Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis
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CRD summary
This review found pregnant women at risk of pre-eclampsia who received daily low-dose aspirin reduced their risk of pre-eclampsia and intra-uterine growth restriction, particularly when aspirin treatment commenced in early pregnancy. The review was generally well conducted and the authors’ conclusions appear likely to be reliable.

Authors’ objectives
To evaluate the effects of low-dose aspirin commenced in early pregnancy on the incidence of pre-eclampsia and intra-uterine growth restriction (IUGR) in women identified as being at risk of pre-eclampsia.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to July 2008 for relevant studies; search terms were reported. Recently published meta-analyses were checked to identify additional references. There were no language restrictions.

Study selection
Randomised controlled trials (RCT) of pregnant women at risk of pre-eclampsia that compared treatment with low-dose aspirin (50 to 150mg acetylsalicylic acid daily alone or in combination with less than 300mg dipyridamole) to either placebo or no treatment were eligible for inclusion. Studies with inappropriate concealment of allocation or with losses to follow-up or attrition of more than 20% were excluded.

The included trials were published between 1985 and 2005. The primary outcome was occurrence of pre-eclampsia. Secondary outcomes included IUGR, gestational hypertension, placental abruption, preterm birth, low birth weight and gestational age at delivery. Women were classified as being at risk of pre-eclampsia using a range of criteria that included nulliparity, serum markers, body mass index, ethnicity, previous history of pre-eclampsia or other hypertensive disorders and abnormal uterine artery Doppler ultrasound results. The comparator in most studies was placebo; a few studies used concomitant dipyridamole.

Two reviewers performed the study selection; any disagreements were resolved by discussion with a third reviewer.

Assessment of study quality
The methodological quality of each study was assessed in terms of randomisation methods, use of intention-to-treat analyses and use of blinding. Adequacy of allocation concealment and reporting of follow-up/attrition in the trials were used as inclusion criteria for the review.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Two reviewers independently extracted intention-to-treat data to calculate relative risks (RR) for each dichotomous outcomes, mean differences for continuous outcomes and 95% confidence intervals for relative risks and mean differences. The results for each outcome were stratified on the basis of gestational age at the commencement of aspirin treatment.

Methods of synthesis
Pooled relative risks and 95% CIs were calculated using a DerSimonian and Laird random-effects model. Mean differences were weighted by the inverse of the population variance and combined using random effect models. I² was used to evaluate statistical heterogeneity. Visual inspection of funnel plots was used with Egger’s test to assess
publication bias. Numbers needed to treat were calculated. Planned subgroup analyses were undertaken on subgroups stratified by gestational age at entry (16 weeks or less or completed gestation of more than 16 weeks), statistical model, use of blinding, aspirin dose (80mg or less daily and 81mg or more daily), use of dipyridamole, risk of pre-eclampsia and trial size using mixed regression weighted by the size of each study.

Results of the review
Thirty-four RCTs were included in the review. Sample sizes ranged from 33 to 6,275 women. Data were reported on women enrolled prior to 16 weeks gestation in 12 trials. Twenty-two trials reported data collected from women who were enrolled after 16 weeks completed gestation. Twenty-three trials adequately reported randomisation methods. Intention-to-treat analyses were used in 14 trials. Double-blinding was reported in 16 trials and single blinding in two trials. There was no blinding in five trials and blinding was not reported in six trials.

Twenty-seven RCTs (n=11,348) assessed the incidence of pre-eclampsia. There were statistically significant decreases in incidence across trials that included women who commenced treatment with low-dose aspirin both before and after 16 completed weeks gestation (RR 0.68, 95% CI 0.54 to 0.86, I²=52%). There was a slightly statistically significant reduction in IUGR across 24 trials (n=8,733) that examined this outcome (RR 0.85, 95% CI 0.72 to 1.00, I²=28%).

Statistically significant benefits were observed for women who commenced treatment with low-dose aspirin prior to 16 weeks gestation. There was less risk of pre-eclampsia (RR 0.47, 95% CI 0.34 to 0.65; nine trials, n=764), severe pre-eclampsia (RR 0.09, 95% CI 0.02 to 0.37; three trials, n=278), IUGR (RR 0.44, 95% CI 0.30 to 0.65; nine trials, n=853), IUGR less than the 10th centile (RR 0.44, 95% CI 0.30 to 0.74; five trials n=414), gestational hypertension (RR 0.62 95% CI 0.45 to 0.84; seven trials, n=548) and preterm birth (RR 0.22, 95% CI 0.10 to 0.49; four trials, n=387). There were no differences between the low-dose aspirin and control groups in the risk of placental abruption. No statistical heterogeneity was reported for risks of pre-eclampsia and IUGR, but I² values were not reported for the other outcomes.

For the women who started treatment with low-dose aspirin after 16 weeks completed gestation, there were significant reductions in risk of gestational hypertension (RR 0.63, 95% CI 0.47 to 0.85; 14 trials, n=4,303) and preterm birth (RR 0.90, 95% CI 0.83 to 0.97; 16 trials, n=10,398). There were no statistically significant differences in risks of pre-eclampsia, IUGR and placental abruption.

Visual appraisal of the funnel plot suggested a possibility of publication bias with an absence of small studies that showed no benefits in groups of women enrolled prior to 16 weeks completed gestation; the result of the Egger's test confirmed this (p=0.03) for this group of women.

Authors' conclusions
The results of the review suggested that pregnant women with moderate or high risk of pre-eclampsia benefited from daily low-dose aspirin for prevention of pre-eclampsia and IUGR. Benefits were greater when aspirin treatment commenced in early pregnancy.

CRD commentary
The review addressed a clear question. Criteria for inclusion of studies were defined. Appropriate electronic databases were searched for relevant studies. There were no language restrictions. Few attempts were made to identify unpublished studies and funnel plots and the Egger's test indicated that there was potential for publication bias. Steps were taken to minimise errors and bias during study selection and data extraction. The methodological quality of the included studies was adequately assessed. The authors' statistical pooling of results appeared to be justified. Sources of heterogeneity were appropriately explored. The authors correctly acknowledged the limitations of the review (particularly likely presence of publication bias) and stated that additional research was required to confirm the results of the review.

The review was well conducted and the authors' conclusions appear likely to be reliable.

Implications of the review for practice and research
**Practice:** The authors stated that it was possible to identify women at risk of pre-eclampsia in the first trimester of pregnancy and to prevent adverse outcomes with low-dose aspirin treatment commenced prior to 16 weeks completed gestation.

**Research:** Whether there was a gestational age threshold after which treatment with aspirin did not yield a benefit and whether or not treatment until the end of pregnancy was beneficial remained unclear. Future research should determine the optimal dose of aspirin and should investigate comparisons with heparin in high-risk populations. Due to the risk of publication bias found in this review, a large well-designed randomised controlled trial should be undertaken to confirm the results of the review.

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