Effects of low-dose aspirin in in-vitro fertilization

Enrique F. Schisterman[a], **Audrey J. Gaskins**[a], and **Brian W. Whitcomb**[b]

[a]Division of Epidemiology, Statistics, and Prevention Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, Maryland [b]Department of Biostatistics and Epidemiology, University of Massachusetts at Amherst, Massachusetts, USA

Abstract

Purpose of review—In theory, use of aspirin in IVF is based on its anti-inflammatory, vasodilatory, and platelet aggregation inhibition properties, which improve blood flow to a woman's implantation site. It is hypothesized that this effect on blood flow will improve success rates.

Recent findings—Clinical studies investigating the use of low-dose aspirin (LDA) as an adjuvant therapy to IVF have produced conflicting results. The conflicting results have come as a consequence of the heterogeneous mixture of clinical trials with lack of adequate power. Even after multiple meta-analyses, differing estimates of effect were calculated as to whether aspirin should be used in conjunction with IVF.

Summary—Conflicting results leave the question of the effects of LDA in IVF unanswered. More trials are required for analysis to have adequate statistical power and until then the data remain unclear. At this point, there are not enough data to show that aspirin has a beneficial effect on the outcomes of IVF, but absence of effect is not adequate grounds to overturn the current clinical practice for those using LDA in efforts aimed at achieving success with IVF.

Keywords

aspirin; implantation; in-vitro fertilization; pregnancy

Introduction

There has been great interest in the use of low-dose aspirin (LDA) for IVF. Given its low cost and availability, even a small effect of LDA on success rates could potentially have significant quality-of-life and cost implications, so long as treatment-related risks are minimal. Currently, fewer than 20 studies of the use of LDA in IVF have been published, with varying study designs and mostly small sample sizes. Results of these studies have varied. The state of the science regarding the effect of aspirin on IVF has been assessed in four meta-analyses/systematic reviews conducted in the past year [1••,2•,3•,4••] along with one new retrospective study [5•]. These meta-analyses have made different clinical recommendations; however, we will show that there is minimal disagreement in these summaries of existing results, and it lies in its interpretation.

Correspondence to Enrique F. Schisterman, PhD, 6100 Executive Blvd, Room 7B03, Rockville, MD 20852, USA, Tel: +1 301 435 6893; fax: +1 301 402 2084; schistee@mail.nih.gov.

Background

Trends in women's age in attempts to become pregnant and use of IVF in combination with the widespread availability of low-cost LDA makes the question of the effectiveness of LDA in IVF one with real public health relevance. In theory, aspirin has been used for its antiinflammatory, vasodilatory, and platelet aggregation inhibition properties in order to improve blood flow, promote fertility, and lead to higher success with IVF. This theory along with the low cost, high availability and minimal side effects of LDA gives it the potential to greatly benefit women who are undergoing IVF and have significant quality-of-life and cost implications.

Overview of meta-analyses

Four recently published meta-analyses evaluated evidence from clinical trials on the effects of LDA on a range of IVF outcomes [1••,2•,3•,4••]. These metaanalyses and their measured outcomes are summarized in Table 1. Gelbaya *et al.* [4••] evaluated the effect of LDA on the likelihood of pregnancy in women undergoing IVF/intracytoplasmic sperm injection (ICSI) treatments. A total of six randomized controlled trials (RCTs) and a combined total of 2515 women were included in the meta-analysis comparing the use of aspirin alone versus placebo or no treatment after exclusion of trials and assessment of methodological quality. Nonsignificant estimates were observed regarding effects of aspirin on clinical pregnancy [relative risk (RR) 1.09, 95% confidence interval (CI) 0.92–1.29], miscarriage (RR 1.17, 95% CI 0.84–1.63), and cycle cancellation rate (RR 0.88, 95% CI 0.54–1.43). It was concluded that LDA is not associated with improved outcomes. Thus, the authors advised the cessation of LDA use with IVF.

A meta-analysis by Khairy *et al.* [2•] included seven trials and a combined total of 1241 women undergoing IVF treatment. Poustie *et al.* [3•] published a similar meta-analysis around the same time that included the same studies and concluded similar results. Subgroup analyses of infertile patients, such as oocyte recipients or poor responders that had been excluded by Gelbaya *et al.*, were included. A large RCT (Waldenstrom *et al.* [6], $n = 1022$) was not included in this analysis because it was a quasi-randomized study that lacked concealment of allocation. This meta-analysis evaluated the effects of aspirin on live birth rates, but in doing so only pooled two studies – one that utilized an extremely small sample size ($n = 28$) in a subgroup of infertile women showing beneficial effects and the other with a much larger sample size ($n = 374$) in the general IVF population but showing a less significant reverse effect [7,8]. The results of the meta-analysis on clinical pregnancy, live birth, miscarriage, or ectopic pregnancy rate did not show a significant benefit of using aspirin therapy. Noting the small sample size of the study, these authors suggest that a trial would need to randomize more than 2500 women to obtain an 80% power to detect a difference in live births and minimize the possibility of a false-negative finding. They conclude that clinicians should not recommend the continued use of aspirin therapy with IVF. Both studies urged researchers to construct larger, well designed clinical trials to further clarify the heterogeneity between current RCTs.

A meta-analysis by Ruopp *et al.* [1••] found evidence of the LDA having beneficial effects on IVF. The authors included 10 studies amounting to the largest pooled sample of events and suggested issues with statistical modeling, study selection, and statistical inference as reasons for discordance with conclusion of previous study. Ruopp *et al.* describe small increases in pregnancy rates with use of LDA in the full and subgroup analyses and inadequate power of 0.56 or less for assessment of clinical pregnancy rates based on available data. The authors suggest withholding recommendations, given the limited data and inconclusivity of analyses.

Previous studies and their use in meta-analysis

As an approach for consolidation of existing evidence, meta-analysis is dependent on the ability to combine independently conducted studies. Even when attempting to pool data from separately conducted randomized trials, it is important to assess whether individual studies are similar enough that a combined estimate will be a meaningful description of the set of studies. Individual estimates of treatment effect will vary by chance because of finite sample size and sampling variability but when this variance is in excess or more than what would be expected by chance alone, statistical heterogeneity occurs. Studies of LDA in IVF have not been uniform with regard to aspirin dosages, the timing of start and stop of treatment and type of study population. These differences may render comparison across studies less meaningful, as they suggest nonnegligible differences in the questions they address. In trying to systematically consolidate available evidence through meta-analysis, one must balance use of inclusion criteria to exclude non-comparable studies while trying to maintain an adequate study population size.

When including studies performed on at-risk subgroups such as poor responders, the real effect can be inflated if their response is more noticeable or can be masked if the treatment is futile. For example, Urman *et al.* [9] and Rubinstein *et al.* [10] had similar sample size numbers with similar sized aspirin and placebo groups but had different criteria for patient selection and very different results. Urman *et al.* performed a RCT only on patients undergoing going IVF for male factor infertility and found an insignificant clinical pregnancy RR of 0.91 (95% CI 0.69–1.21). Rubinstein *et al.* performed a RCT only on the main group of women excluded from RCT by Urman *et al.*; these women were those with tubal factor infertility and who might be thought of as better responders. Although demographics of the participants were similar to those of studies by Urman *et al.* Rubinstein *et al.* found a significant RR of 1.52 (95% CI 1.12–2.06) giving evidence to the claim that there might be better/worse responders to IVF.

The narrow range of dosage used in IVF studies makes this an unlikely contribution to inter-study differences but still noteworthy. For example, a study by Waldenstrom *et al.* evaluated LDA at a dosage of 75 mg and found a positive effect of aspirin on clinical pregnancy rates in IVF (RR 1.18, 95% CI 1.01–1.38), whereas a study by Pakkila *et al.* used a dosage of 100 mg and found no beneficial effect (RR 0.92, 95% CI 0.65–1.31). However, Rubinstein *et al.* also used an aspirin dosage of 100 mg but found differing results – an increased rate of pregnancy versus the placebo (RR 1.52, 95% CI 1.12–2.06). Nevertheless, dose is an important consideration to questions of incidence of side effects as well as IVF success. Timing and duration of the dosage ranged from initiation of aspirin 1 month prior to the initiation of gonadotrophin to initiation of aspirin on the day of embryo transfer and cessation of aspirin at 8 weeks to cessation at delivery. Similarly to dosage, both beneficial and null effects were seen in both long-term and short-term aspirin use.

Reasons for discordant findings of studies, meta-analyses

In order to help serve the purpose of evidence-based medical decision making, a unified interpretation of the evidence is important. On the basis of the same set of existing studies as available data, the described meta-analyses have yielded a range of estimates, differing conclusions, and opposite recommendations. The scenario allows for a straightforward comparison to determine the sources for this discordance, which can be categorized as regarding estimates or regarding recommendations. As we will describe, reasons for discordance in effect estimates include differences regarding the studies included in the analysis (i.e., inclusion criteria), the specific hypothesis being tested, and the method of analysis. Reasons for disagreement in recommendation are less clear and include differences regarding interpretation of findings and determination of potential benefits of aspirin treatment and uncertainty regarding the risks related to treatment.

Divergent effect estimates of meta-analyses

Varying inclusion criteria used by the described meta-analyses have contributed to different findings. Some variation in inclusion criteria has resulted from data requirements for the primary hypothesis. For example, a study of LDA on live births must be restricted to those studies with information published on this outcome. Regardless, this inconsistency has led to studies with varying sample sizes and statistical power, as previously described. Moreover, given the small number of available studies to begin with, data from each have substantial leverage so that estimates are impacted.

Another point of difference between the meta-analyses is in regard to the statistical models used. On the whole, differences in the results of meta-analyses based on fixed-effects and random-effects models arise only when the study results are not homogeneous, as in this case. Moreover, these differences, which are often (but not necessarily) small, take on particular importance when looking for small effects, as those of LDA on IVF are likely to be. All of the meta-analyses evaluated found the heterogeneity between studies to be borderline significant, but individual study results ranged between findings of effect or no effect. Beyond the results of tests of homogeneity, there is an inherent difference in the question each of the two models attempts to answer [11]. Thus, the choice of models should be based on which question is most relevant to the analysis and not on the heterogeneity. Random-effects models are not necessarily a solution to issues with heterogeneity [11–13].

Divergent recommendations

The divergent recommendations presented in the previous meta-analyses are a result of misinterpretations of underpowered null findings. The nonsignificant point estimates for pregnancy, miscarriage, and cancellation rates with CIs overlapping the null hypothesis that these studies found led to inferences that need to be clarified. The point estimates in all the meta-analyses were similar in magnitude for the various outcomes, but differed largely in the wideness of their CIs. CIs including the null are observed not only in the face of a true null hypothesis, but when study power is inadequate to detect a true alternative hypothesis. Power calculations for the evaluation of many of the most relevant outcomes such as clinical pregnancy rates per embryo transfer were 0.56 or less regardless of the group of studies utilized. For the live birth rate calculations, this power was substantially lower, as there have only been two studies with a combined total of 402 women (and cycles) published on this outcome, despite it being the most relevant and important outcome of IVF [7,8]. This lack of power means acceptance of the null that occurred in the past four meta-analyses would not be an argument against aspirin but rather absence of utility or failure to detect utility that exists. Thus, in a preliminary evaluation of studies whose pooled sample size lacks ample power inclusion of the null should not be grounds to support or disprove a hypothesis.

There is also substantial evidence from multiple large trials and meta-analyses that LDA has been used without significant complications during pregnancy excluding small, increased risk of minor side effects [14–16]. Kozer *et al.* [15] performed a meta-analysis that included randomized trials as well as cohort and case–control studies on aspirin use during the first trimester of pregnancy. These authors estimated an overall odds ratio (OR) for congenital malformations with LDA use of 1.33 (95% CI 0.94–1.89); when analysis was restricted to clinical trials, the estimated OR was 1.03 (95% CI 0.94–1.13). Assessing five case–control studies, exposure to aspirin was associated with an increased risk of gastroschisis (OR 2.37, 95% CI 1.44–3.88) [15]. In an additional meta-analysis, LDA during pregnancy was found to have no effect on perinatal mortality, risk of perinatal complication, or risk of miscarriage [16]. Taken together, evidence does not support teratogenic effects of LDA treatment during pregnancy or reasons for discontinued use.

We note here an important distinction between systematic reviews and meta-analysis. The former is aimed at consolidating evidence from different studies. It is reproducible and systematic, can be quantitative, but does not require statistical testing so it is never premature. Informally, all researchers do this whenever considering the findings of a given study in light of the totality of evidence. Conversely, meta-analysis is a statistical method for hypothesis testing and estimation. As such, questions of statistical power are relevant. Adequate sample size is required for appropriate inference and for meta-analysis results to serve as informative evidence. Given the suspected small effect size of LDA and the lack of evidence supporting the teratogenic effects of aspirin during pregnancy, considerable uncertainty remains. It is only clear that more research is needed to elucidate the association between aspirin and IVF success. In the absence of evidence, recommended alterations of current practice are too early. More trials are required for meta-analysis on the effects of LDA on outcomes in IVF to have adequate power to reach definitive findings that could warrant a change in treatment, especially in the context of determining LDA's effect on live birth rate.

Conclusion

After review of the most recent meta-analyses concerning aspirin and IVF, the current evidence is insufficient to base recommendations regarding the use of LDA treatment in conjunction with IVF. In particular, given the small effect that aspirin is expected to have on birth outcomes, sample size is a critical consideration for interpretation of meta-analysis – at present, the available size is not large enough. As aspirin is a commonly used and readily available drug, if it is shown to have beneficial effects (even if they are small) on pregnancy outcomes, it could have a significant impact on public health. There has been no clear demonstration that the adverse effects of aspirin outweigh beneficial effects, which would justify altering current practice. In the absence of clear evidence, however, clinicians should continue their current practice with regard to aspirin use until more trials are conducted and information comes to light.

Acknowledgments

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 300).

1••. Ruopp MD, Collins TC, Whitcomb BW, Schisterman EF. Evidence of absence or absence of evidence? A reanalysis of the effects of low-dose aspirin in in vitro fertilization. Fertil Steril 2008;90:71–76. [PubMed: 17889863]Most recently published meta-analysis on aspirin and IVF. It is the only meta-analysis that found a beneficial effect of aspirin on clinical pregnancy rates and recommended no change in the clinical use of aspirin.

2•. Khairy M, Banerjee K, El-Toukhy T, et al. Aspirin in women undergoing in vitro fertilization treatment: a systematic review and meta-analysis. Fertil Steril 2007;88:822–831. [PubMed: 17509593]This meta-analysis found no evidence of improved reproductive outcomes with IVF in

women using LDA. The authors emphasized the lack of power in their analysis and the need for a definitive trial.

3•. Poustie VJ, Dodd S, Drakeley AJ. Low-dose aspirin for in vitro fertilisation. Cochrane Database Syst Rev 2007:CD004832. [PubMed: 17943828]This meta-analysis found no significant difference between clinical pregnancy rates or live birth rates between LDA treatment and control groups. The authors recommended that until evidence from an appropriately powered trial is available, aspirin treatment should not be recommended.

4••. Gelbaya TA, Kyrgiou M, Li TC, et al. Low-dose aspirin for in vitro fertilization: a systematic review and meta-analysis. Hum Reprod Update 2007;13:357–364. [PubMed: 17347160]This article was the first meta-analysis to be published on aspirin and IVF. It found no significant differences in outcomes in patients receiving LDA and those receiving placebo or no treatment. The authors recommended that aspirin should not be routinely recommended for women undergoing IVF/ICSI.

5•. Frattarelli JL, McWilliams GD, Hill MJ, et al. Low-dose aspirin use does not improve in vitro fertilization outcomes in poor responders. Fertil Steril 2008;89:1113–1117. [PubMed: 17612539] This retrospective cohort study assessed the utility of aspirin in improving pregnancy outcomes in IVF in patients with a diagnosis of poor response. This article found an increase in many IVF-stimulation parameters but a decrease in fertilization rates.

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Table 1

Overview of recent meta-analyses and outcomes measured

Meta-analysis	Studies	*N*	Relative risk (95% confidence interval)
Gelbaya *et al.*			
CP/ET	6	2515	1.09 (0.92–1.29)
CP/cycle	4	1142	1.08 (0.82–1.44)
PR/ET	3	1612	1.13 (0.97–1.31)
LB/cycle	1	374	0.87 (0.57–1.34)
LB/ET	2	1729	1.08 (0.83–1.40)
Miscarriage/CP	3	658	1.17 (0.84–1.63)
EP/CP	3	658	1.22 (0.34–4.38)
Khairy *et al.*			
CP/patient	7	1241	1.11 (0.95–1.31)
LB/patient	2	402	0.94 (0.64–1.39)
Miscarriage/patient	2	649	1.06 (0.53–2.11)
EP/patient	2	649	2.24 (0.7–7.24)
Poustie *et al.*			
CP/patient	7	1240	1.09 (0.93–1.28)
LB/patient	2	401	0.94 (0.63–1.39)
Miscarriage/patient	3	676	1.17 (0.61–2.27)
EP/patient	2	648	2.24 (0.69–7.22)
MP/patient	1	28	1.73 (0.38–7.98)
MB/patient	1	28	0.87 (0.14–5.32)
Ruopp *et al.*			
CP/ET	10	2801	1.15 (1.03–1.27)
Implantation/ET	3	612	1.08 (0.69–1.71)
Miscarriage/ET	4	671	1.19 (0.86–1.65)

CP, clinical pregnancy; EP, ectopic pregnancy; ET, embryo transfer; LB, live birth; MB, multiple birth; MP, multiple pregnancy; PR, pregnancy rate.