Effects of aspirin consumption during pregnancy on pregnancy outcomes: meta-analysis
Kozer E, Costei A M, Boskovic R, Nulman I, Nikfar S, Koren G

CRD summary
The review assessed the safety of aspirin during pregnancy. The authors concluded that aspirin reduced the rate of pre-term deliveries, but not perinatal death, in women with moderate to high-risk pregnancies. The authors' conclusions seem appropriate. However, the lack of detail about the methodology of the review makes the reliability of the conclusions uncertain.

Authors' objectives
To assess the safety of aspirin treatment during pregnancy in relation to foetal and neonatal outcomes.

Searching
MEDLINE (from 1966 to April 2001), EMBASE (from 1980 to 2000), TOXLINE (from 1994 to 2000), EBM Reviews, and the Cochrane Database of Systematic Reviews (1991 to 2000) were searched; the keywords used were reported. REPROTOX, teratology texts and the bibliographies of all included studies were also searched. Only full publications were included in the review. Foreign language papers were included if they had an English abstract.

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

Specific interventions included in the review
Studies evaluating exposure to aspirin were eligible for inclusion. Exposure in the included studies ranged from a brief exposure (e.g. 37 weeks to delivery), to long exposure (e.g. throughout pregnancy). The dose of aspirin ranged from 20 to 100 mg/day.

Participants included in the review
Studies of pregnant women were eligible for inclusion.

Outcomes assessed in the review
Studies reporting prematurity, pregnancy duration, birth weight, small for gestational age, miscarriage, neonatal death, still birth or perinatal death, Apgar score, neonatal asphyxia, and bleeding in the neonate, were eligible for inclusion. All such outcomes were reported in the review.

How were decisions on the relevance of primary studies made?
One reviewer screened titles and abstracts. Two reviewers independently screened full papers, while a third reviewer resolved any disagreements.

Assessment of study quality
The authors did not formally assess validity. However, they did report whether the RCT was placebo-controlled and whether it was single- or double-blinded, but they did not state the method of randomisation used in the included studies.

Data extraction
Two reviewers extracted data from the included studies independently, with any disagreements being resolved by consensus.
Methods of synthesis
How were the studies combined?
Pooled weighted mean differences (WMDs) and 95% confidence intervals (CIs) were calculated for duration of pregnancy and birth weight, while the pooled relative risk (RR) and 95% CIs were calculated for all other outcomes. A random-effects model was used.

How were differences between studies investigated?
The chi-squared test was used to investigate statistical heterogeneity between the studies. Subgroup analyses were performed to evaluate the effect of the timing of aspirin exposure during pregnancy. Study details were tabulated, grouped by presence or absence of pre-eclampsia and the risk level of the women being studied.

Results of the review
Thirty-eight RCTs (n=30,349) were included in the review.

Prematurity.
When the results of all 22 studies were pooled, women taking aspirin had a lower risk of pre-term delivery than women receiving a placebo (RR 0.92, 95% CI: 0.86, 0.98). A subgroup analysis of 14 studies evaluating the risk of pre-term delivery in women exposed to aspirin before 24 weeks' gestation was less conclusive. Two studies reported a significantly lower risk of pre-term delivery in women taking aspirin compared with placebo, but when all 14 studies were pooled the RR was 0.92 (95% CI: 0.84, 1.00).

A subgroup analysis of 6 studies evaluating the risk of pre-term delivery in women exposed to aspirin after 24 weeks' gestation showed no significant reduction in pre-term delivery in women taking aspirin compared with placebo (RR 0.66, 95% CI: 0.41, 1.04).

Birth weight.
When the results of all 29 studies were pooled, women who took aspirin gave birth to heavier babies than women who took a placebo (WMD 43 g, 95% CI: 18, 67).

A subgroup analysis in women exposed to 75 mg/day aspirin also showed a significantly higher birth weight for babies born of women taking aspirin compared with offspring of women taking a placebo (WMD 43 g 95% CI: 15, 71). However, unlike the other analyses undertaken, the studies in this analysis were statistically heterogeneous (chi-squared P=0.021).

A subgroup analysis in women exposed to more than 75 mg/day aspirin showed no significant difference in birth weight between babies born of women taking aspirin and those of women taking a placebo.

Twelve studies reported on the incidence of small for gestational age. There was no statistically significant difference between babies born of women taking aspirin and those of women taking a placebo. A subgroup analysis of 6 studies where women started taking aspirin before 24 weeks' gestation showed similar results (i.e. no significant difference) in the incidence of small for gestational age.

Miscarriage.
Seven RCTs reported no difference in the risk of miscarriage between women taking aspirin in their first or second trimester, compared with women taking a placebo.

Still birth or perinatal death.
One of the 20 studies reported a statistically significant reduction in risk of perinatal mortality in women taking aspirin compared with placebo. When the results of the 20 studies were pooled, there was no significant effect of aspirin exposure on perinatal mortality.
No statistically significant effect of aspirin exposure on perinatal mortality was found in the subgroup analysis of women taking aspirin before 24 weeks' gestation, women taking up to 75 mg/day of aspirin compared with placebo, higher doses of aspirin compared with placebo, or when still birth and perinatal death were analysed separately.

Apgar score.

There was no statistically significant difference in the risk of an Apgar score lower than 7, five minutes after delivery, in babies born of women taking aspirin compared with those of women taking a placebo (7 RCTs).

Neonatal asphyxia.

There was no significant difference in neonatal asphyxia in babies born of women taking aspirin compared with those of women taking a placebo (3 RCTs).

Bleeding in the neonate.

There was no significant difference in neonatal bleeding between women taking aspirin and women taking a placebo (12 RCTs).

**Authors’ conclusions**

For women with moderate to high-risk pregnancies, aspirin treatment seemed to have a small but significant effect on reducing the rate of pre-term deliveries, but did not reduce the rate of perinatal death.

**CRD commentary**

The review question and inclusion criteria were clearly stated. Several electronic databases and additional sources were searched. However, restricting the inclusion of foreign language papers to those with an English abstract means that some studies might have been missed. Unlike the second stage of study selection, which was carried out in duplicate, the first stage was carried out by a single reviewer, thus increasing the possibility of error and bias. The authors did not report a systematic validity assessment of each study, though they did restrict the review to RCTs and report some of the methodology used in the included studies.

Appropriate measures of effect were calculated and statistical heterogeneity was investigated. It is unclear whether the subgroup analyses were planned a priori, and there was no justification for the use of 75 mg/day as the cut-off point in these subgroup analyses. The authors' conclusions appear appropriate given the evidence presented.

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

The authors did not state any implications for practice or further research.

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