META-ANALYSIS

Role of aspirin in the prevention of preeclampsia in previously hypertensive pregnant women: A Meta-Analysis

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Abstract

Objective: To determine the role of low-dose aspirin in preventing preeclampsia for previously hypertensive pregnant women.

Method: The meta-analysis was conducted from February to May 2021 and comprised search on PubMed and Cochrane Library databases for randomised controlled trials consisting of previously hypertensive women aged 18-55 years, aspirin dosage range 60-100mg, and a comparison between aspirin and placebo groups. Duration of intervention till the end of gestation, the dosage of aspirin given, risk ratios or odds ratio with the confidence intervals, and preeclampsia were the main variables recorded. Data was analysed using RevMan 5.4.

Result: Of the 144 articles found, 4(%) were included, having 2238 participants. Pooled estimates revealed that aspirin, compared to placebo, did not significantly reduce the manifestation of preeclampsia (p=0.06). Besides, heterogeneity between the different trials was moderate at 59%.

Conclusion: Aspirin was not found to substantially diminish the risk of incidence of preeclampsia, but it did show some beneficial effects.

Keywords: Preeclampsia, Low-dose aspirin, Hypertensive pregnant women. (JPMA 73: 838; 2023)

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Introduction

Preeclampsia occurs in pregnancy, resulting in high blood pressure, and has a global incidence of 5-14%.[1] The prevailing treatment choice is antiplatelet therapy, including low-dose aspirin, after 12 weeks of pregnancy and supplements, such as calcium.[2] Calcium supplements have been shown to benefit pregnant women with extreme calcium deficiencies, but in the developed countries, calcium deficiencies to such a vast extent are rarely seen.[3] Low-dose aspirin with prophylaxis has had a considerable role in preventing preeclampsia because coagulation abnormalities and hypertension are partially due to the distribution of normal functions in vaso-dilating and vaso-constricting prostaglandins. Low-dose aspirin therapy simultaneously decreases thromboxane levels more than prostacyclin levels, thus decreasing the chances of vasoconstriction and blood coagulation in the placenta.[3]

Chronic hypertension is one of the major risk factors, and it could cause a combination of hypertension along with superimposed preeclampsia, resulting in the worsening of high blood pressure and protein in the urine, leading to an array of health complications in the pregnancy, such as foetal growth restriction (FGR), preterm birth and placental abruption.[2] Although a previous meta-analysis has compared drugs, such as heparin and aspirin, in preventing preeclampsia,[4] it grouped all antiplatelet agents under a single line of treatment or intervention, and also combined both normotensive and hypertensive patients under one group. No particular meta-analysis has been conducted on comparing studies that have mentioned the effects of only aspirin in preventing preeclampsia for previously hypertensive women. The current study was planned to assess and determine the role of aspirin in preventing preeclampsia for previously hypertensive pregnant women.

Materials and Methods

The meta-analysis was conducted from February to May 2021 and comprised search on PubMed and Cochrane Library databases. The search terms included aspirin OR acetylsalicylic AND hypertensive pregnant women AND preeclampsia OR placental insufficiency OR postpartum haemorrhage OR preterm birth. The studies included were published randomised controlled trials (RCTs) consisting of previously hypertensive women aged 18-55 years at high risk of preeclampsia, aspirin dosage range 60-100mg as recommended by American College of Obstetricians and Gynaecologists (ACOG)[5] and a comparison between aspirin and placebo groups. According to National Institute for Health and Care Excellence (NICE) guidelines, preeclampsia is defined as a new onset of hypertension with systolic

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blood pressure >140mmHg and diastolic blood pressure >90mmHg after 20 weeks of pregnancy with the combination of one or more complications, such as proteinuria.[6] Thus, a low dosage range of 60-100 mg/day was selected to maintain homogeneity among the studies.

The exclusion criteria were based on the availability of only abstracts, articles in a language other than English, or retracted articles. If the chronic hypertensive pregnant participants were combined among other high-risk groups for the outcome of preeclampsia, such studies were also excluded. Ongoing studies were excluded due to the unavailability of results. The definition of preeclampsia was determined in line with NICE guidelines.[6] The model for analysis was fixed-effects, but random-effects were also noted.

The articles retrieved from the search were screened for duplicates. They were then evaluated by two independent reviewers who were blinded, and then filtered for inclusion. The population, intervention, control and outcome (PICO) format was used.[7] A third reviewer was consulted for any disparities. Quality assessment of the selected RCTs was done based on Consolidated Standards of Reporting Trials (CONSORT) guidelines.[8] Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to maintain the organisation and standard of reporting the information.[7]

Data collection was done on an Excel sheet with a slightly modified Cochrane template.[9] The variables included were: year of study, region, income status of the country, frequency of preeclampsia, the dosage of aspirin, aspirin group versus placebo, hypertensive pregnant women, neonatal outcomes, trimester of intervention, duration of intervention, risk ratio, confounders, other drugs used, and bias categories.

For statistical analysis, Review Manager version 5.4 (RevMan 5.4) was used. Forest plots were made and evaluated pictorially to get the conclusion of the pooling. The results of the included trials were stated as adjusted risk ratio (ARR) with 95% confidence interval (CI) using random-effect modelling. A funnel plot was also modelled to analyse the risk of biases visually. P<0.05 was considered statistically significant. Heterogeneity was evaluated, and between 30% and 60% was considered moderate heterogeneity according to the Cochrane Handbook.[9]

Results

Of the 144 RCTs seen, only four studies, numbers 2, 10, 11, and 12 were included (Figure 4). Of them, 2(50%) mentioned RR, while 2(50%) did not. To maintain data homogeneity, the ratios were derived.

The four 3,10–12 studies included a total of 2238 patients; 1104(49.3%)in the aspirin arm and 1134(50.7%) in the placebo arm. Baseline characteristics and detailed quality assessment of incorporated trials were noted (Table).

Comprehensive forest plots, for both fixed (Figure 2) and random (Figure 3) effects, condensed the findings of the meta-analysis. Of the 1104(49.3%) patients in the aspirin group, 228(20.6%) had preeclampsia, and of the remaining 1134(%) in the placebo group, 232(20.4%) patients ended up with preeclampsia. Among the 4 studies included, 3(75%)3,11,12 showed RR of 0.49 (95% CI: 0.19-1.30), 1.04 (95% CI: 0.61-1.78) and 1.39 (95% CI: 0.79-2.57), and they crossed the central line on the forest plot, rendering it non-

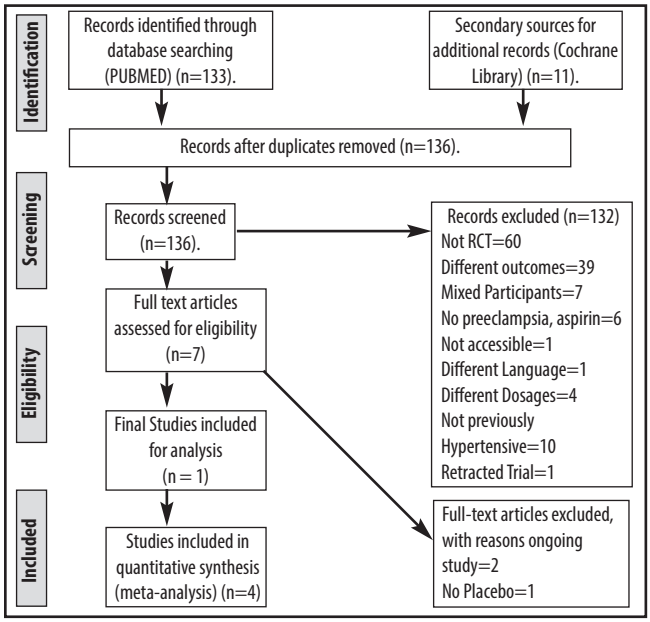

Figure-1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart

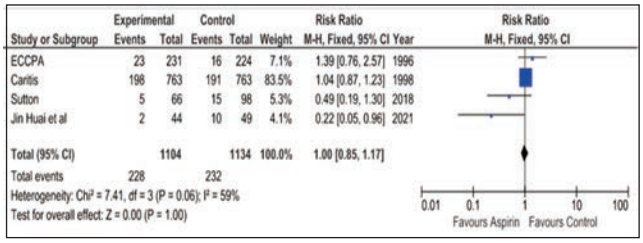

Figure-2: Forest plot (fixed).

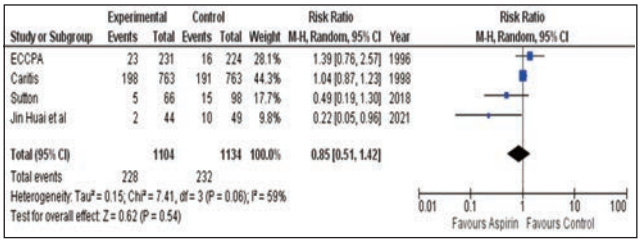

Figure-3: Forest plot (random).

significant. The remaining study10 presented RR of 0.22 (95% CI: 0.05-0.96), and did not cross the central line, favouring aspirin.

The funnel plot showed moderate heterogeneity (59%). The plot was symmetrical, indicating no bias, but one study10 was present at the lower borderline of the X-axis (Figure 2). Aspirin did not completely trim down the effect of preeclampsia significantly though few benefits of aspirin cannot be denied (RR 1.00, 95% CI: 0.85-1.17; *p*=0.06).

Discussion

The 4 studies included in this meta-analysis monitored the effects of aspirin on preventing the occurrence of

Table: Studies included in the meta-analysis on low-dose aspirin and preeclampsia.

Year of study	5-Jan-21	Oct-18	Jan-96	12-Mar-98
Author	Jing Huai et al[8]	Sutton et al[10]	Ecppa study[9]	Caritis et al[3]
Region	Beijing , China	Pittsburgh , USA	Brazil	Pittsburgh , USA
Low/middle/high income countries	middle income	high income	middle income	high income
Trials	Preventive effect of aspirin on preeclampsia in high-risk pregnant women with stage 1 hypertension.	Maternal Outcomes Associated With Lower Range Stage 1 Hypertension.	ECPPA: randomised trial of low dose aspirin for the prevention of maternal and foetal complications in high risk pregnant women. ECPPA (Estudo Colaborativo para Prevenção da Pré-eclampsia com Aspirina) Collaborative Group.	Low-dose aspirin to prevent preeclampsia in women at high risk. National Institute of Child Health and Human Development Network of Maternal-Foetal Medicine Units.
Participants	stage 1 hypertension	stage 1 hypertension	stage 1 hypertension	stage 1 hypertension
Outcomes	Preeclampsia	Preeclampsia	Preeclampsia	Preeclampsia
Secondary neonatal outcomes	Small for gestational age (SGA <10th percentile)	NICU admission	intrauterine growth retardation (IUGR), still birth , neonatal death, neonatal bleeds.	Infant small for gestational age , Perinatal death , Neonatal intraventricular hemorrhage.
Age of participants	≥ 18 yrs < 55 yrs	21.9±5.5 yrs	<20 yrs - ≥ 40 yrs	30±6 yrs - 21.9±5.5 yrs
Trimester of intervention	first trimester or start of second trimester.	second trimester	second trimester	first - mid of third trimester
Intervention duration	at or before 16 weeks	13 - 25 weeks	13 - 26 weeks	between 12 - 32 weeks
Duration of follow up	form the mid of first trimester till birth	from second trimester till birth	from second trimester till birth	from second trimester till birth
Dosage	100 mg of aspirin	60 mg of aspirin	60 mg of aspirin	60 mg of aspirin
Preeclampsia (aspirin)	(affected/total) 2/44	5/66	23/231	198/763
Placebo	(affected/total) 10/49	15/98	16/224	191/763
Measure of association	0.139 (0.027-0.716) (OR)	0.49 (0.19-1.30) (RR)	1.44 (0.74-2.80) (OR)	1.1 (0.8-1.4) (RR)
Case definition	Preeclampsia is being defined as having systolic blood pressure >=140 mmHg and diastolic blood pressure >=90 mmHg accompanied with proteinuria defined as having protein in urine >=300 mg/24 hr , protein to creatinine ratio >= 0.3 mg/dl and dipstick reading 2+.	Preeclampsia stated as having systolic and diastolic blood pressures at >=140 mmHg and >=90 mmHg respectively, plus proteinuria >=300 mg/24 hr , 2+ dipstick reading and protein/creatinine ratio 0.3mg/dl.	Preeclampsia defined as hypertension (diastolic blood pressure 90mmHg plus 25mmHg)plus proteinuria.	preeclampsia was stated as new onset proteinuric hypertension.
Confounder	Nulliparity,maternal age , prepregnancy body mass index (BMI)	Age, body mass index (BMI), race, and smoking.	Age, diabetes, renal disease, history of preeclampsia, IUGR.	Week of gestation at entry, week of gestation at delivery, systolic bp at entry, parity, race.
Drugs used other than aspirin	N/A	N/A	N/A	79% participant consumed antihypertensive medication.
Randomization	Randomised	Randomised	Randomised	Randomised
Allocation concealment	None	Yes	Yes	Yes computerized
Lost to follow-up	60 excluded for incomplete data at first follow-up.	89 women excluded because of incomplete BMI data.	96% of included women did the post-delivery follow-up.	19 women in aspirin group and 17 in placebo group were excluded because of missing data.
Blinding	Open-label	Double-blinded	Double-blinded	Double-blinded

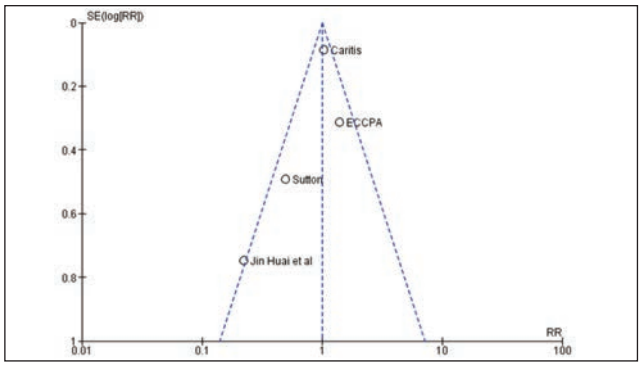

Figure-4: : Funnel plot.

preeclampsia as an outcome. Other complications of preeclampsia include FGR, preterm birth, and placental abruption, which has also been reported along with preeclampsia in the studies included.[10,11] Hence, by decreasing the incidence of preeclampsia, other complications can also be prevented. Chronic hypertension with the occurrence of preeclampsia arises in women who have previously suffered long-lasting hypertension before pregnancy, thus developing worsening higher blood pressure and protein in the urine, which could lead to other complications in pregnancy.[2] Accordingly, those women who are previously hypertensive or diagnosed with chronic hypertension are at a higher risk. Of 1104 participants, 228 were found to have preeclampsia in the aspirin group. In the placebo group of 1134, 232 women developed preeclampsia. Though the results neither favour nor disprove the use of aspirin, caution should be taken when interpreting them due to the limited number of studies included in the meta-analysis.

Aspirin at a dosage of <300mg can inhibit the cyclooxygenase-1 enzyme, decreasing prostaglandins and thromboxane levels, simultaneously inhibiting subsiding inflammation and platelet aggregation.[13] The hypothesis of preeclampsia linked with vascular and coagulation abnormalities due to abnormal prostacyclin and thromboxane A2 (TXA2) amounts led to initial studies being conducted on the role of aspirin in the prevention of preeclampsia.[1] Three of the studies[10-12] recommended aspirin, as mentioned in the conclusion portions and seen by the correlation on the forest plots. One study[3] has relatively similar outcomes in both groups. The aspirin dosage used for 3 of the studies[3,11,12] was 60mg, but one study[10] reported a much higher dose of 100mg.

Two of the studies were reported in 1996[11] and 1998,[3] whereas the remaining two were reported in 2017[12] and 2021.[10] Though there is a vast time gap between the studies analysed, the impact of the results remains homogenous regarding the role of aspirin in preventing preeclampsia. The delay in the timeline was due to the unavailability of articles meeting the study's inclusion criteria.

Comorbidities, like diabetes, obesity and hypertension, were also present among the participants of the included studies[3,8-10] with one study[3] having 79% of its participants taking antihypertensive medication.

The duration of the intervention was also recorded. Three of the studies[3,11,12] introduced aspirin within 12-13 weeks of pregnancy, whereas one study[10] introduced the intervention before or during the 16th week. The regions where the trials had been conducted included Brazil, Pittsburgh in the United States, and Beijing in Chin), and the reported incidence of preeclampsia in these regions is 6.7% of 2988 cases,[14] 1 in 25 pregnancies[15] and 9.5%[16] of all pregnancies, respectively.

No considerable impact of aspirin was shown in the results and the Forest plot in preventing preeclampsia. Differences among the studies recorded in the variables could have a part in the outcome of the results. Additionally, participants may vary in controlled or uncontrolled hypertension and stages of hypertension when taking part in the original RCTs. Other risk factors could further contribute to preeclampsia, such as the history of previous preeclampsia, first pregnancy, age, race, obesity, multiple pregnancies, interval between pregnancies, history of other conditions, and in vitro fertilisation.[3] As such, results could be dependent on multivariate factors.

Considering the heterogeneity in the current meta-analysis, which was at 59% due to variables, such as dosage, duration and stage of intervention, and previous controlled or uncontrolled hypertension, could affect the results. Furthermore, the data results must be carefully interpreted due to the limitation of the studies included[3,10-12] and the vast gap in the timeline.

The current meta-analysis has its own limitations. Firstly, the study only included previously hypertensive pregnant women. Secondly, only a limited number of studies were available. Thirdly, only RCTs were included to preserve the quality of the research and the bias factor. As a result of these limitations, the current findings should be interpreted with caution. It is important to deduce that the decision to prescribe low-dose aspirin must be taken at the level of individual patient after considering all the alternatives available and the adverse effects associated with it. Further, more non-randomised controlled trials should be conducted to monitor the impact of low-dose aspirin on preeclampsia.

Conclusion

Although low-dose aspirin is considered safe and showed some obstetric benefits in the studies analysed, it could not be favoured in absolute terms to prevent preeclampsia in previously hypertensive women. The mechanism of aspirin decreases the production of thromboxane, causing anti-inflammatory effects and providing some benefits against preeclampsia. The effect of aspirin could be multifactorial depending on the patient's severity of hypertension, risk of developing preeclampsia, dosage and time of intervention.

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