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ASPIRIN, NONSTEROID ANTIINFLAMMATION AS A PROPHYLAXIS IN REDUCING THE INCIDENCE OF PREECLAMPSIA: A SYSTEMATIC REVIEW

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Abstract

Background: *Numerous randomized trials have reported the efficacy and safety of aspirin use during pregnancy and the variable effects of aspirin on the incidence of preeclampsia.*

Aim: *This study aims to summarize and evaluate the efficacy of aspirin in preventing preeclampsia.*

Methods: *A systematic search strategy was conducted across several electronic reference databases (PubMed, Cochrane Library, Google Scholar) and included articles published between 2019–2023. Duplicate publications, review articles, editorials, and incomplete articles were excluded.*

Results: *Database searches identified a total of 92.832 articles. Of these, 100 articles passed the screening process, resulting in 22 articles for full-text assessment. Among them, 12 articles did not evaluate the outcome of interest. Hence, we found 10 appropriate studies included.*

Conclusion: *Low-dose aspirin administration prior to 20 weeks of gestation reduces the incidence of preeclampsia significantly. However, additional research is required to investigate the long-term efficacy and safety of low-dose aspirin administration during pregnancy by assessing the long-term outcomes in expectant women and their infants.*

Keywords: *Aspirin, Preeclampsia, Prophylaxis, Prevention*

INTRODUCTION

Preeclampsia is defined as hypertension occurring after 20 weeks of gestation with proteinuria or other indications of end-organ damage.[1,2] Preeclampsia affects 2% to 8% of all pregnancies and it is a significant cause of maternal and perinatal morbidity and mortality, especially when it occurs early in pregnancy.[3] Although a substantial quantity of research has been devoted to identifying preventive measures for preeclampsia, the incidence has remained relatively stable over the past few decades. This could be attributed to the incomplete understanding of the pathophysiology underlying preeclampsia. Increasing evidence suggests that suboptimal trophoblastic invasion leads to an imbalance of angiogenic and antiangiogenic proteins, resulting in pervasive inflammation and endothelial damage, increased platelet aggregation, and thrombotic events associated with placental infarcts. Below 300 mg, aspirin selectively and irreversibly inactivates the cyclooxygenase-1 enzyme, inhibiting the production of prostaglandins and thromboxane and reducing inflammation and platelet aggregation. As a result of this, it has been hypothesized that aspirin may be beneficial for preventing preeclampsia.[3] A case report published in 1978 suggested the first potential use of aspirin for the prevention of preeclampsia[4], followed by the first randomized controlled trial (RCT) published in 1985.[5] Since then, numerous randomized trials have reported the safety of aspirin use during pregnancy and the variable effects of aspirin on the incidence of preeclampsia.[3] Here we aims to summarize and evaluate the efficacy of aspirin in preventing preeclampsia

Method

Search Strategy

This study is a qualitative systematic review. The data is obtained through electronic database search in Medline (PubMed), Cochrane Library, and Google Scholar. The keywords used are “Aspirin” AND “Preeclampsia” AND “Prophylaxis” OR “Prevention”. The selected articles are based on inclusion and exclusion criteria.

Table 1. Literature search strategy

Database	Keywords	Results
PubMed	Aspirin” AND “Preeclampsia” AND “Prophylaxis” OR “Prevention”	23053
Cochrane Library	Aspirin” AND “Preeclampsia” AND “Prophylaxis” OR “Prevention”	60.349
Google Scholar	Aspirin” AND “Preeclampsia” AND “Prophylaxis” OR “Prevention”	9430

Eligibility Criteria

All studies were assessed for eligibility. The inclusion criteria of the included studies were original articles (observational studies including cohort, case control, cross-sectional, or randomized clinical trials) published in the last 5 years between 2019 and 2023, full-text articles available, published in English, and studied the efficacy of aspirin in reducing the incidence of preeclampsia. The exclusion criteria of the studies are articles that are not indexed by Scopus, editorials, reviews, and articles that did not evaluate the focus of interest of this study. The research selection was carried out in three successive phases. The titles and abstracts of all search results were initially screened and evaluated for relevance. Second, complete access was gained to all potentially eligible studies. Finally, the systematic review included only those studies that met our inclusion criteria. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline is used for the selection.

Data Extraction and Parameter Measured

All the authors extracted the data from the articles. The following datas are collected: Author, year of publication, study design, sample size, inclusion criteria, age of the study subjects, gestational age at entry to completion of the intervention, treatment arms, follow-up period, and efficacy. The primary outcome was a reduction in preeclampsia incidence. All disagreements regarding the methodology, article retrieval, and statistical analysis were resolved by consensus among the authors.

Results

The databases search identified a total of 92.832 articles (Table 1). Of these, 100 articles passed the screening process, resulting in 22 articles for full-text assessment. Among them, 12 articles did not evaluate the focus of interest. Hence, we found 10 appropriate studies included (Figure 1). The summary of the main findings of the selected studies is presented in Table 2.

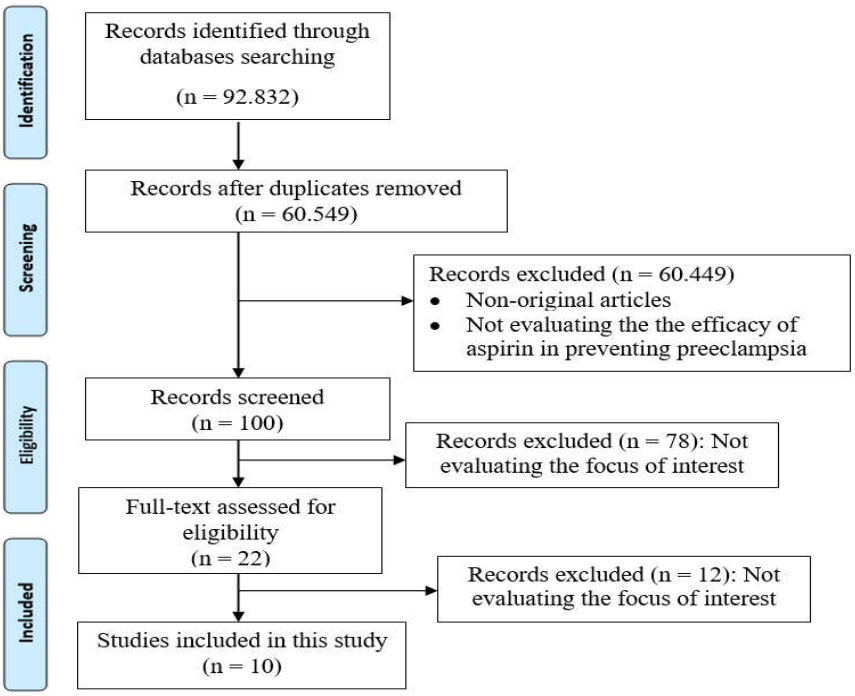

Figure 1. PRISMA flow diagram

Table 2. Summary of included studies

Author (Year)	Study design	Sample size	Inclusion criteria	Age (years)	Gestational age at entry to completion	Treatment arms	Follow-up period	Efficacy
Gu et al. 2020[6]	Prospective RCT	1105	Pregnant women at high-risk for PE, with one or more high-risk factors or with 2 or more medium-risk factors. • High-risk factors: history of PE or gestational hypertension, chronic hypertension, multiple pregnancies, kidney disease, type 1 or type 2 diabetes and autoimmune diseases such as SLE and APS. • Medium risk factors: primipara, age ≥35 years, BMI ≥30 kg/m^2, family history of PE, poor social and economic status, personal history (PCOS, low birth weight infant or infant younger than gestational age, > 10 years since the previous pregnancy and history of an adverse pregnancy outcome).	Mean age across groups: 31–33	12 weeks of gestation to delivery	Aspirin 25 mg/d, 50 mg/d, 75 mg/d, and placebo	3 months post-partum	Low-dose aspirin significantly reduced the incidence of PE and early-onset PE.
Tolcher et al. 2020[7]	Secondary analysis of RCTs	5647	Pregnant women at low-risk and high-risk for PE: • Low-risk: normotensive, nulliparous • High-risk: women with pregestational insulin-treated diabetes mellitus, chronic hypertension, multiple gestations, or a history of PE in a previous pregnancy.	NR	13–26 weeks of gestation to delivery	Aspirin 60 mg/d and placebo	NR	The incidence of PE was significantly reduced among low-risk non-Hispanic white women who received aspirin as compared to placebo, but not overall or among Hispanics or non-Hispanic blacks. Analysis of high-risk women did not demonstrate a difference in the efficacy of aspirin by ethnicity and race.
Shanmugalingam et al. 2020[8]	Clinical trial	220	Pregnant women at high-risk for PE and <20 weeks of geastation	NR	<20 weeks of gestation to delivery	Aspirin 100 mg, Aspirin 150 mg	Until delivery	Aspirin is an effective prophylactic agent with an absolute risk

								reduction of 51% (number needed to treat, 2) when adherence is ≥90%, compared with women with inadequate adherence.
Abdi et al. 2020[9]	RCT	90	Pregnant women with gestational age of 12 to 15 weeks and a history of PE in previous pregnancies.	Mean age: Aspirin group: 29.5 Placebo group: 31.1	12–15 to 36 weeks of gestation	Aspirin 80 mg/d and placebo	Until delivery	• BP was significantly lower in aspirin group • Aspirin may have a preventive effect on PE in the current pregnancy (aOR = 0.23, p = 0.013).
Hoffman et al. 2020[10]	Secondary analysis of RCT	**11 976**	Nulliparous women, have been pregnant for at least 6 weeks and 0 days, and no longer than 13 weeks and 6 days	14–40	From randomisation until 36 weeks and 7 days of pregnancy or delivery	Aspirin 81 mg/d, placebo	Until delivery	Low-dose aspirin started between 6 weeks and 0 days of gestation and 13 weeks and 6 days of gestation resulted in a lower incidence of premature delivery before 37 weeks due to PE.
Huai et al. 2021[11]	Secondary analysis of RCT	397	• Maternal age ≥18 years and <55 years • Singleton pregnancy with a live fetus at gestational age 12–20 weeks • High risk of developing PE: preexisting diabetes, or chronic hypertension (at least one) or presence of ≥2 intermediate-risk factors of obesity (BMI ≥ 28 kg/m2), advanced maternal age (≥35 years), family history of PE, or nulliparity	Mean age: Normotension: 32.4 Stage 1 hypertension: 32.1	12–20 weeks to 34 weeks of gestation	Aspirin 120 mg/d, control group	NR	• In the control group, the PE occurrence was significantly higher in stage 1 hypertensive woman than in the normotensive women (aOR 3.960, 95% CI 1.299–12.074, p = .016) while no difference was observed in the aspirin group (aOR 0.921, 95% CI 0.140– 6.070, p = .932). • In stage 1 hypertension, the incidences of PE were significantly lower in the aspirin group (aOR 0.139, 95% CI 0.027–0.716, p = .018)
Do et al. 2021[12]	Prospective cohort	410	Pregnant women with preexisting diabetes and a single living fetus <20 gestational weeks	Mean: 32	10 weeks to 36 weeks of gestation	Aspirin 75–150 mg/d	Until delivery	Implementation of prophylactic aspirin for all pregnant women with diabetes did not reduce the prevalence of PE.
Shen et al. 2021[13]	Secondary analysis of RCT	1592	Maternal age >18 years, no serious mental illness or learning difficulties, singleton pregnancy with live fetus with no major abnormality demonstrated on the 11-13 weeks scan	Mean age across groups: 31.24 to 32.68	11 to 14 until 36 weeks' gestation	Aspirin 150 mg/d, placebo	Until delivery	In pregnancies at high-risk of preterm PE, very high-risk results (estimated risk ≥1 in 50) are associated with the development of preterm preeclampsia despite aspirin prophylaxis.
Diguisto et al. 2022[14]	RCT	1100	Pregnant nulliparous women aged 18 years with a singleton pregnancy at a gestational age < 16 weeks of gestation with a lowest pulsatility index ≥ 1.7 or a bilateral protodiastolic notching for both uterine	Mean age: Aspirin: 28.3 Placebo: 28.7	From inclusion until 34th weeks of gestation	Aspirin 160 mg/d and placebo	Until delivery	Low-dose aspirin was not associated with a lower rate of PE.

			arteries on an ultrasound performed between 11+0 and 13+6 weeks.					
Lin et al. 2022[15]	RCT	898	(1) age ≥18 years and <55 years; (2) singleton pregnancy; (3) live fetuses at the gestational age of 12 to 20 weeks; (4) high risk of developing PE: (a) at least 1 high risk factor, such as history of PE, DM (type 1 or 2), or chronic hypertension; or (b) at least 2 of the following intermediate risk factors, including obesity (prepregnancy BMI ≥28 kg/m2), advanced maternal age (≥35 years), family history of preeclampsia (mother or/and sister) or nulliparity; (5) ability to undergo all procedures protocol; (6) a written informed consent.	Mean: Aspirin group: 32.88 Control group: 32.78	12 to 20 weeks ofgestation until 34 weeks of gestation	Aspirin 100 mg, Control	Until deliver y	100 mg of aspirin per day, initiated from 12 to 20 gestational weeks until 34 weeks of gestation, did not reduce the incidence of

Discussion

The use of aspirin for the prevention of preeclampsia was first suggested by a case report in 1978 that describing better outcomes with daily use of aspirin from midtrimester in the third pregnancy of a woman whose two previous pregnancies had been severely affected by preeclampsia and fetal growth restriction.[4] Then, a first RCT was published. Beaufils et al. conducted the first RCT evaluating the effect of aspirin on placenta-mediated complications, randomly assigning 102 women at high risk of preeclampsia and fetal growth restriction, based primarily on their obstetrical history, to receive daily doses of aspirin at 150 mg and dipyridamole at 300 mg beginning at 12 weeks of gestational age or usual care. In the control arm, there were six occurrences of preeclampsia, five of perinatal death, and four more of fetal growth restriction; none of these events occurred in the treatment arm.[5] Numerous RCTs followed over the next few decades, yielding inconclusive results, which were largely explained by a high degree of heterogeneity in trial participant selection, included women's baseline risk, aspirin dosage, gestational age of prophylaxis initiation, and preeclampsia definition.[3]

In this systematic review, of the 10 studies included, only six studies found that aspirin can reduce the incidence of preeclampsia. The remaining, 4 studies showed there is no significant effect of aspirin in reducing the incidence of preeclampsia. Previous systematic review and meta-analysis conducted in East Asians and non-East Asians populations showed that low-dose aspirin is effective at reducing the incidence of preeclampsia in both East Asians and non-East Asians, but has different effects on IUGR in East Asians and non-East Asians.[16] Another systematic review and meta-analysisi conducted by Choi et al. found that prior to 20 weeks of gestation, low-dose aspirin administration significantly reduces the incidence of pre-eclampsia and related neonatal outcomes without increasing hemorrhage risk.[17]

In order to facilitate placentation, physiological factors imply that aspirin should be administered early in pregnancy. Nonetheless, the optimal timing is ambiguous. Bujold et al. published a meta-analysis of randomized trials pertaining to this topic. Initiation of aspirin at or before 16 weeks of gestation was associated with a significant reduction in the incidence of preeclampsia and fetal growth restriction.[18] No significant benefit was observed for PE (RR 0.81, 95% CI, 0.63-1.03) or fetal growth restriction (RR 0.98, 95% CI, 0.63-1.10) when aspirin treatment was initiated after 16 weeks of gestation.[19] Following first-trimester screening for preterm preeclampsia, women at high risk should receive aspirin prophylaxis beginning at 11–14+6 weeks of gestation at a dose of 150 mg to be taken every night until delivery, or until preeclampsia is diagnosed, or until 36 weeks of gestation, whichever comes first. All expectant women should not be prescribed low-dose aspirin.[20] The optimal gestational age to discontinue aspirin is unknown. The March 2019 FIGO guidelines recommend discontinuing aspirin at 37 weeks of pregnancy or two weeks prior to a planned early delivery[19], but it is possible that aspirin could be discontinued at the end of placentation. Furthermore, calcium replacement (1 g elemental calcium/d) or calcium supplementation (1.5–2 g elemental calcium/d) may reduce the burden of both early-onset and late-onset preeclampsia in women with low calcium intake (800 mg/d).[20] In the majority of the included studies, low-dose aspirin is administered before 20 weeks of gestation and continued through the third trimester or until delivery.

Despite the fact that this study subjects is mostly from placebo-controlled RCTs which means that the possibility of publication bias, certain limitations must be acknowledged, the included RCTs utilized various study designs and preeclampsia definitions. Due to the fact that preeclampsia is characterized as a syndrome of elevated blood pressure with organ dysfunctions, patients with preeclampsia may exhibit a variety of symptoms, and diagnostic criteria varied between studies. In addition, the characteristics of sample populations, including the underlying risk factors for preeclampsia, differed between studies.

Conclusion

Initiating low-dose aspirin administration prior to 20 weeks of gestation reduces the incidence of preeclampsia significantly. However, additional research is required to investigate the long-term efficacy and safety of low-dose aspirin administration during pregnancy by assessing the long-term outcomes in expectant women and their infants.

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