Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data

Askie L M, Duley L, Henderson-Smart D J, Stewart L A

CRD summary
This review of individual patient data evaluated the efficacy of antiplatelet agents for the primary prevention of pre-eclampsia. Antiplatelet agent prophylaxis reduced the risk of pre-eclampsia, pre-term birth before 34 weeks' gestation and serious adverse outcomes of pregnancy, without increasing the rate of bleeding events. The review conclusions are likely to be reliable.

Authors' objectives
To evaluate the use of antiplatelet agents for the primary prevention of pre-eclampsia.

Searching
Trials were identified through a computerised bibliographic search of the Cochrane Pregnancy and Childbirth Group's Specialised Register to December 2005. The authors also sought unpublished trials. A steering committee and a writing committee was established to identify additional trials and undertake the meta-analysis.

Study selection

Study designs of evaluations included in the review
This review included individual patient data (IPD) from randomised controlled trials (RCTs).

Specific interventions included in the review
Studies evaluating one or more antiplatelet agents versus placebo or no antiplatelet agent in the primary prevention of pre-eclampsia were eligible. The interventions considered in the review included aspirin at doses of 50 to 150 mg/day given alone or in combination with dipyridamole, dipyridamole and/or heparin, and ozagrel. Therapy was started before 20 weeks' gestation in 59% of the enrolled women.

Participants included in the review
Studies including women at risk of developing pre-eclampsia were eligible. Trials that included women starting antiplatelet agents after partum or who had a diagnosis of pre-eclampsia at inclusion were excluded. Fifty-four per cent of the included women were in their first pregnancy, 92% had a singleton pregnancy, 70% were aged 20 to 35 years and 90% had at least one risk factor.

Outcomes assessed in the review
The primary outcomes were pre-eclampsia, intra-uterine death or death of the baby before discharge from hospital, pre-term birth at less than 34 weeks' gestation, infant small for gestational age at birth and serious adverse events. The secondary outcomes included maternal death, bleeding events before or after partum, placental abruption, proteinuria before 34 weeks' gestation, serious maternal morbidity, Caesarean delivery, infant admission to a neonatal special care or intensive care unit, need for neonatal ventilation and neonatal bleeding.

How were decisions on the relevance of primary studies made?
At least two reviewers from the steering group independently selected the studies, with any disagreements being resolved by discussion. The relevance of the trials was established through communication with trial investigators.

Assessment of study quality
The authors reviewed each trial to assess the validity of randomisation to study treatment and allocation concealment, as well as the comparability of baseline characteristics between treatment groups. The authors checked the internal
consistency of the data and verified with the trialists the uniformity between the results provided and those published previously.

**Data extraction**
The trial investigators provided IPD for their trial as anonymised data for each randomised patient. Data were recoded as necessary. Relevant trial investigators were contacted, if necessary, to obtain additional information and to verify the finalised data.

**Methods of synthesis**

How were the studies combined?
For each outcome, results from trials with at least 80% of data available for that outcome were combined on an intention-to-treat (ITT) basis using a fixed-effect model. Robustness was assessed by a random-effects model. The numbers-needed-to-treat or -harm were calculated.

How were differences between studies investigated?
Statistical heterogeneity was tested using the I-squared statistic. Subgroup and sensitivity analyses were performed for the main outcomes. Pre-specified subgroups were defined according to aspirin total daily dose, the presence of risk factors at entry in the study, and a gestational age above or below 20 weeks. Sensitivity analysis was performed by excluding studies without a placebo and by including studies with less than 80% of participant data.

**Results of the review**
IPD from 31 RCTs (including IPD for 32,217 women and 32,819 babies) were included in the review. The authors stated that other eligible trials were identified, but in 7 of these it was not possible to trace the investigators; one trialist refused to participate, data from 17 trials were lost or irretrievable, and the investigators of 2 trials did not provide the data.

Twenty-six of the 31 included trials were judged to be good quality.

Compared with control treatment, antiplatelet agents were associated with a significantly lower risk of pre-eclampsia (relative risk, RR 0.90, 95% confidence interval, CI: 0.84, 0.97, p=0.004), delivery before 34 weeks (RR 0.90, 95% CI: 0.83, 0.98, p=0.011) or serious adverse outcomes during pregnancy (RR 0.90, 95% CI: 0.85, 0.96, p=0.001). There was no evidence of statistical heterogeneity for the outcome of pre-eclampsia (p=0.12, I-squared 26.3%). The authors calculated that 114 women had to be treated with an antiplatelet agent to prevent one case of pre-eclampsia. The overall results remained consistent when using the trialists' definition of pre-eclampsia (RR 0.88, 95% CI: 0.81, 0.96), or the PARIS (Perinatal Antiplatelet Review of International Studies) definition of pre-eclampsia (RR 0.90, 95% CI: 0.83, 0.97).

Mortality of the foetus or baby and the incidence of small for gestational age infants were comparable between antiplatelet agents and control groups. The use of antiplatelet agents was associated with a significantly lower risk (10%) of the combined outcome pre-eclampsia, delivery before 34 weeks' gestation, foetal or baby death before discharge, small for gestational age infant, and maternal death (RR 0.90, 95% CI: 0.85, 0.96).

Maternal outcomes such as proteinuria onset before 34 weeks, severe hypertension, placental abruption and Caesarean delivery did not differ between the intervention and control treatment.

Antiplatelet agents reduced the risk of pre-term birth before 37 weeks (RR 0.93, 95% CI: 0.89, 0.98, p=0.003) and the need for neonatal assisted ventilation (RR 0.79, 95% CI: 0.67, 0.95, p=0.010). It was estimated that 78 infants had to receive an antiplatelet agent through their mother to prevent one from needing assisted ventilation. The incidence of mother's or infant's bleeding events was similar between antiplatelet agents and controls.

Antiplatelet agents appeared to have similar benefits across the various predefined subgroups.
Authors' conclusions
Antiplatelet agents were associated with a reduced risk of pre-eclampsia, birth before 34 weeks' gestation and serious adverse outcomes during pregnancy.

CRD commentary
This meta-analysis of IPD addressed a well-defined question in terms of the participants, intervention, outcomes and study design. The authors searched one trial register and a collaborative group of trial investigators was established to maximise the retrieval of IPD and to conduct the meta-analysis. Publication bias was not assessed, but the authors did attempt to retrieve unpublished trials. The validity of the eligible trials was assessed by checking the raw data from each trial and verifying any inconsistency or missing data with the trial investigators. No trials were reported to have failed the data checking procedures. The number of excluded studies, as well as the number of participants in trials for which data could not be retrieved, were specified. At least two reviewers made decisions about inclusion and exclusion, and the criteria used for study selection were reported.

Statistical variation between studies was assessed and the authors stated that there was no significant statistical variation for the main outcome; this supports the authors' decision to pool the studies in a meta-analysis. The data appear to have been analysed using appropriate techniques for the meta-analysis of IPD, and the rationale for the subgroup analysis was clear. The authors' cautious conclusions appear appropriate and, based on the evidence presented, are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that women at risk of pre-eclampsia should be informed about the pre-eclampsia risk reduction with antiplatelet agents, to allow them an informed choice about whether or not they should receive these drugs during their pregnancy. Research: The authors did not state any implications for research.

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