Prevention of preeclampsia with low-dose aspirin: a systematic review and meta-analysis of the main randomized controlled trials

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CRD summary
The review investigated the effect of low-dose aspirin in women at low risk and high risk of pre-eclampsia. It concluded that aspirin is associated with a small reduction in the incidence of pre-eclampsia in women at high risk. The conclusion appears to follow from the evidence presented, although relevant studies might have been missed and the lack of detail about the methods makes it difficult to verify the findings.

Authors' objectives
To determine the effectiveness of low-dose aspirin in the prevention of pre-eclampsia in women at low risk and high risk of pre-eclampsia.

Searching
MEDLINE and the Cochrane Library were searched from January 1983 to December 2003 for published studies; the search terms were not reported. The reference lists of published articles or chapters from textbooks were screened for other potentially relevant studies.

Study selection
Study designs of evaluations included in the review
Double-blinded randomised controlled trials (RCTs) with appropriate concealment of allocation were eligible for inclusion.

Specific interventions included in the review
Studies of low-dose aspirin administered for the prevention of pre-eclampsia, compared with placebo, were eligible for inclusion. The dose of aspirin ranged from 60 to 100 mg/day in low-risk women and from 50 to 150 mg/day in high-risk women.

Participants included in the review
Women at low risk or high risk of developing pre-eclampsia were eligible for inclusion. The criteria for identifying women at high risk of pre-eclampsia were one or a combination of the following risk factors and tests.

Risk factors: essential chronic arterial hypertension prior to the pregnancy, insulin-treated diabetes, or an antecedent of severe pre-eclampsia (eclampsia, HELLP syndrome, blood-pressure of 160/110 mmHg, imminence of eclampsia, respiratory distress or renal failure).

Tests: positive tests such as Doppler ultrasonography, the rollover test, or the angiotensin II sensitivity test.

Women at low risk were those without any of the above risk factors or tests. Trials with mixed populations were excluded. The gestational age of women in the trials ranged from 12 to 32 weeks in low-risk women and from 12 to 33 weeks in high-risk women.

Outcomes assessed in the review
Studies reporting data on the incidence of pre-eclampsia were eligible for inclusion. Pre-eclampsia was defined as increasing blood-pressure after 20 gestational weeks that was associated with proteinuria of at least 300 mg per 24 hours.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the studies for inclusion, but the authors did not state how any disagreements
Assessment of study quality
The authors stated that the validity of the trials was assessed according to the criteria suggested by the Cochrane Handbook, notably the concealment of allocation. Studies with unsatisfactory quality were excluded.

Two reviewers independently performed the quality assessment and any disagreements were resolved by discussion. The study was excluded if agreement between the two reviewers was not possible.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
The data were tabulated separately for women at low-risk and high-risk of pre-eclampsia. A Mantel-Haenszel fixed-effect model was used to calculate and compare the summary relative risk (RR) with 95% confidence intervals (CIs) in women at low-risk and high-risk of pre-eclampsia.

How were differences between studies investigated?
The chi-squared test was used to assess statistical heterogeneity amongst the studies. The absence of an experimental intervention effect was also tested (RR=1). Clinical heterogeneity was assessed by exploring the effect of gestational age, duration and dosage of aspirin, and the criteria used to define women at high risk of developing pre-eclampsia.

Results of the review
Twenty-two RCTs (n=33,598) were included. Five trials (n=16,700) were in low-risk women and 17 trials (n=16,898) were in high-risk women.

The incidence of pre-eclampsia was 3.75% in low-risk women and 9.01% in high-risk women.

In low-risk women, there was no statistically significant difference between low-dose aspirin and placebo in reducing the risk of pre-eclampsia (RR 0.95, 95% CI: 0.81, 1.11, P=0.51); there was statistically significant heterogeneity between the studies (P=0.01).

In high-risk women, low-dose aspirin was associated with a statistically significant reduction in the incidence of pre-eclampsia (RR 0.87, 95% CI: 0.79, 0.96, P=0.004); there was no evidence of statistically significant heterogeneity between the studies (P=0.06).

There was no significant correlation between dose of aspirin and the prevention of pre-eclampsia (correlation coefficient, r=0.064).

Authors' conclusions
Low-dose aspirin is mildly beneficial in the prevention of pre-eclampsia in high-risk women, but no beneficial effect was observed in women at low risk of developing pre-eclampsia.

CRD commentary
The review question and inclusion criteria were clear. The search strategy was restricted to published studies retrieved from two electronic databases and the search terms were not reported, so relevant studies might have been missed. The authors adequately described how they performed the study selection and quality assessment processes. Although study quality was assessed, only some components of the quality assessment were reported and the authors did not provide
details of how studies were excluded on the basis of quality. The possibility of bias cannot, therefore, be ruled out.

The authors discussed possible reasons for heterogeneity between the studies: for example, aspirin dosage, time and duration of treatment, time the study was conducted, and the criteria used to define patients at high risk of developing pre-eclampsia. Overall, the authors’ conclusion appears to be supported by the evidence presented, although it is not possible to verify the validity of their conclusion given the lack of detail concerning the methods and the restriction of the search to published studies retrieved from two electronic databases and scans of bibliographies.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors stated that further research is needed to assess the effect of low-dose aspirin on the incidence of pre-eclampsia in subgroups of patients, particularly according to parity, risk for pre-eclampsia, and the presence of any prothrombotic factor or disease; and to explore the pathophysiological process involved in pre-eclampsia. Future trials should carefully evaluate the duration of aspirin administration.

**Bibliographic details**


**PubMedID**

16254678

**DOI**

/S1807-59322005000500010

**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Aspirin /administration & dosage; Drug Administration Schedule; Female; Humans; Platelet Aggregation Inhibitors /administration & dosage; Pre-Eclampsia /etiology /prevention & control; Pregnancy; Pregnancy, High-Risk; Randomized Controlled Trials as Topic; Risk Assessment; Risk Factors

**AccessionNumber**

12006003360

**Date bibliographic record published**

31/03/2007

**Date abstract record published**

31/03/2007

**Record Status**

This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.