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Early Administration of Low-Dose Aspirin for the Prevention of Preterm and Term Preeclampsia: A Systematic Review and Meta-Analysis

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Key Words
Preeclampsia · Aspirin · Preterm

Abstract
Objective: To compare the effect of early administration of aspirin on the risk of preterm and term preeclampsia. ***Method:*** A systematic review and meta-analysis of randomized controlled trials were performed. Women who were randomized to low-dose aspirin or placebo/no treatment at or before 16 weeks of gestation were included. The outcomes of interest were preterm preeclampsia (delivery <37 weeks) and term preeclampsia. Pooled relative risks (RR) with their 95% confidence intervals (CI) were computed. ***Results:*** The search identified 7,941 citations but only five trials on a combined total of 556 women fulfilled the inclusion criteria. When compared to controls, aspirin initiated ≤16 weeks of gestation was associated with a major reduction of the risk of preterm preeclampsia (RR 0.11, 95% CI 0.04–0.33) but had no significant effect on term preeclampsia (RR 0.98, 95% CI 0.42–2.33). ***Conclusion:*** Low-dose aspirin administrated at or before 16 weeks of gestation reduces the risk of preterm but not term preeclampsia.

Introduction

Preeclampsia, which affects about 2–8% of pregnancies, is thought to be the consequence of impaired trophoblastic invasion of the maternal spiral arteries [1, 2]. There is evolving evidence that both the degree of impaired placentation and the incidence of adverse fetal and maternal short- and long-term consequences of preeclampsia are inversely related to the gestational age at onset of the disease [3–9].

There is extensive evidence from randomized studies that the prophylactic use of low-dose aspirin is associated with 10% reduction in the prevalence of preeclampsia in women at risk of this pregnancy complication [10]. However, the effectiveness of aspirin may be related to the onset of treatment. Bujold et al. [11] reported that when low-dose aspirin is started after 16 weeks of gestation there is no significant decrease in the risk of the disease, whereas with treatment starting at or before 16 weeks there is a halving in the risk. This finding suggests that early administration of aspirin may reduce the risk of preeclampsia, possibly by improving placentation. It is therefore possible that early-onset use of aspirin may be

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Table 1. Characteristics of included studies

Study (first author)	Onset of treatment	Participants	Inclusion criteria	Intervention	Definition of preeclampsia
August, 1994 [21]	13–15 weeks	49 women	Chronic hypertension or previous severe preeclampsia	ASA 100 mg vs. placebo	Rise of 30 mm Hg SBP and rise of 15 mm Hg DBP with proteinuria and hyperuricemia or HELLP syndrome
Bakhti, 2011 [22]	8–10 weeks	164 women	First pregnancy in women with no previous vascular or renal disease	ASA 100 mg vs. no treatment	BP ≥140/90 mm Hg with proteinuria (>300 mg/day)
Ebrashy, 2005 [23]	14–16 weeks	139 women	Risk factor for preeclampsia or fetal growth restriction (previous history of the disease, essential hypertension, positive family history or underlying vascular disorder, maternal age <20 or >40 years, and gestational diabetes mellitus) combined with abnormal uterine artery Doppler	ASA 75 mg vs. no treatment	BP ≥140/90 mm Hg with proteinuria (>300 mg/day)
Vainio, 2002 [24]	12–14 weeks	86 women	Anamnestic risk factor (history of chronic hypertension, familial risk of preeclampsia (mother or sister), gestational diabetes, age <20 or >40 years, previous pre-eclampsia, previous intrauterine growth retardation, or previous intrauterine death) with abnormal uterine Doppler (constant bilateral diastolic notch was found in the uterine arteries)	ASA 0.5 mg/kg/day vs. placebo	BP ≥140/90 mm Hg with proteinuria (≥300 mg/day)
Villa, 2010 [25]	13–14 weeks	121 women	Women with risk factor for preeclampsia (<20 or >40 years old, obesity, chronic hypertension, Sjögren's syndrome, history of diabetes or preeclampsia or SGA or fetal death) in combination with bilateral second-degree notch on uterine artery Doppler	ASA 100 mg vs. placebo	BP ≥140/90 on two consecutive measurements and proteinuria (≥300 mg/day)

BP = Blood pressure; S = systolic; D = diastolic.

more effective in preventing preterm than term preeclampsia.

The aim of this systematic review and meta-analysis of randomized studies that evaluated the benefits of low-dose aspirin started at or before 16 weeks of gestation is to examine the effects on the risk of preterm and term preeclampsia in a population of women at risk of preeclampsia.

Method

Sources

Relevant citations were extracted from Embase, PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science from 1965 to October 2011. Keywords and MeSH terms were combined to generate lists of studies: 'aspirin', 'antiplatelet', 'salicy*', 'ASA', 'pregnancy-complication', 'hypertens*', 'blood press*', '*eclamp*', 'PIH', 'toxaemi*', 'IUGR'. No language restriction was imposed. The first reviewer (S.R.) sorted all articles by citations and abstract for more detailed evaluation. The second sort was revised by two reviewers (S.R., E.B.) and all relevant trials were entirely reviewed by the same two reviewers. Quality and integrity of this review were validated with PRISMA: preferred reporting items for systematic reviews and meta-analyses [12].

Study Selection

Only prospective, randomized, controlled trials were included. The population in the studies involved pregnant women at risk of preeclampsia treated with low-dose aspirin at or before 16 weeks of gestation. No restrictions were applied to risk criteria for preeclampsia (table 1). Low-dose aspirin was defined as 50–150 mg of acetylsalicylic acid (ASA) daily, alone or in combination with <300 mg of dipyridamole, another antiplatelet agent. The control group had to be allocated to placebo or no treatment. Study quality was evaluated by using Cochrane Handbook Criteria for judging risk of bias tool, and studies with high risk of bias were considered for exclusion [13].

Outcomes Measures

The outcome measures were preterm preeclampsia (delivered before 37 completed weeks' gestation) and term preeclampsia. The American College of Obstetricians and Gynecologists defines preeclampsia as blood pressure of 140 mm Hg systolic or higher or 90 mm Hg diastolic or higher that occurs after 20 weeks of gestation in a woman with previously normal blood pressure plus proteinuria, defined as urinary excretion of 0.3 g protein or higher in a 24-hour urine specimen or 2+ protein on dipstick [14].

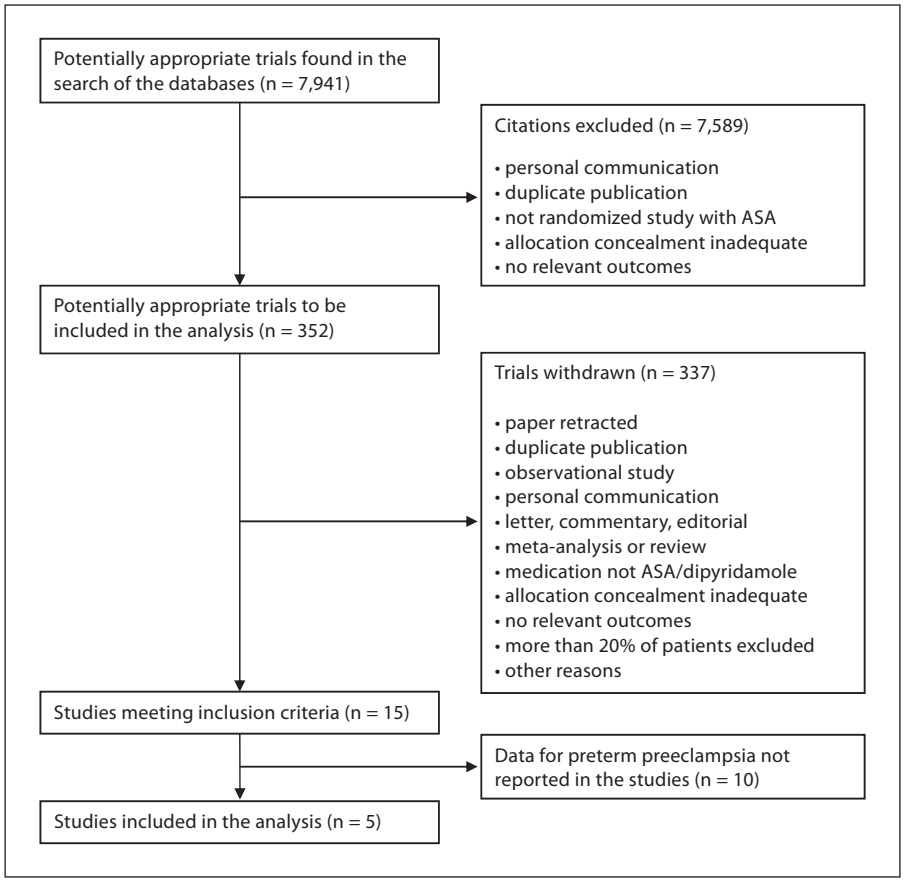

Fig. 1. Processes of selection of the articles.

Table 2. Relative risk of preterm and term preeclampsia associated with the use of low-dose aspirin at or before 16 weeks' gestation

Study (first author)	Risk of bias[1]	Preeclampsia, %				Relative risk (95% CI)	
		preterm		term		preterm	term
		aspirin	controls	aspirin	controls		
August, 1994 [21]	3/4/0	0	20	12.5	0	0.09 (0.01, 1.62)	7.28 (0.40, 133.89)
Bakhti, 2011 [22]	5/1/1	1.2	11	0	0	0.11 (0.01, 0.86)	not estimable
Ebrashy, 2005 [23]	7/0/0	0	36.5	34.2	27	0.02 (0.00, 0.30)	1.27 (0.76, 2.13)
Vainio, 2002 [24]	7/0/0	0	2.3	4.7	20.9	0.33 (0.01, 7.96)	0.22 (0.05, 0.97)
Villa, 2010 [25]	6/1/0	1.6	8.3	11.5	10	0.20 (0.02, 1.63)	1.15 (0.41, 3.22)
Total		0.71	15.8	13.1	11.7	0.11 (0.04, 0.33), $p < 0.01$	0.98 (0.42, 2.33), $p = 0.97$

[1] Number of criteria that were considered at low risk/unclear risk/high risk for bias according to the Cochrane Handbook Criteria for judging risk of bias tool.

However, as the definition of preeclampsia varies between countries, we accepted all similar definitions [15, 16].

Statistical Analysis

All studies were combined and analyzed with Review Manager 5.0.25 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) software. Individual risk ratios (RR) were calculated for each study, and pooled for global analysis with 95% confidence intervals (CI). Analysis of preeclampsia was divided into preterm preeclampsia and term preeclampsia. Global RR was calculated according to DerSimonian and Laird random effect models in case of heterogeneity [17, 18].

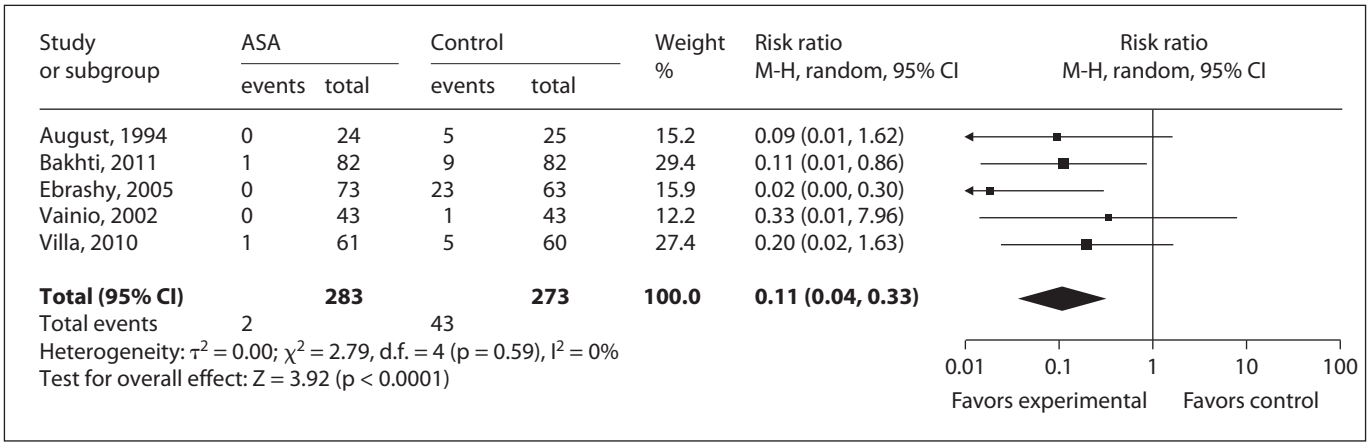

Fig. 2. Forest plot of the effect of low-dose aspirin initiated at or before 16 weeks' gestation on the risk of preterm preeclampsia.

Heterogeneity between studies was analyzed with Higgins' I^2 and considered to be high over 50% [19]. The distribution of trials was examined with funnel plots to assess publication bias [20].

Results

The literature search identified 7,941 potentially eligible studies (fig. 1). Of these, only five studies on a combined total of 556 women were included in the final analysis because they fulfilled the three entry criteria: (1) treatment with aspirin or placebo initiated at or before 16 weeks of gestation, (2) information provided on preterm and term preeclampsia, and (3) judged for low-risk or unclear risk of bias. The control group received placebo in three of these studies and no treatment in two (table 1) [21–25].

We found that low-dose aspirin administered at or before 16 weeks of gestation was associated with a significant reduction in the risk of preterm preeclampsia, but not term preeclampsia (table 2; fig. 2, 3). A random model was used for both outcomes because of high heterogeneity between the included studies for at least one outcome; the heterogeneity for preterm preeclampsia was 0% and for term preeclampsia it was 54%. Analysis of the funnel plot was precluded because of the small number of included studies. According to Cochrane Handbook Criteria for judging risk of bias tool, the included studies were judged to have low or unclear risk of bias [13].

Discussion

This meta-analysis was restricted to randomized controlled trials which firstly examined the use of low-dose aspirin initiated at or before 16 weeks of gestation and secondly provided data on both outcome measures of interest: preterm preeclampsia, as defined by delivery of women with preeclampsia before 37 completed weeks of gestation, and term preeclampsia. The inclusion criteria were met by only five studies on a total of 556 patients. Nevertheless, the results demonstrate a major beneficial effect of low-dose aspirin prophylaxis started at or before 16 weeks of gestation in reducing preterm preeclampsia. In contrast, the use of aspirin was not associated with a significant reduction in the risk of term preeclampsia.

A meta-analysis of 31 trials on a combined total of 32,217 pregnancies reported that use of low-dose aspirin was associated with a 10% reduction in the prevalence of both preeclampsia and delivery before 34 weeks' gestation [10]. However, this study did not examine the differential effect of early initiation of treatment. In our previous meta-analysis we found that the effect of aspirin was substantially higher if treatment is initiated at or before 16 weeks rather than after this gestation [11]. The findings of our present study extend the results of the previous one by demonstrating that the use of aspirin starting at or before 16 weeks may be particularly effective in preventing severe preeclampsia requiring preterm delivery.

A major limitation of our meta-analysis is the small number of studies fulfilling the entry criteria. Moreover, the presence of heterogeneity for term preeclampsia suggests the presence of variance between included studies.

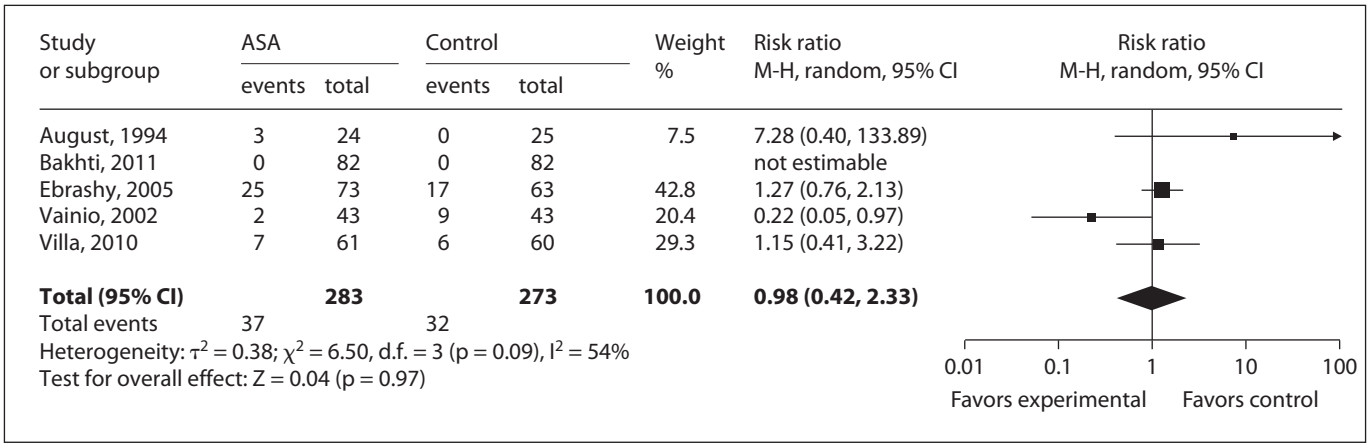

Fig. 3. Forest plot of the effect of low-dose aspirin initiated at or before 16 weeks' gestation on the risk of term preeclampsia.

However, the strength of the association and the great homogeneity for preterm preeclampsia suggests that the findings are likely to be valid. Nevertheless, the results require validation by major randomized studies in which the entry criterion would be high risk for preeclampsia identified by first-trimester screening and the outcome measures would be the risk of preeclampsia at a different gestational age, as well as the associated perinatal mortality and morbidity.

Preterm preeclampsia is more severe than term preeclampsia and is associated with a higher incidence of adverse maternal and perinatal consequences [3–8]. Our finding of a reduction in the risk of preterm preeclampsia by about 89% is compatible with the finding of the previous meta-analysis where the reduction in severe preeclampsia was about 91% (RR 0.09, 95% CI 0.02–0.37) [11]. Our finding is also in agreement with data of Beaufils et al. [26] who found strong benefits of low-dose aspirin initiated at 14–16 weeks for the prevention of severe preeclampsia and preeclampsia diagnosed before 37 weeks. Beaufils et al. [26] found that aspirin was associated with a reduction of severe preeclampsia (RR 0.07, 95% CI 0.00–1.25). We were not able to obtain the data for preeclampsia with delivery before 37 weeks for this study.

Pathological studies have shown that the prevalence of placental lesions in women with preeclampsia is inversely related to the gestational age at delivery [6, 27]. Furthermore, epidemiological studies have reported that preterm preeclampsia is associated with low birth weight, whereas in term preeclampsia the birth weight is often normal or increased [28–31]. Studies investigating the use of Doppler ultrasound in the assessment of impedance to blood flow in the uterine arteries, as an indirect measure of impaired placentation, have demonstrated that the pulsatility index is increased mainly in preterm compared to term preeclampsia [32]. A multicenter screening study in more than 30,000 singleton pregnancies reported that the uterine artery pulsatility index at 22–24 weeks' gestation was above the 95th percentile in 77% of women who developed preeclampsia requiring delivery before 34 weeks, in 36% of those delivering at 34–37 weeks and in 22% of those delivering at term [8].

In conclusion, our meta-analysis showed that the initiation of low-dose aspirin prophylaxis at or before 16 weeks' gestation resulted in a 89% reduction of preeclampsia delivered before 37 weeks' gestation, but had no effect on the risk of term preeclampsia. The most likely explanation for our findings is that early administration of low-dose aspirin improves placentation. Such an effect would result firstly in a reduction in the overall risk of the disease and secondly in a shift from early-onset severe disease requiring preterm delivery to a milder disease presenting at term. This hypothesis warrants to be tested in future large-scale randomized studies on the effect of low-dose aspirin in women with evidence of impaired placentation in early pregnancy [33–35].

Disclosure Statement

The authors have no conflicts of interest to disclose.

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