Evidence of absence or absence of evidence: a reanalysis of the effects of low-dose aspirin in in vitro fertilization

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CRD summary
The authors concluded that low-dose aspirin during in vitro fertilisation may increase clinical pregnancy rates but that more research is required; there was no reason to discontinue aspirin use. Evidence appeared to support the authors’ conclusions, but incomplete reporting of review methods and lack of assessment of study quality make it difficult to comment on their reliability.

Authors’ objectives
To evaluate the effects of low-dose aspirin during in vitro fertilisation and compare findings with those of a previous meta-analysis.

Searching
MEDLINE, Web of Science, EMBASE, TOXLINE, DART (Developmental and Reproductive Toxicology database) and the Cochrane Database of Systematic Reviews were searched from inception to February 2007. Search terms were reported. In addition, reference lists of selected studies were handsearched. Only studies with an English language abstract were included.

Study selection
Prospective controlled trials (including randomised controlled trials (RCTs) and matched controlled trials) that evaluated low-dose aspirin (less than 150mg) during in vitro fertilisation or intracytoplasmic sperm injection were eligible for inclusion. Studies that evaluated aspirin combined with other drug treatments were excluded. The review assessed pregnancy rates, implantation rates and miscarriage rates.

The included studies compared aspirin (75 to 100mg) with placebo or no treatment. Included studies commenced and discontinued treatment at different points of the treatment or pregnancy cycle (details were reported).

Two reviewers independently selected studies. Disagreements were resolved with the help of a third reviewer.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
For each study, data required to create 2x2 tables were extracted, and risk ratios (RR) and 95% confidence intervals (CI) were calculated.

The authors did not state how data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
Pooled risk ratios and 95% confidence intervals were calculated using the fixed-effect Mantel-Haenszel method. Studies were weighted by sample size. Heterogeneity was assessed using the $\chi^2$ (taking $p>0.05$ as indicative of homogeneity) and the $I^2$ statistics. Results of random-effects meta-analyses were also reported. Subgroup analysis was used to re-analyse data including only studies using fresh embryo transfer and only including studies in the meta-analysis conducted by Gelbaya et al (for reference see Other Publications of Related Interest field). The analysis by Gelbaya excluded conference abstracts, subgroups of infertile patients and studies using frozen embryo transfer.

Results of the review
Nine RCTs and one matched RCT were included (n = 2,801 in vitro fertilisation cycles). The number of in vitro fertilisation cycles ranged from 28 to 1,380 per study.

Low-dose aspirin was associated with a statistically significant increase in the rate of clinical pregnancy per embryo transfer compared to no aspirin (RR using fixed-effect model 1.15, 95% CI 1.03 to 1.27; 10 studies). Significant heterogeneity was found (p=0.07, $I^2=43.5\%$).

There was no statistically significant difference between aspirin and no aspirin in the implantation rate (RR 1.08, 95% CI 0.69 to 1.71; three studies; 612 embryos transferred) or the miscarriage rate per clinical pregnancy (RR 1.19, 95% CI 0.86 to 1.65; four studies; 671 in vitro fertilisation cycles).

Results for subgroup analysis using fixed-effect and random-effects models were also reported.

Authors' conclusions
Low-dose aspirin during in vitro fertilisation may increase clinical pregnancy rates but more research is required. There was no reason to discontinue aspirin use.

CRD commentary
The review question was clearly stated and inclusion criteria specified. Several relevant sources were searched and conference abstracts were apparently included, but no attempts were made to minimise language bias. Appropriate methods were used to minimise reviewer error and bias during the selection of studies, but it was not clear whether similar steps were taken in the extraction of data. Only RCTs were included but study validity was not assessed, so results from these studies and any synthesis may not be reliable. No information was provided about participants, so the generalisability of results was unclear. In addition, it was not clear if multiple in vitro fertilisation treatments from individual patients were included. If this were the case, then analyses should have been adjusted to take account of this. Data were pooled using meta-analysis and heterogeneity was assessed. Evidence appeared to support the authors’ conclusions, but incomplete reporting of review methods and lack of assessment of study quality make it difficult to comment on their reliability.

Implications of the review for practice and research
Practice: The authors stated that until there is a sufficient data to definitively evaluate the effects of low-dose aspirin during in vitro fertilisation, clinicians should continue with their current practice regarding the administration of aspirin.

Research: The authors stated that more studies are required to provide data for an analysis that is adequately powered to determine if low-dose aspirin is of benefit during in vitro fertilisation.

Funding
Intramural Research Program of the National Institutes of Health, Epidemiology Branch, Division of Epidemiology, Statistics and Preventative Research, National Institute of Child Health and Human Development, Bethesda, Maryland.

Bibliographic details

PubMedID
17889863

DOI
10.1016/j.fertnstert.2007.06.033

Original Paper URL
http://www.fertstert.org/article/S0015-0282(07)01258-7/abstract
Additional Data URL
http://humupd.oxfordjournals.org/cgi/content/full/13/4/357

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Abortion, Spontaneous; Aspirin /pharmacology; Dose-Response Relationship, Drug; Embryo Implantation /drug effects; Evidence-Based Medicine; Female; Fertilization in Vitro /drug effects; Humans; Meta-Analysis as Topic; Pregnancy; Pregnancy Rate; Research Design; Sperm Injections, Intracytoplasmic /drug effects; Treatment Outcome

AccessionNumber
12008104745

Date bibliographic record published
23/12/2008

Date abstract record published
13/01/2010

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.