Letters to the Editor

Is it time for a meta-analysis?

Sir,

Recent issue of the Hum Reprod Update included a meta-analysis by Gelbaya et al. (2007) that systematically evaluated the current state of evidence regarding the effects of aspirin in IVF. The authors found non-significant point estimates for pregnancy, miscarriage and cancellation rates with confidence intervals overlapping the null hypothesis. Based on these results, the authors concluded that aspirin has no effect on pregnancy in IVF and as a result, suggest abandoning the treatment in clinical practice. We question the approach employed by these authors and, more importantly, suggest they have reached a flawed interpretation of their results.

The random-effects modelling used by Gelbaya et al. has received much criticism in the published literature (Peto, 1987; Pettiti, 1994). Random-effects models have an inherent loss of precision by introducing an in-between study variance, and make the dubious assumption that the set of trials included in the meta-analysis are representative of a hypothetical total body of trials. The naïve attractiveness of the random-effects model is that one might address the effects of heterogeneity between studies by introducing a between-study component of variance. Gelbaya et al. state that ‘owing to significant heterogeneity among trials, we used the random-effects model (DerSimonian and Laird, 1986) to derive the summary estimates of the effect of treatment’. In reality, the inter-study component of variance of the random-effects model may not sufficiently account for actual inter-study heterogeneity. It has been suggested (Thompson and Pocock, 1991) that the random-effects model should only be used when the absence of inter-study heterogeneity can be assumed, because any significant between-study heterogeneity dominates the weights assigned to the studies. Consequently, in the presence of substantial between-study heterogeneity, small and large trials become weighted the same, and the summary statistic is greatly affected by the inclusion of small trials into the analysis.

In addition, before one performs a meta-analysis, one ought first to consider whether total weight justifies the exercise. Confidence intervals including the null are observed not only in the face of a true null hypothesis, but also when study power is inadequate to detect a true alternative hypothesis. The hypothesized positive effect of aspirin use on IVF outcomes is clearly of interest, but even great interest cannot make up for an absence of evidence; one must question whether a meta-analysis for this question is premature. Recommendation of policy changes to abandon treatment based on coverage of the null are unwarranted, especially in this case with such few studies in the analysis.

Meta-analysis can be a powerful tool for consolidating information and borrowing statistical power from across the scientific community; however, this consolidation does not guarantee adequacy of evidence to support or disprove a hypothesis. The complexity of meta-analysis, and the weight its findings carry, requires careful consideration of a number of methodologic issues. Specifically, there are shortcomings in the analytic approach and statistical inferences of Gelbaya et al. that significantly impact their conclusions. As a result, we believe that more trials are required for meta-analysis on the effects of low-dose aspirin on outcomes in IVF to have adequate power. Until that point, conclusions regarding an effect or lack thereof are wanting of solid support and clinicians should continue their current practice with regard to aspirin use until more information comes to light.

References


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Reply: ‘Is it time for meta-analysis?’

Sir,

In their letter, Dr Ruopp and co-authors question the statistical approach and the validity of our meta-analysis on the use of low-dose aspirin in women undergoing in vitro fertilization (IVF) (Gelbaya et al., 2007). They also go some way to suggest that we have reached a flawed interpretation of the results. Their argument is that random-effects models have an inherent loss of precision by introducing an in-between study variance and that random-effects model should only be used when the absence of inter-study heterogeneity can be assumed.

With fixed-effects models, it is assumed that there is a sole common effect estimates for all studies, i.e. the true effect of