: *This study aims to show prevention of superimposed preeclampsia with low-dose aspirin.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 39 articles, whereas the results of our search on SagePub brought up 106 articles. The results of the search conducted for the last year of 2013 yielded a total 25 articles for PubMed and 50 articles for SagePub. The result from title screening, a total 10 articles for PubMed and 22 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.*

Conclusion: *Aspirin initiated at or before 16 weeks of gestation is associated with a greater reduction in the incidence of PE, perinatal death, and other adverse perinatal outcomes as compared to aspirin initiated after 16 weeks of gestation.*

Keyword: *Superimposed preeclampsia, aspirin, pregnancy.*

INTRODUCTION

Preeclampsia is a multisystem disorder of pregnancy that is usually defined as hypertension and proteinuria diagnosed after 20 weeks of gestation. Hypertension in pregnancy is defined as a systolic blood pressure of 140 mmHg or more and a diastolic blood pressure of 90 mmHg or more in two separate measurements at least 4–6 h apart. However, correct measurement of blood pressure is indispensable in diagnosing hypertension. There is currently no official role of ambulatory blood pressure measurement in the diagnosis of hypertensive pregnancy disorders. Preeclampsia may be difficult to diagnose, especially in patients with chronic diseases associated with hypertension or proteinuria.

Preeclampsia can lead to liver and kidney failure, seizures (eclampsia), and abnormalities of the clotting system. Since 2013, the traditional definition has been reviewed and, in the absence of proteinuria, it is specified that preeclampsia may be diagnosed as hypertension in association with recent onset of thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, or new-onset cerebral or visual disturbances. This wide definition has introduced more inconsistency in the way preeclampsia is diagnosed in clinical practice. Preeclampsia occurs in 1–8% of pregnant women, a range of prevalence related to variability in the risk factors of pregnant women from one country to another.[1] Antiplatelet drugs act by decreasing platelet aggregation and inhibiting thrombus formation.

The most common antiplatelet agent is aspirin, which is also known as acetylsalicylic acid. It is widely available without prescription, usually as 300 mg tablets, and used as an anti-inflammatory drug for minor aches and pains, and to reduce fever. Aspirin has its antiplatelet effect by inhibiting the production of thromboxane, which under normal circumstances binds platelet molecules together to create a patch over damage to the wall of blood vessels. Low-dose aspirin (usually 75 mg) is used for long-term therapy to help prevent heart attacks, strokes and blood clots (thrombosis) in people at high risk. It is also used after heart attacks, to prevent another happening. Aspirin does have side effects. When taken at higher doses and for prolonged periods (in doses up to 300 mg, for more than five years), it can lead to gastrointestinal and cerebral bleeding. However, as aspirin for prevention of pre-eclampsia is prescribed at the lower end of this range of doses, and for limited duration, these more serious problems are unlikely.[2]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast of the prevention of superimposed preeclampsia with low-dose aspirin. It is possible to accomplish this by researching or investigating prevention of superimposed preeclampsia with low-dose aspirin. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about the prevention of superimposed preeclampsia with low-dose aspirin. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used "Prevention of superimposed preeclampsia with low-dose aspirin" as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *(("Superimposed preeclampsia"[MeSH Subheading] OR "preeclampsia"[All Fields] OR "Aspirin" [All Fields]) AND ("Low dose aspirin"[All Fields] OR " management of superimposed preeclampsia"[All Fields]) AND ("management of preeclampsia"[All Fields]) OR ("Aspirin in superimposed preeclampsia [All Fields]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

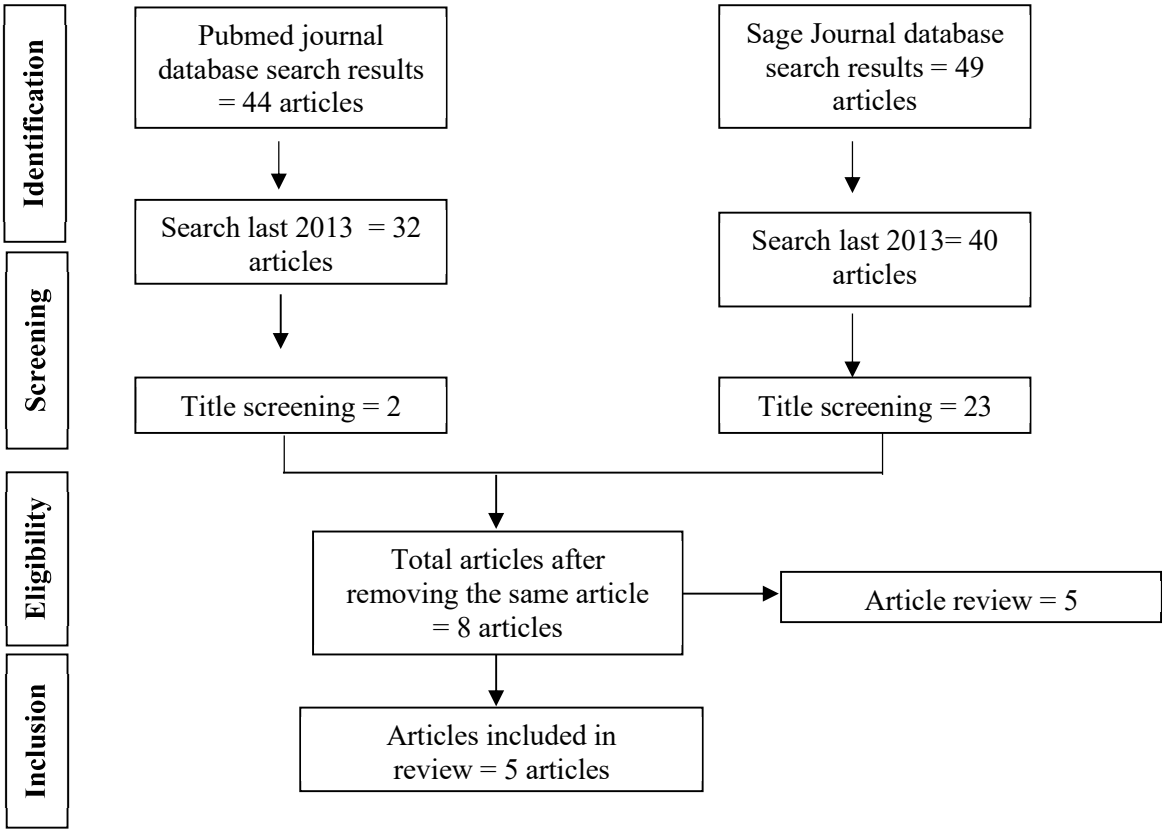

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 44 articles, whereas the results of our search on SagePub brought up 49 articles. The results of the search conducted for the last year of 2013 yielded a total 32 articles for PubMed and 40 articles for SagePub. The result from title screening, a total 2 articles for PubMed and 23 articles for SagePub. In the end, we compiled a total of 8 papers. We included five research that met the criteria.

Souza, EV *et al* (2014)[3] showed besides larger sample sizes, future studies could test the introduction of combined supplementation at an earlier gestational age (i.e., between 16-20 weeks), determine the dietary calcium ingestion of the participants (e.g., through a food questionnaire), and perform bioavailability studies to ascertain the actual absorption of aspirin and calcium. According to the findings of this pilot study, the combined supplementation of aspirin and calcium starting at 20-27 weeks of gestation produced a nonsignificant decrease in the incidence of superimposed preeclampsia and fetal growth restriction in hypertensive women with abnormal uterine artery Doppler findings.

Banala, C *et al* (2020)[4] showed an overall 70% institutional adherence to the 2016 ACOG recommendation of 81mg aspirin in patients with CHTN for superimposed preeclampsia prevention. However, the daily 81 mg of aspirin initiated

between 12 to 16 weeks of pregnancy did not decrease the incidence of superimposed preeclampsia, severe features, SGA or PTB in patients with CHTN.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Souza, EV *et al*., 2014[3]	Brasil	A randomized, double-blind, placebo-controlled study	65 women	A total of 49 women with chronic hypertension and abnormal uterine artery Doppler at 20-27 weeks gestation were randomly assigned to receive placebo (N = 26) or 100 mg aspirin plus 2 g calcium (N = 23) daily until delivery. The main outcome of this pilot study was development of superimposed preeclampsia. Secondary outcomes were fetal growth restriction and preterm birth. The rate of superimposed preeclampsia was 28.6% lower among women receiving aspirin plus calcium than in the placebo group (52.2 *vs* 73.1%, respectively, P=0.112). The rate of fetal growth restriction was reduced by 80.8% in the supplemented group (25 *vs* 4.8% in the placebo *vs* supplemented groups, respectively; P=0.073). The rate of preterm birth was 33.3% in both groups. The combined supplementation of aspirin and calcium starting at 20-27 weeks of gestation produced a nonsignificant decrease in the incidence of superimposed preeclampsia and fetal growth restriction in hypertensive women with abnormal uterine artery Doppler.
Banala, C *et al*., 2020[4]	United States	A retrospective study	457 women	We identified 457 pregnant women with chronic hypertension, 203 in the post-ACOG group and 254 in the pre-ACOG group. Aspirin 81 mg was offered to 142 (70%) in the post-ACOG group and 18 (7.0%) in the pre-ACOG group. Maternal demographics were not significantly different. The overall incidence of superimposed preeclampsia was not significantly different: 87 (34.3%) vs. 72 (35.5%), p=0.79 in the pre and post ACOG guideline groups, respectively. Superimposed preeclampsia with severe features significantly

				increased: 32 (12.6%) vs 9 (4.4%), p<0.01 while superimposed preeclampsia without severe features significantly decreased: 55 (21.7%) vs 63 (31.0%) p=0.03. There were no significant differences in small for gestational age neonates or preterm birth <37 weeks incidences between groups. There were no significant differences in the subgroup analysis based on the severity of chronic hypertension requiring antihypertensive medication, history of preeclampsia, or pregestational diabetes.
Xiao, Y *et al.*, 2023[5]	China	A retrospective study	115 pregnant	In the LDA group, 64 (55.65%) of 115 pregnant women took aspirin before 16 weeks of gestation. Besides, 12 (10.43%) and 34 (22.52%) women developed PE in the LDA group and control group, respectively; the aspirin prophylaxis was associated with a lower risk of PE (odds ratio = 0.40, 95% confidence interval = 0.20–0.82, *P* = 0.0098). In addition, LDA is slightly more effective when initiated before 16 weeks of gestation or in those without chronic hypertension, when compared with their counterparts.
Boelig, RC *et al.*, 2020[6]	Pennsylvania	A Prospective Cohort Study	292 participants	Pre- (n = 156) and post screen (n = 136) cohorts were similar except for race and multifetal gestation. Prescreen, rate of provider recommendation for aspirin was 74%. Of those with prior preeclampsia, 96% were recommended aspirin, compared with 64% of patients with other risk factors (p < 0.001). Post screen, provider recommendation of aspirin improved to 95% (p < 0.001). Rate of preeclampsia/gestational hypertension were similar between cohorts; however, there was a reduced adjusted risk in overall preterm birth <37 weeks (adjusted odds ratio [aOR] = 0.50 [0.25–0.99]) and preterm birth <34 weeks (aOR = 0.33 [0.13–0.88]) post screening tool implementation.

Tolcher, MC *et al*., 2020[7]		Randomized controlled trials	3135 participants	In the Low-Risk Aspirin trial of 3135 women, the risk of preeclampsia was significantly reduced among non-Hispanic white women who received aspirin compared with non-Hispanic white women who received placebo (relative risk, 0.19; 95% confidence interval, 0.06e0.63; P¼.007). The risk of preeclampsia was not different when comparing the aspirin and placebo groups among the Hispanic, nonHispanic black, or other ethnicity and race groups. The efficacy among non-Hispanic white women persisted after consideration of compliance and gestational age at randomization (relative risk, 0.07; 95% confidence interval, 0.009e0.51; P¼.009). As noted in the original trial, there was an increased risk of placental abruption in the aspirin group overall compared with placebo (P¼.025). The risk of stillbirth was significantly increased among non-Hispanic black women who received aspirin compared with non-Hispanic black women who received placebo (P¼.048). In the HighRisk Aspirin trial of 2539 women, 269 were Hispanic (10.6%), 832 were non-Hispanic white (32.8%), 1426 were non-Hispanic black (56.2%), and 12 were categorized as other (0.5%). Stratification by ethnicity and race did not reveal a decreased incidence of preeclampsia for any of the subgroups (P>.05). Moreover, there was no significant difference in other measured outcomes including preterm delivery at

Xiao, Y *et al* (2023)[5] showed he initial time of aspirin administration in the current study was between 12 and 24 weeks of gestation, because pregnant women had a different time of their first prenatal appointment in real-world clinical practice. However, this also gave us the opportunity to reveal that LDA was more effective when administered before 16 weeks of gestation. Finally, the total sample size of the current study was relatively small, which may limit our power to perform some subgroup analyses. Therefore, additional real-world studies of larger samples are warranted. 75 mg per day of aspirin can reduce the incidence of PE in high-risk pregnancies and use LDA prior to 16 weeks of gestation is more effective in real-world clinical practice.

Boelig, RC *et* al (2020)[6] showed prior to implementation of a simple screening questionnaire, approximately 25% of high risk patients did not receive the recommendation of aspirin for preeclampsia prevention. High-risk patients who lack a history of preeclampsia were less likely to be advised of aspirin prophylaxis. Use of a simple universal screening

tool at time of NT ultrasound significantly improved utilization of aspirin for preeclampsia prevention and may improve patient outcomes.

Tolcher, MC *et al* (2020)[7] showed when considered with our previously published and recent work, these findings presented are of clinical significance and collectively suggest that broad, unselective use of aspirin among low-risk women is not currently supported by data or national recommendations with reported potential benefit only among few women. Our findings of a substantial improvement in the efficacy of aspirin for preventing preeclampsia among low-risk non-Hispanic white women support future exploration of the pharmacogenetics of aspirin metabolism and the potential impact of genomics-driven aspirin resistance on preeclampsia prevention.

DISCUSSION

Preeclampsia (PE) is a pregnancy-specific disorder that affects approximately 3–5% of pregnant women worldwide, especially in developing countries. PE can cause maternal impairment including kidney damage, liver damage, hemolysis, neurology injuries including seizures (eclampsia), stroke, and death. Preterm delivery and fetal growth restriction due to PE often have lifelong consequences for the child. These may include cerebral palsy and neurodevelopmental impediment, respiratory disease, hypertension, renal insufficiency, insulin resistance, obesity, cardiovascular disease, and impaired work capacity. In 2014, the International Society for the Study of Hypertension in Pregnancy (ISSHP) defined the diagnostic criteria for PE as new-onset hypertension (≥ 140 mmHg systolic or ≥ 90 mmHg diastolic) after 20-week gestation with the coexistence of either proteinuria (≥ 300 mg/day) or other maternal organ dysfunction such as renal insufficiency, liver involvement, neurological or hematological complications, uteroplacental dysfunction, or fetal growth restriction.[8,9]

Women with chronic hypertension are at an increased risk of several pregnancy-related complications, including superimposed preeclampsia (PE), fetal growth restriction, placental abruption, preterm birth, and cesarean section. Chronic hypertension is not only a significant risk factor for PE (risk ratio 5.1, 95% confidence interval [CI] 4.0–6.5), but is also associated with increased risk of future CVDs. A recent retrospective Chinese low-risk cohort study estimated an increase in adverse pregnancy outcomes including preeclampsia associated with stage 1 hypertension in early gestation. Moreover, hypertensive disorders in pregnancy significantly increased with different body mass index (BMI)-based groups. Therefore, it is worthwhile to discuss whether stage 1 hypertension in prepregnant or early gestational women should be treated as a risk factor, and whether it requires additional management.[10]

The role of aspirin in PE prevention has been studied since 1978, when Goodlin and colleagues[7] described a patient with recurrent PE and thrombocytopenia who seemed to benefit from aspirin. To date, the effect of aspirin on PE prevention has been extensively analyzed. However, there is no standardized protocol regarding aspirin use, because the dosage, initial time, and screening methods of the high-risk population differ between studies. A study showed that effect of aspirin in the prevention of preterm PE may not apply in pregnancies with chronic hypertension. And meta-analysis showed that aspirin initiated at or before 16 weeks of gestation is associated with a greater reduction in the incidence of PE, perinatal death, and other adverse perinatal outcomes as compared to aspirin initiated after 16 weeks of gestation. Hence, further studies are needed to determine the specific high-risk population and active window.[10,11]

CONCLUSION

Aspirin initiated at or before 16 weeks of gestation is associated with a greater reduction in the incidence of PE, perinatal death, and other adverse perinatal outcomes as compared to aspirin initiated after 16 weeks of gestation.

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