A meta-analysis of low dose aspirin for the prevention of intrauterine growth retardation
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Authors' objectives
To determine more precisely the effect of prophylactic low-dose aspirin on intra-uterine growth retardation and perinatal mortality.

Searching
Eighteen medical databases including MEDLINE (from 1964 onwards) and EMBASE (from 1974 onwards) were searched using the terms 'acetylsalicylic acid', 'aspirin', 'pregnancy', 'randomised' and 'meta-analysis'. References from retrieved reports and review articles were also examined. Only reports published in the English language were considered.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) of aspirin alone or in combination with another antiplatelet agent were included.

Specific interventions included in the review
Aspirin (doses ranged from 50 to 150 mg/day) alone or in combination with another antiplatelet agent (225 or 300 mg/day dipyridamole), and placebo. Treatment commencement ranged from week 12 to week 28.

Participants included in the review
Pregnant women. In most included trials, women with chronic conditions (including renal failure and hypertension) were excluded. Patient inclusion and exclusion criteria for the individual trials are given.

Outcomes assessed in the review
The outcomes were intra-uterine growth retardation and perinatal mortality.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The following aspects were examined to assess the quality of the RCTs: inclusion and exclusion criteria, placebo-control, blinding, randomisation, assessment of compliance, and number of patients enrolled but excluded from the statistical analyses. The authors do not state how the papers were assessed for quality, or how many of the authors performed the quality assessment.

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

Methods of synthesis
How were the studies combined?
The odds ratio (OR) and 95% confidence interval (CI) were calculated for each trial, and for all combined studies (excluding those studies with zero events in both treatment and control group).

Subgroup analysis was undertaken according to patient population (high- and low-risk) and treatment regimen (average
gestational age at start of treatment).

Funnel plots were used to assess the possibility of publication bias.

How were differences between studies investigated?
A chi-squared test for heterogeneity was performed. Sensitivity analyses of both the overall results and the subgroup results were carried out by excluding trials that were not double-blind, or those which were not double-blind and placebo-controlled.

Results of the review
Thirteen trials (13,324 women: 6,694 in the treatment groups and 6,540 in the control groups) were included.

Only 2 studies reported a significant reduction in the odds of intra-uterine growth reduction with aspirin treatment. All other studies showed non significant results. The combined OR was 0.82 (95% CI: 0.72, 0.93, p=0.003), representing a significant risk reduction of 18% with aspirin therapy.

None of the studies showed a significant protective effect of aspirin therapy on perinatal mortality. The combined OR was 0.84 (95% CI: 0.66, 1.08, p=0.18).

Subgroup analysis suggests that aspirin was more effective at higher doses (100 to 150 mg/day) than lower doses (50 to 80 mg/day): ORs for intra-uterine growth reduction were 0.36 (95% CI: 0.22, 0.59) and 0.87 (95% CI: 0.76, 0.99), respectively. In addition, treatment started before 17 weeks' gestation was more effective than that started after: ORs for intra-uterine growth reduction were 0.35 (95% CI: 0.21, 0.58) and 0.87 (95% CI: 0.76, 0.99), respectively.

A sensitivity analysis excluding trials of lower methodological quality did not substantially alter the results.

Funnel plots show that the possibility of publication bias cannot be dismissed. The tests for heterogeneity for both outcomes yielded non significant results, but given the low power of the test, heterogeneity in the complete set of trials cannot be dismissed.

Authors' conclusions
The results show that early aspirin treatment reduced the risk of intra-uterine growth retardation. Low-dose aspirin should not be used routinely in pregnant women until those most likely to benefit from aspirin treatment have been clearly identified.

CRD commentary
This is a thorough and well-written review, with clear inclusion criteria, details of primary studies, quality assessment, and descriptions of how decisions were made. Only published studies were included in the review, but the authors address the issue of publication bias.

It is unclear why the authors did not use the Cochrane Collaboration Pregnancy and Childbirth Database to identify potentially relevant trials, especially as the database was referenced in the introduction to the review.

This is a methodologically-sound review, but the results should be treated with caution given the possibility of both publication bias and heterogeneity in the included studies, as identified by the authors.

Implications of the review for practice and research
Diagnostic studies are required to determine which women are at the greatest risk from intra-uterine growth reduction and pre-eclampsia and are, therefore, the most likely to be helped by aspirin.

Bibliographic details

**PubMedID**
9141582

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Anti-Inflammatory Agents, Non-Steroidal /administration & dosage; Aspirin /administration & dosage; Female; Fetal Growth Retardation /prevention & control; Humans; Infant Mortality; Infant, Newborn; Odds Ratio; Pregnancy; Prenatal Care; Randomized Controlled Trials as Topic; Sensitivity and Specificity

**AccessionNumber**
11997000651

**Date bibliographic record published**
30/04/1998

**Date abstract record published**
30/04/1998

**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.