Acetylsalicylic acid for the prevention of preeclampsia and intra-uterine growth restriction in women with abnormal uterine artery Doppler: a systematic review and meta-analysis

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CRD summary
The authors concluded that low-dose acetylsalicylic acid treatment initiated early in pregnancy reduced the incidence of pre-eclampsia and its consequences in women with ultrasonographic evidence of abnormal placentation. The findings reflected the evidence, but as acknowledged by the authors they were limited by a lack of studies and the small numbers of women recruited at less than 20 weeks' gestation.

Authors' objectives
To assess the influence of gestational age at the time of introduction of low-dose acetylsalicylic acid (ASA) on the incidence of pre-eclampsia and intrauterine growth restriction (IUGR) in women at increased risk on the basis of abnormal uterine artery Doppler.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched without language restrictions from 1965 to 2008. Search terms were reported. Bibliographies of recent two meta-analyses were handsearched for additional articles.

Study selection
Randomised controlled trials (RCTs) that compared low-dose ASA (50 to 150mg/day) with either placebo or no treatment in pregnant women at increased risk of pre-eclampsia (identified on the basis of abnormal uterine artery Doppler measurements) were eligible for inclusion. Studies were excluded if more than 20% of women were lost during follow-up or excluded from the analyses. The primary outcome was pre-eclampsia (defined by the combination of systolic blood pressure ≥140mmHg and/or diastolic blood pressure ≥90mmHg, with ≥300g of urinary protein/24 hours or 1+ or more on dipstick); a range of secondary outcomes was considered (see paper).

Trials recruited patients prior to 16 weeks, between 17 and 19 weeks and 20 weeks or over. All trials used ASA (50 to 150mg) daily as treatment. In two-thirds of trials the control group received a placebo. Average rate of pre-eclampsia in the control group was 22% (range 5% to 41%).

Citations were reviewed for relevance by two reviewers. All potentially relevant studies were independently reviewed by two additional reviewers. Disagreements were resolved by consensus

Assessment of study quality
Methodological quality was assessed using the criteria: randomisation, blinding, allocation concealment, intention-to-treat and loss to follow-up. It was unclear how many reviewers performed the validity assessment.

Data extraction
Data were extracted to enable calculation of weighted risk ratios (RR) for the outcomes of interest. It was unclear how many reviewers performed the data extraction.

Methods of synthesis
Risk ratios and 95% confidence intervals (CIs) were pooled in a fixed-effect meta-analysis (Mantel-Haenszel method). Heterogeneity was assessed using the $X^2$ and $I^2$ statistics, with heterogeneity considered statistically significant at $p<0.05$ or $I^2>50\%$. A priori subgroup analyses were conducted to explore differential effects of gestational age at entry to the trial (≤16 weeks, 17 to 19 weeks and ≥20 weeks). Publication bias was assessed visually in a funnel plot. Numbers needed to treat (NNT) to prevent one additional case of pre-eclampsia were calculated.

Results of the review
Nine RCTs (n=1,347, range 26 to 560) were included in the review. Two trials recruited women at 16 weeks or less
(n=229), one between 17 and 19 weeks (n=104) and six 20 weeks or more (n=1,014). Five studies conducted double-blinding and six conducted intention-to-treat analysis. Loss to follow-up was less than 5.7%. There was no evidence of publication bias. There was a discrepancy in patient numbers between the tables and the text.

A greater reduction in the incidence of pre-eclampsia was associated with ASA treatment beginning earlier in gestation compared with treatment beginning in late gestation. A significant 52% reduction in the risk of pre-eclampsia compared with the control group was observed when treatment commenced at 16 or less weeks gestation (RR 0.48, 95% CI 0.33 to 0.68, NNT=5; two studies). At both 17 to 19 weeks (RR 0.55, 95% CI 0.17 to 1.76; one study) and 20 or more weeks gestation (RR 0.82, 95% CI 0.62 to 1.09; six studies) there was a non-significant reduction in the risk of pre-eclampsia compared with the control group.

Significant reductions in the incidence of severe pre-eclampsia (RR 0.10, 95% CI 0.01 to 0.74), gestational hypertension (RR 0.31, 95% CI 0.13 to 0.78) and IUGR (RR 0.51, 95% CI 0.28 to 0.92) were associated with commencing ASA treatment at 16 or less weeks gestation.

There was no significant heterogeneity for these comparisons.

**Authors' conclusions**
ASA treatment initiated early in pregnancy was an efficient method of reducing the incidence of pre-eclampsia and its consequences in women with ultrasonographic evidence of abnormal placentation diagnosed by uterine artery Doppler studies.

**CRD commentary**
The review question and inclusion criteria were clear. The authors searched a small number of relevant databases. There were no language restrictions, which reduced the chances that language bias was introduced. No specific attempts were made to locate unpublished studies and so some studies may have been missed. The risk of publication bias was assessed and no evidence was found, but this was limited by the small number of included studies. The authors reported that they used methods to reduce error and bias in the selection of studies; it was unclear whether this extended to data extraction and study quality assessment. Study quality was assessed using appropriate criteria; details for each criterion were reported. The chosen method of synthesis appeared to be appropriate given the absence of statistical heterogeneity. Generally this was a well-conducted review and the findings reflected the available evidence, but as acknowledged by the authors the findings were limited by a lack of studies and the small numbers of women recruited at less than 20 weeks' gestation.

**Implications of the review for practice and research**
The authors did not state any implications for practice.

**Research:** The authors stated that larger studies were required to assess the potential use of serum, biophysical or genetic markers for the identification of high-risk populations who could be targeted for ASA prevention, as well as further investigation into the role of gestational age at the time of introduction of other treatments such as anti-oxidants, folic acid and other therapies that had been suggested for the prevention of pre-eclampsia.

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