Aspirin for prevention of preeclampsia in women with historical risk factors: a systematic review
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CRD summary
This review examined the effectiveness of aspirin in preventing perinatal death and pre-eclampsia in women with predisposing factors. The authors concluded that aspirin can reduce the risk of pre-eclampsia and perinatal death in women who have known historical risk factors. Statements on the safety of aspirin were derived largely from observational studies, which were not part of the current systematic review.

Authors' objectives
To examine the effectiveness of aspirin in preventing perinatal death and pre-eclampsia in women with predisposing factors.

Searching
MEDLINE (from 1966 to 2001), EMBASE (from 1980 to 2001), the Cochrane Library (Issue 3, 2001), the National Research Register (Issue 3, 2001), SciSearch (from 1974 to 2001) and conference proceedings (ISI Proceedings, from 1990 to 2001) were searched; the search terms were provided. Frequently cited articles were used in the Science Citation Index to identify additional citations. Unpublished trials were sought from researchers. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies comparing low-dose aspirin with placebo or no treatment were eligible for the review. In the included studies, the dose of aspirin ranged from 50 to 150 mg/day. In some studies aspirin was combined with dipyridamole (150 to 300 mg). In most of the studies the intervention was administered any time from 12 or 13 weeks onwards until delivery; however, other studies did not start treatment until 15, 16, 17, 18, or even 20 weeks.

Participants included in the review
Studies of pregnant women with historical predisposing factors for pre-eclampsia were eligible for the review. The historical predisposing factors were to include previous pre-eclampsia, chronic pre-existing hypertension, diabetes, renal disease, and extremes of age at conception. The included studies were of women with these predisposing factors, although some studies were of women who had a history of more general pregnancy complications such as inter-uterine growth restriction or still birth. The ages of the women and other demographic details were not reported.

Outcomes assessed in the review
Studies that reported any clinically relevant perinatal or maternal outcome were eligible. The primary outcome measures were perinatal death and pre-eclampsia (proteinuric hypertension).

How were decisions on the relevance of primary studies made?
Two reviewers independently selected citations and then full manuscripts, except in the case of non-English papers which were selected or rejected by a single reviewer with command of the pertinent language. Any disagreements were resolved by consensus or arbitration involving a third reviewer.

Assessment of study quality
The included studies were assessed for their adequacy in terms of randomisation, concealment of allocation, control, blinding, use of intention-to-treat analysis, and follow-up rates. Two reviewers independently performed the quality assessment. Agreement between the reviewers was assessed through the percentage agreement and kappa statistic; a kappa level of 0.7 was considered the minimum acceptable level.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data on the number of events and number of women in the treatment and control groups were extracted from each study in 2x2 tables.

**Methods of synthesis**
**How were the studies combined?**
The trials were combined in a meta-analysis. The odds ratios (ORs) were pooled using Peto's method. These results were then compared with those generated using fixed-effect and random-effects models. Weighted mean differences were calculated for continuous variables using means and standard deviations from individual trials. Publication bias was explored using Egger's method and funnel plots.

**How were differences between studies investigated?**
Heterogeneity was investigated by visual evaluation of forest plots and using the chi-squared test. An evaluation of the causes of heterogeneity, using variation in features of the population, intervention, outcome and study quality, was planned.

**Results of the review**
Fourteen trials (n=12,416) were included.

All of the included RCTs had adequate (at least 90%) follow-up. Only 8 trials were double-blind and only 7 trials had conducted an intention-to-treat analysis.

The meta-analysis using Peto's method showed a statistically significant difference in favour of aspirin for perinatal mortality (13 trials; OR 0.79, 95% CI: 0.64, 0.96), pre-eclampsia (13 trials; OR 0.86, 95% CI: 0.76, 0.96), and spontaneous pre-term birth (7 trials; OR 0.86, 95% CI: 0.79, 0.94). There was no significant difference for rate of abruption (7 trials; OR 0.98, 95% CI: 0.79, 1.21). These results were robust to pooling when using either a fixed-effect or random-effects model. There was no statistical heterogeneity.

For birth weight (8 trials), there was evidence of heterogeneity so pooling was performed using a random-effects model. There was a significant increase in the mean birth weight with aspirin: weighted mean difference 215 g (95% CI: 90, 341).

There was no obvious publication bias. The effect of study quality was not reported.

**Authors' conclusions**
Aspirin can reduce the risk of pre-eclampsia and perinatal death in women who have known historical risk factors.

**CRD commentary**
This review addressed a specific question with fairly well-defined inclusion criteria, although these criteria were applied with some latitude in terms of population, intervention and outcome measure. The literature search appears to have covered a comprehensive range of electronic sources, with attempts to include unpublished studies and no language restrictions. In addition, publication bias was tested for. The quality of the included trials was assessed adequately; however, the results of this assessment were not commented upon nor incorporated into the analysis. The methods of the review were described appropriately, except for some details about the data extraction, and details of
the primary studies were tabulated.

The meta-analyses were generally appropriate and the results were presented helpfully in forest plots. The source of the heterogeneity identified for one outcome measure (birth weight) was not explored, and it is unclear how appropriate this pooling was. The authors' conclusions on the effectiveness of aspirin at the doses covered in this review are supported by the findings presented. However, statements on the safety of aspirin, which the authors incorporated into their conclusions and recommendations for practice, were derived largely from observational studies. The review of these observational studies was not part of the current systematic review and it is unclear how reliable these statements are.

Implications of the review for practice and research
Practice: The authors stated that because of the importance of pre-eclampsia and perinatal death, and the safety and low cost of aspirin, aspirin therapy should be considered in women with risk factors.

Research: The authors stated that research is needed to address the possible cost-benefits of implementing this strategy to health care systems and society.

Bibliographic details

PubMedID
12798543

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Aspirin /therapeutic use; Birth Weight; Female; Humans; Infant Mortality; Infant, Newborn; Infant, Premature; Obstetric Labor, Premature /prevention & control; Odds Ratio; Platelet Aggregation Inhibitors /therapeutic use; Pre-Eclampsia /prevention & control; Pregnancy; Randomized Controlled Trials as Topic; Risk Factors

AccessionNumber
12003001229

Date bibliographic record published
31/03/2005

Date abstract record published
31/03/2005

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.