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

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Am J Perinatol 2012;29:551–556.

Abstract

Objective To determine whether early administration of aspirin prevents severe and mild preeclampsia.

Study Design A systematic review and meta-analysis of randomized controlled trials were performed. Studies in which women were randomized at or before 16 weeks' gestation to low-dose aspirin versus placebo or no treatment were included. The outcomes of interest were severe preeclampsia and mild preeclampsia. Pooled relative risks with their 95% confidence intervals (CIs) were calculated.

Results Among 7941 citations retrieved, 352 were completely reviewed and four studies (392 women) fulfilled the inclusion criteria and were analyzed. When compared with controls, aspirin started at $\leq$16 weeks was associated with a significant reduction in severe (relative risk: 0.22, 95% CI: 0.08 to 0.57) but not mild (relative risk: 0.81, 95% CI: 0.33 to 1.96) preeclampsia.

Conclusion Low-dose aspirin initiated at or before 16 weeks reduces the risk of severe preeclampsia, but not mild preeclampsia.

Keywords
- pregnancy
- preeclampsia
- aspirin
- systematic review
- meta-analysis

Preeclampsia, which affects 2 to 8% of pregnancies, is a major cause of maternal and perinatal morbidity and mortality.[1,2] It is usually defined as hypertension and proteinuria that occur at or after 20 weeks' gestation in women with previously normal blood pressure. The disease is considered to be severe when it is associated with liver damage, thrombocytopenia,

received
November 25, 2011
accepted after revision
December 17, 2011
published online
April 11, 2012

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Tel: +1(212) 584-4662.

DOI http://dx.doi.org/10.1055/s-0032-1310527.
ISSN 0735-1631.

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fetal growth restriction (FGR), and symptoms such as headache, visual disturbance, and right upper-quadrant pain.[3] However, published reports use differing criteria for the diagnoses of preeclampsia and severe preeclampsia. A growing body of evidence suggests that severe and mild preeclampsia develop from two distinct pathophysiological processes. Women with preterm preeclampsia are at higher risk of severe preeclampsia and eclampsia, and their adverse consequences.[4–7]

Bujold et al found that low-dose aspirin initiated at or before 16 weeks' gestation could prevent ~50% of preeclampsia and 55% of FGR.[8] It has been suggested that low-dose acetylsalicylic acid therapy inhibits thromboxane more than prostacyclin production and thereby protects against vasoconstriction and pathological blood coagulation in the placenta.[9] The use of low-dose aspirin given in early pregnancy has been associated with improvement of uterine artery blood flow resistance, suggesting a greater remodeling of the spiral artery.[10,11] Therefore, we hypothesized that low-dose aspirin could be more effective in the prevention of severe preeclampsia than in the prevention of mild disease. We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) that evaluated the benefits of low-dose aspirin prophylaxis started before 16 weeks' gestation in the prevention of severe preeclampsia.

Methods

Sources

Keywords and MeSH terms "aspirin," "antiplatelet," "salicy*," "ASA," "pregnancy-complication," "hypertens*," "blood press*," "*eclamp*," "PIH," "toxaemi*," "IUGR" were combined for electronic databases search. Relevant citations were extracted from Embase, PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science from 1965 to October 2011. No language restriction was imposed. All articles were sorted by the first reviewer (S.R.) for more detailed evaluation. Citation and abstract were retrieved for the second sort and was reviewed by two reviewers (S.R., E. B.). All relevant trials were entirely reviewed by the same two reviewers. Other systematic reviews were used for additional search.[12–14] Quality and integrity of this review were validated with PRISMA (preferred reporting items) for systematic reviews and meta-analyses.[15]

Study Selection

This meta-analysis includes only prospective, randomized, controlled trials. The population in the studies involved pregnant women at risk of preeclampsia treated with low-dose aspirin initiated at or before 16 weeks of gestation. No restrictions were applied to risk criteria for preeclampsia. Low-dose aspirin was defined as 50 to 150 mg of acetylsalicylic acid daily, alone or in combination with 300 mg of dipyridamole or less, another antiplatelet agent. The control group had to be allocated to placebo or no treatment. Studies' qualities were evaluated using Cochrane Handbook Criteria for judging risk of bias tool, and studies with high risk of bias were considered for exclusion.[16]

Outcomes

The primary outcome was the occurrence of severe or mild preeclampsia. The American College of Obstetricians and Gynecologist 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.[17] Severe preeclampsia is diagnosed if, in addition to the above criteria, one or more of the following criteria is present: sustained (at least 6 hours) systolic blood pressure of at least 160 mm Hg, or sustained diastolic blood pressure of at least 110 mm Hg, severe proteinuria 5 g or higher protein in 24 hours, or 3+ on dipstick), oliguria of less than 500 mL in 24 hours, cerebral or visual disturbances, pulmonary edema or cyanosis, epigastric or right upper-quadrant pain, impaired liver function, thrombocytopenia, FGR.[17] However, as the definition of severe preeclampsia varies between countries; we accepted all definitions that we considered similar. When data regarding severe preeclampsia were not provided, we contacted the corresponding author or first author for additional information. When not specifically provided, the number of mild preeclampsia was calculated as the cases of all preeclampsia minus the cases of severe preeclampsia.

Statistical Analysis

Studies were combined and analyzed with Review Manager 5.0.25 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) software. Individual risk ratios (RRs) were calculated for each study, and pooled for global analysis with 95% confidence intervals (CIs). Analysis of preeclampsia was divided into severe preeclampsia and mild preeclampsia. Global RR was calculated according to DerSimonian and Laird random effect models in case of heterogeneity.[18,19] Heterogeneity between studies was analyzed using the Higgins' I^2.[20] The distribution of trials was examined with funnel plots to assess publication bias.[21]

Results

The literature search identified 7941 potentially eligible studies, and 352 were reviewed (►**Fig. 1**). The inclusion criteria were met by 15 studies but only four were included (392 women) for the final analysis because information on severe and mild preeclampsia were available. In three studies, women randomized to the control received placebo,[11,22,23] and in the fourth study, they received no treatment (►**Table 1**).[24]

Administration of aspirin initiated at or before 16 weeks' gestation was associated with a significant reduction in the risk of overall preeclampsia (RR: 0.52, 95% CI: 0.38 to 0.76, $p < 0.01$) and severe preeclampsia, but not mild preeclampsia (►**Table 2** and ►**Figs. 2** and **3**). The eight studies that were not included in the meta-analysis because of unavailable data regarding severe/mild preeclampsia but where the overall rate of preeclampsia was reported demonstrated a similar effect of aspirin on preeclampsia (RR: 0.22, 95% CI 0.10 to 0.46, $p < 0.01$).[25–32]

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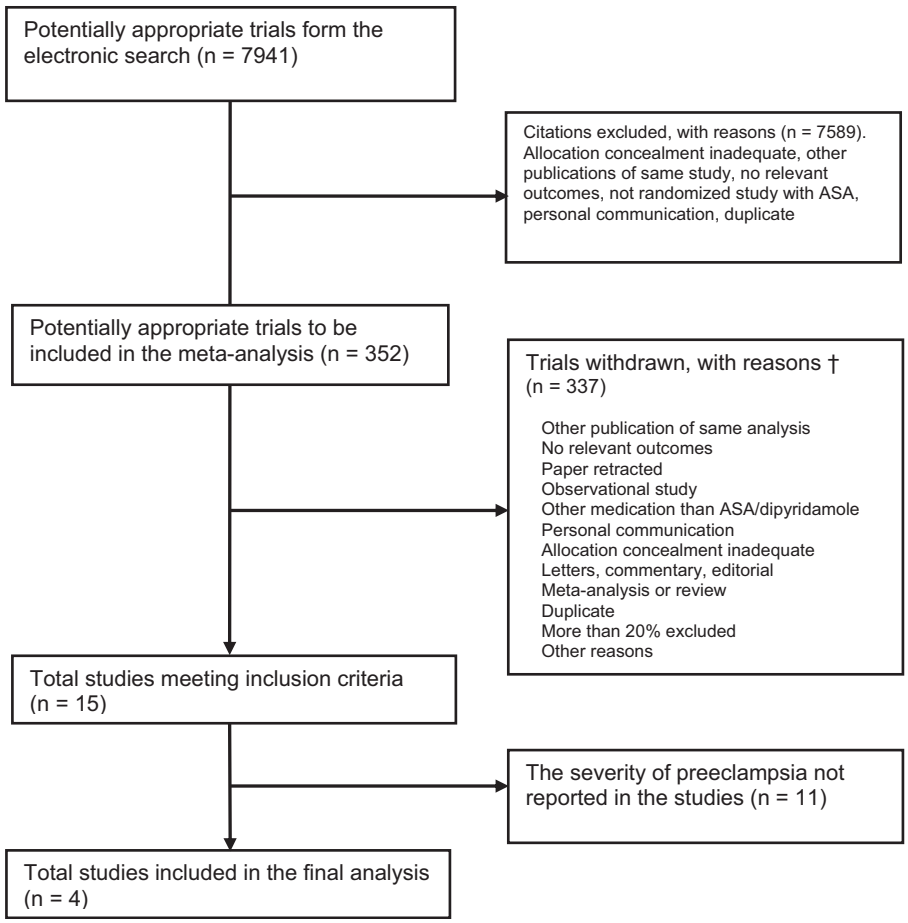

Figure 1 Flow diagram showing the selection process of articles. ASA, acetylsalicylic acid.

In the included studies, the homogeneity for the reduction in the relative risk of severe preeclampsia was high (I^2: 0%), whereas the homogeneity for the effect on the relative risk of mild preeclampsia was moderate (I^2: 49%). Random model was used for both outcomes because heterogeneity between studies including the same population was present for at least one outcome. 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, all studies were judged to have low or unclear risk of bias.[16]

Discussion

The results of this meta-analysis, which includes the results of one additional RCT to those provided in our previous report,[8] is in complete agreement with the results of our previous report demonstrating a major beneficial effect of early onset, low-dose aspirin in halving the overall risk of preeclampsia, and this effect was particularly marked in the case of severe preeclampsia whose relative risk was reduced by ~90%. In contrast, the use of aspirin was not associated with a significant reduction in the relative risk of mild preeclampsia.

One likely explanation for a high effectiveness of early onset, low-dose aspirin in the prevention of severe preeclampsia but not of mild disease is that the pathophysiology of the two conditions is different and only the former is susceptible to the effects of aspirin. There is supportive evidence from Doppler ultrasound studies that in a high proportion of cases of severe preeclampsia with associated FGR, unlike cases of mild disease without FGR, impedance to flow in the uterine arteries is increased.[33] Such increased impedance to flow is thought to be a consequence of inadequate trophoblastic invasion of the maternal spiral arteries and their conversion from narrow muscular vessels to wide nonmuscular channels.[34]

It is possible that early onset, low-dose aspirin improves placentation and, therefore, reduces the risk of severe preeclampsia. An alternative explanation for our findings is that in all cases of preeclampsia there is impaired placentation, but a spectrum of placental impairment is reflected in the severity of the clinical manifestations of the disease. In this case, the beneficial effect of aspirin on placentation could actually reduce substantially the risk of those cases that were destined to develop mild preeclampsia and convert the predestined severe to mild preeclamptic cases.

The main weaknesses of our study are the small number of studies included in the analysis and the heterogeneity in the

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Table 1 Characteristics of Included Studies

First Author, Year	Gestational Age at Initiation of Treatment (wk)	Participants (*n*)	Inclusion Criteria	Intervention	Definition of Preeclampsia	Criteria for Severe Preeclampsia
August, 1994[22]	13–15	49	Chronic hypertension or previous severe preeclampsia	ASA 100 mg vs placebo	Rise of 30 mm Hg of SBP and 15 mm Hg of DBP with proteinuria and hyperuricemia or HELLP syndrome	Severe disease necessitating premature delivery
Ebrashy, 2005[24]	14–16	136	Abnormal uterine artery Doppler and risk factors for preeclampsia and intrauterine growth restriction	ASA 75 mg vs no treatment	SBP $\geq$140 and DBP $\geq$90 mm Hg with proteinuria $>$300 mg/d	SBP reached 160 mm Hg, DBP reached 110 mm Hg, proteinuria reached 2 g in 24-h urine sample, urine output was $<$500 mL/d, platelet count was $<$100,000 per mm^3, and liver enzymes were increased
Vainio, 2002[11]	12–14	86	Anamnestic risk factor with abnormal uterine Doppler	ASA 0.5 mg/kg/d vs placebo	SBP $\geq$140 and DBP $\geq$90 mm Hg with proteinuria $\geq$300 mg/d	Birth weight $<$10th percentile
Villa, 2010[23]	13–14	121	Anamnestic risk factor with abnormal uterine Doppler (bilateral second-degree uterine artery notch)	ASA 100 mg vs placebo	BP $\geq$140/90 in consecutive measurements and proteinuria $\geq$0.3 g/24 h	BP $\geq$160 systolic and/or $\geq$110 diastolic and/or proteinuria $\geq$5 g/24 h

ASA, acetylsalicylic acid; BP, blood pressure; DBP, diastolic blood pressure; HELLP syndrome, hemolysis, elevated liver enzymes, and low platelet count; SBP, systolic blood pressure.

definition of severe preeclampsia. Because most of the studies potentially eligible were completed before 2000, the primary data are no longer available for accurate classification of severity. This is especially true as current definitions of severe preeclampsia perform poorly in identifying true incremental risk of either adverse maternal or adverse perinatal outcomes.[35] However, the diagnosis of preeclampsia remains more reliable when combined with severity criteria, and this could be another reason for our findings because the diagnosis of mild preeclampsia can be considered more subjective.

Our meta-analysis is also limited by the absence of very large trials. The six largest trials that evaluated the impact of low-dose aspirin in preeclampsia recruited women after 16 weeks' gestation.[36–41] The absence of studies showing no beneficial effects in the funnel plot suggests the possibility of publication bias. Moreover, the small number of studies that reported the prevalence of severe preeclampsia and/or preterm preeclampsia precludes the interpretation of funnel plots for those outcomes. However, the great homogeneity of the results between the studies included in our meta-analysis for severe preeclampsia suggests a good validity of our findings. Two eligible studies were excluded because they did not report the cases of mild preeclampsia, preventing the comparison between severe and mild disease.[26,27] However,

Table 2 Relative Risk of Severe Preeclampsia and Mild Preeclampsia Associated with the Use of Low-Dose Aspirin at or Before 16 Weeks' Gestation

Outcomes	Prevalence of the Outcomes (%)		Relative Risk (95% Confidence Intervals)	*p* Value	I^2
	Aspirin	Controls			
Severe preeclampsia	2.0	12.6	0.22 (0.08, 0.57)	$<$0.001	0%
Mild preeclampsia	16.9	22.0	0.81 (0.33, 1.96)	0.63	49%

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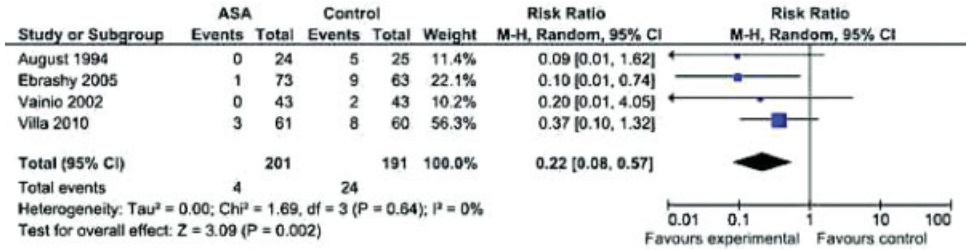

Figure 2 Forest plot of the effect of low-dose aspirin initiated at or before 16 weeks' gestation on the prevalence of severe preeclampsia. ASA, acetylsalicylic acid; CI, confidence interval; DPI, dots per inch; M-H, Mantel-Haenszel.

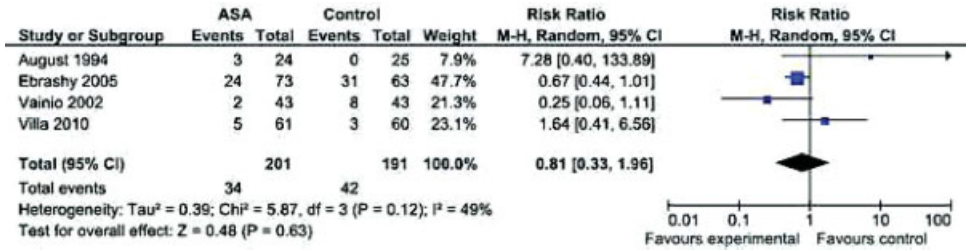

Figure 3 Forest plot of the effect of low-dose aspirin initiated at or before 16 weeks' gestation on the prevalence of mild preeclampsia. ASA, acetylsalicylic acid; CI, confidence interval; DPI, dots per inch; M-H, Mantel-Haenszel.

adding those studies to the analysis would have only strengthened the association of low-dose aspirin and risk reduction of severe preeclampsia (six studies, RR: 0.18, 95% CI: 0.08 to 0.41). These two studies were included in the eight studies that did not differentiate between mild and severe preeclampsia and therefore could explain the important effect of aspirin found in that subgroup.

Our meta-analysis included studies that recruited women at high risk for preeclampsia using a wide variety of inclusion criteria, and the majority of the women had a previous history of preeclampsia. We believe that definitive trials are required to determine whether low-dose aspirin can prevent the adverse maternal and perinatal consequences of severe preeclampsia in high-risk women who may be identified through predictive screening programs.[42–45] Such trials should consider evaluating the role of aspirin resistance combined, or not, with adjustment of aspirin dosage.[42,46–48] Based on the current study, such large-scale trials should aim to decrease the risk of the adverse maternal and perinatal outcomes associated with severe rather than mild preeclampsia.

In conclusion, our meta-analysis confirms that low-dose aspirin initiated between 7 and 16 weeks' gestation is associated with a significant reduction in severe preeclampsia, in a population of women identified at high risk for preeclampsia.

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