Review Article

Aspirin in Preeclampsia: Current Evidence and Future Scope of Research

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Abstract

Maternal mortality remains a global health problem. Preeclampsia and eclampsia, major hypertensive disorders in pregnancy, remain the fourth leading cause of maternal mortality. The role of aspirin to prevent preeclampsia has been explored in the last 3 decades. This article summarizes the various studies done so far on the role of aspirin in preeclampsia and seeks to develop a hypothesis regarding the indication, dose and efficacy of aspirin therapy in the prevention of preeclampsia. Aspirin, when administered at 12–20 weeks of gestation at a dose of 75–150 mg seems to have a role in primary and secondary prevention of preeclampsia in high-risk pregnant women. The existing screening algorithms for preeclampsia have a high false positive rate. Therefore, a need for further research to develop a better screening algorithm for detection of women at a high risk of preeclampsia is warranted. The results, from the recent Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) study, reported better prevention of preeclampsia with a 150 mg dose of aspirin. Hence, more data from multicentric randomized controlled trials are required to establish the safety and higher effect size of 120–150 mg dose aspirin compared to the 75–100 mg dose of aspirin for prevention of preterm preeclampsia.

Introduction

Maternal mortality remains a global health problem, with disproportionately high incidence among low and middle income countries.[1] Despite a 44% drop in maternal mortality worldwide from 1990 to 2015, it remains unacceptably high. About 830 women die due to pregnancy and childbirth-related causes every day, and 99% of these deaths occur in developing countries. Preeclampsia (PE) and eclampsia, major hypertensive disorders in pregnancy, remain the fourth most common cause of maternal mortality.[1]

PE refers to new-onset hypertension and proteinuria in a previously normotensive woman after 20 weeks of gestation.[2] It is associated with maternal complications, both short and long term. The risk increases when the onset of PE is earlier (less than 32 weeks), severe (blood pressure of more than 160 mmHg systolic and 110 mmHg diastolic) and in those with pre-existing medical conditions.[3] It affects about 2–8% of pregnancies and remains a major cause of maternal mortality and morbidity, preterm birth, perinatal death and fetal growth restriction.[4,5]

Although many hypotheses have been proposed, the etiology of PE still remains unclear. PE is thought to be associated with deficient production of prostacyclin and an increased production of thromboxane A_2 (TXA_2) by placenta and platelets.[6] These findings have led to the use of antiplatelet agents in the prevention or amelioration of PE in pregnancy. Aspirin is an antiplatelet agent that inhibits cyclooxygenase production to a much higher degree than TXA_2. In PE, aspirin is thought to rectify the imbalance between cyclooxygenase and TXA_2.[7] Therefore, low-dose aspirin (LDA) administration has been tried in various trials to examine its effect in the primary and secondary prevention of PE.

Keywords: Aspirin; Preeclampsia; Preterm preeclampsia; Maternal mortality.

Abbreviations: PE, Pre-eclampsia; TXA_2, Thromboxane A_2; LDA, Low Dose Aspirin; CLASP, Collaborative Low-Dose Aspirin Study in Pregnancy; IUGR, Intra-Uterine Growth Retardation; CI, Confidence interval; WHO, World Health Organisation; ACOG, American College of Obstetricians and Gynecologists; OR, Odds Ratio; RR, Relative Risk; ASPRE, Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention; SPREE, Screening Programme for preeclampsia; NICE, National Institute for Health and Care Excellence.

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Table 1. Studies of aspirin use in prevention of PE

Publication, Year	Risk for pregnancy for PE	No of trials included	Patients included	Dose	Gestational age for initiation of aspirin treatment	Relative risk	Remarks
Wallenburg *et al.*,[7] 1986		1	46	60 mg	28 weeks		Ingestion of LDA from 28 weeks' gestation until delivery may prevent PIH and PE in primigravidae with an increased sensitivity to angiotensin II
Ruano *et al.*,[13] 2005	Low	5	16,700 women	60–100 mg	12–32 weeks	0.95 (0.81–1.11)	13% reduction of preterm PE in high-risk pregnant women
	High	17	16,898 women	60–150 mg	12–33 weeks	0.87 (0.79–0.96)	
Askie *et al.*,[14] 2007		31	32,217 women	50–150 mg	Before 20 weeks	0.90 (0.84–0.97)	PE was reduced by 10% (95% CI: 3.0%–16.0%)
Trivedi *et al.*,[8] 2011		19	28,237 women	50–150 mg	7–32 weeks	0.86 (0.64–1.1)	No correlation between the dose of aspirin and prevention of PE [correlation coefficient $r = 0.13$ (95% CI: 0.34–0.55; $p = 0.58$)]
Bujold *et al.*,[15] 2012		4	392 women	50–150 mg	Before 16 weeks	0.22 (0.08–0.57)	LDA when started at 16 weeks or earlier, was associated with a significant reduction in PE (RR: 0.47, 95% CI: 0.34–0.65)
Henderson *et al.*,[16] 2014		13	12,184 women			0.76 (0.62–0.95)	No evidence could be found in stratified comparisons between the timing of aspirin administration (<16 weeks) or the dose used had different effects on PE prevention
Xu *et al.*,[17] 2015		29	21,403	60–150 mg	12–32 weeks	0.71 (0.57–0.87)	LDA is more effective in reducing incidence of PE or IUGR if used before 16 gestational weeks than if used later; LDA increases the incidence of placental abruption (OR: 1.35, 95% CI: 1.05–1.73) but not of other major complications
					≤16 weeks	0.37 (0.27–0.50)	
					>16 weeks	0.77 (0.62–0.97)	
Roberge *et al.*,[18] 2016		45	20,909	50–150 mg			When aspirin was initiated at ≤16 weeks, there was a significant reduction and a dose-response effect for the prevention of PE; When aspirin was initiated at >16 weeks, there was a smaller reduction of PE (without relationship with aspirin dosage)
			5130		≤16 weeks	0.57 (0.43–0.75)	
			15,779		>16 weeks	0.81 (0.66–0.99)	
USPSTF guidelines[10]				60–150 mg			LDA (ranging from 60 mg to 150 mg daily) given to women at risk for PE reduced their risk by 24%
CLASP trial,[5] 1994		1	9,364 women	60 mg	12–32 weeks		60 mg of aspirin daily at 12–32 weeks' gestation was associated with only a 12% reduction in incidence of PE, which was not significant

Table 1. Studies of aspirin use in prevention of PE - *(continued)*

Publication, Year	Risk for pregnancy for PE	No of trials included	Patients included	Dose	Gestational age for initiation of aspirin treatment	Relative risk	Remarks
Rolnik *et al.*,[12] 2017 (ASPRE trial)	High	1	1,776 women	150 mg	11–14 weeks	0.38 (0.20–0.74)	Aspirin dose from 11–26 weeks till 36 weeks of gestation resulted in a significant reduction (OR: 0.38, 0.95% CI: 0.20–0.74; p = 0.004) in incidence of preterm PE than that with placebo
Yu *et al.*,[11] 2003	High	1	560	150 mg	23 weeks	1.07 (0.75–1.52)	150 mg of aspirin after 23 weeks of gestation did not prevent the development of PE (OR: 0.88, 0.95% CI: 0.56–1.40; p = 0.60) or preterm PE (OR: 0.72, 0.95% CI: 0.35–1.46; p = 0.36)
Meher *et al.*,[19] 2017		23	30,670 women		Before 16 weeks After 16 weeks	0.90 (0.79–1.03) 0.90 (0.83–0.98)	Women at an increased risk of PE should be offered antiplatelet therapy, regardless of whether they are first seen before or after 16 weeks' gestation

CI, confidence interval; IUGR, intrauterine growth retardation; LDA, low-dose aspirin; OR, odds ratio; PE, preeclampsia; RR: relative risk.

Aspirin in PE

The use of aspirin was documented by a randomized controlled trial carried out by Wallenburg and Rotmans in 1986,[8] involving 46 normotensive primigravida patients with a high risk of developing hypertension. The trial suggested that ingestion of LDA from 28 weeks of gestation till delivery can prevent PE in primigravida patients with an increased sensitivity to angiotensin II (indicative of high risk for developing a hypertensive disorder in pregnancy).[8]

The Collaborative Low-Dose Aspirin Study in Pregnancy (known as CLASP) trial—the largest of its kind in aspirin research, carried out over a period of 5 years (1988 to 1992) and involving 9,364 women between 12–32 weeks of gestation-concluded that 60 mg of aspirin daily was associated with only a 12% reduction in the incidence of PE, which was not significant. It also reported no significant effect on incidence of intrauterine growth retardation, stillbirth or intrauterine death. However, it was found to associate with a significant reduction in the incidence of PE in preterm deliveries.[5]

This trial generated curiosity to explore the role of aspirin in the prevention of PE in pregnancy. A meta-analysis done in 2011 by Trivedi *et al*.[9] showed a 21% reduction in the risk of PE among high-risk groups with the use of LDA [relative risk: 0.79, 95% confidence interval (CI): 0.65–0.97]. However, LDA was not found to be effective in reducing the risk in low-risk groups (relative risk: 0.86, 95% CI: 0.64–1.17). The results of various trials are summarized in Table 1.[5–19]

World Health Organisation (WHO) recommends LDA (75 mg) before 20 weeks of pregnancy among women at high risk for PE.[20] However, the United States Preventive Task Force recommendation statement and American College of Obstetricians and Gynecologists (commonly known as the ACOG) recommended a low dose of aspirin (81 mg) prophylaxis from 12 weeks onwards for mothers who are at high risk for PE, based upon meta-analysis results.[10,21] A multicentric trial carried out in four countries in 2003 by Yu *et al*.[11] among 560 women concluded that the administration of 150 mg of aspirin after 23 weeks of gestation did not prevent the development of PE [odds ratio (OR): 0.88, 95% CI: 0.56–1.40; p = 0.60] or preterm PE (OR: 0.72, 95% CI:.35–1.46; p = 0.36).

However, the recent trial of aspirin research in PE, known as the ASPRE Trial-conducted in 2017 by Rolnik *et al*.[12] and involving 1776 pregnant women at high risk of developing PE-showed that 150 mg of daily aspirin dose from 11–26 weeks till 36 weeks of gestation resulted in a significant reduction in incidence of preterm PE (OR: 0.38, 95% CI: 0.20–0.74; p = 0.004), as compared with placebo. Two other studies have investigated the effect of 150 mg dose of aspirin among pregnant women at high risk of PE. One of those studies was conducted among 102 first trimester patients in 1985 and used two antiplatelet agents (300 mg dipyridamole and 150 mg aspirin). The investigators concluded that patients on antiplatelet agents were twice as likely to have a normal pregnancy as compared to the placebo group, both in terms of incidence of PE and duration of pregnancy.[22] The second study, by Trudinger *et al*.[23] in 1988, also explored the effects of 150 mg aspirin on fetal outcome among 46 high-risk patients. Those investigators concluded that the mean percentile birth weight was 22% higher in the aspirin-treated group than in the placebo group. The indications, dosage and efficacy of aspirin therapy in the primary prevention of PE remains a controversy among researchers to date.

Discussion

LDA is effective in secondary prevention of PE in high-risk pregnant women, mainly those with a history of preeclampsia.[11] Overall, we find that aspirin should be administered once a day in the evening, at low doses ranging from 75 mg to 150 mg.[12,20] The efficacy of aspirin in the prevention of PE improves with early initiation (12–20 weeks of gestation).[20,21] Even though LDA has a good maternal and fetal safety profile, the number of studies where patients were exposed to doses over 100 mg is low. The ASPRE study has explored the effect of 150 mg aspirin in preterm PE in

less than 16 weeks' gestation, with promising results.[12] However the safety of a prevention strategy based on 150 mg of aspirin per day has not been proven with adequate power and sample size, and there remains a need for further research and multicentric trial to establish the effect of 150 mg aspirin in prevention of preterm PE.

Indications for aspirin in primary prevention is a matter of debate and further research, but recent publications also suggest a strategy based on first-trimester screening of PE (with clinical parameters, biomarkers and uterine Doppler measurements) and aspirin administration to high-risk pregnant women.[12] The usefulness of this strategy is still under evaluation and more data is needed before its implementation in real practice. This study raises a question. Is screening of PE based on the ASPRE algorithm more effective than the current national guidelines (National Institute for Health and Care Excellence [NICE],[24] ACOG,[21] *etc*.)?

This question is also the subject of an ongoing study in the UK [Screening Programme for pre-eclampsia (SPREE) study]. Preliminary findings of which showed that trimester mini-combined test and combined test for PE screening using the Bayes' theorem-based method are likely to be superior to the current method recommended by NICE (based on maternal demographics and history).[25] However, if we use an ASPRE screening algorithm, 100 mothers have to be administered with 150 mg of aspirin for 6 months to avoid 2–3 preterm PE.[12] The early identification of pregnant women who are at high risk of PE and starting the LDA (75–150 mg) in early gestation periods (12–20 weeks) remains the cornerstone for the prevention of PE.

Future research direction

There are crucial scopes for research in establishing the role and use of aspirin in PE. Though the ASPRE algorithm was found to be better than NICE guidelines in the SPREE study, we agree with Green *et al*.[26] that this screening tool has a high false positive rate. Can we develop a better tool for screening of pregnant women at high risk for PE? Can we identify the pregnant women who will benefit from the aspirin therapy, distinguishing them from those who won't? There is limited available evidence regarding the safety and higher efficacy of 120–150 mg dose of aspirin in PE prevention. Can we generate more data through multicentric studies for establishing the safety and higher effect size of 120–150 mg dose aspirin compared to the 75–100 mg dose of aspirin for prevention of preterm PE?

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Development of concept (PB and SMB), manuscript writing (PB, SMB, H, MB, MP and SD), review of manuscript (PB, SMB, H, MB, MP and SD).

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