Low-dose aspirin for in vitro fertilization: a systematic review and meta-analysis

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CRD summary
The authors concluded that there were no significant differences between low-dose aspirin and control for any pregnancy-related outcomes in women undergoing assisted reproductive technology treatment; treatment with low-dose aspirin cannot, therefore, be routinely recommended. The evidence appears to support the authors’ conclusions, but poor reporting of study quality along with other review limitations make it difficult to assess the strength of the evidence.

Authors’ objectives
To evaluate the effects of low-dose aspirin on pregnancy rates in women undergoing in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI).

Searching
MEDLINE, EMBASE, the Cochrane Controlled Trials Register and the UK National Research Register were searched from 1980 to March 2006; the search terms were reported. No language restrictions were applied. In addition, references and relevant conference proceedings were screened, other reports published by key authors in the field were traced, and journals containing the highest number of relevant reports were handsearched.

Study selection
Studies of any design that evaluated the effects of low-dose aspirin (150 mg or less given once daily), alone or combined with heparin or glucocorticoids, on the outcome for women undergoing IVF or ICSI were eligible for inclusion.

In the included studies, 75 to 100 mg/day aspirin was started at different stages of the treatment cycle and continued for varying durations. Some studies were in unselected patients and others were in selected IVF populations (the selection criteria varied). The review outcomes included pregnancy rate per embryo transfer (ET), clinical pregnancy rate per cycle or ET, clinical pregnancy rate per elective single ET, spontaneous abortion or ectopic pregnancy rate per clinical pregnancy, live birth rate per cycle or ET, implantation rate and cycle cancellation rate. Control groups received placebo or no treatment; in one study the controls received prednisone.

Two reviewers independently selected the studies and resolved any disagreements by consensus.

Assessment of study quality
Study quality was assessed by examining the method of randomisation, allocation concealment, blinding, cointerventions, estimation of sample size, completeness of follow-up and differentiation between patients and cycles.

The authors did not state how the validity assessment was performed.

Data extraction
The number of outcome events in the intervention and comparator groups were extracted and relative risks (RRs) with 95% confidence intervals (CIs) calculated.

Two reviewers independently extracted the data and resolved any disagreements by consensus.

Methods of synthesis
Meta-analyses examining pooled RRs were performed using a random-effects model. There were insufficient studies to assess the potential for publication bias using funnel plots.
Results of the review
Twelve studies (n=3,189 cycles) were included in the review: 10 randomised controlled trials (RCTs) and 2 retrospective studies. Six RCTs (n=2,534) that compared low-dose aspirin alone with placebo or no treatment were included in the meta-analyses.

There were no statistically significant differences between aspirin alone and placebo or no treatment for any of the outcomes assessed. The number of studies providing data for each analysis ranged from 1 to 6, with the number of participants ranging from 82 to 2,515. Heterogeneity was statistically significant only for the analysis of clinical pregnancy rate per cycle (p=0.05).

Authors' conclusions
Since there were no significant differences between low-dose aspirin and control for any pregnancy-related outcome in women undergoing IVF or ICSI, treatment with low-dose aspirin cannot be routinely recommended.

CRD commentary
The review question was stated clearly. Several relevant sources were searched and attempts were made to minimise publication and language bias. Appropriate methods were used to minimise reviewer error and bias during the study selection and data extraction processes, but the methods used to assess validity were unclear. Only RCTs were included and validity was apparently assessed but, since the results of this assessment were not reported, it is not possible to evaluate the quality of the included studies. The authors included only certain RCTs in the meta-analyses but did not explicitly describe the criteria governing eligibility for inclusion in such analyses; this makes the results more difficult to interpret. It was not clear which outcomes were assessed for individual studies and even more unclear whether ICSI was actually assessed. Appropriate methods were used for the meta-analyses and heterogeneity was assessed. The evidence presented appears to support the authors' conclusions, but the lack of reporting of study quality and other limitations of the review make it difficult to assess the strength of the evidence.

Implications of the review for practice and research
Practice: The authors stated that low-dose aspirin should not be given routinely to women undergoing assisted conception.

Research: The authors stated that future studies should assess the effect of low-dose aspirin on stimulation cycle outcome and maternal and neonatal morbidity, as well as the pregnancy rate. There is a need for further studies of aspirin in women with a poor response to ovarian stimulation and women who receive donated oocytes before aspirin can be recommended for these situations.

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Other publications of related interest
Ruopp MD, Collins TC, Whitcomb BW, Schisterman EF. Evidence of absence or absence of evidence: a reanalysis of
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