Turning to the primary papers, we compared the primary outcomes (or first outcome reported) in the abstract, methods and results sections of the primary studies. Of these ten, only one used the term primary end point, two used ‘main outcome measures’, and only three report the same outcome first in all three parts of their own paper (see Table S2). This suggests that the authors did not have a primary outcome in mind when conducting their trial, giving a high probability of selective outcome reporting.

When reading each primary paper carefully, they are all reported in, at best, idiosyncratic ways.

We examined the paper published in the highest impact journal (Nestler et al.) particularly carefully. In the abstract of that paper, with no mention of a primary outcome, the hypothesis was that ‘inositol would improve insulin sensitivity’, and ovulation was reported seventh and last. In the methods section, ‘measurement of ovulation by serum progesterone’ had become the first outcome mentioned, but reverted to last by the main results section. More worryingly, the dramatic headline claim in that paper that 19 women in the inositol group ovulated compared with only six in the placebo group appears to be based on Figure 3, a plot of ovulation by week over 8 weeks. The numbers in that figure are only consistent with those in the text if each woman only ovulated once over the 6-week period, which is possible although somewhat surprising. It is also hard to reconcile only one raised progesterone per woman over 6 weeks because serum progesterone was reportedly being measured weekly. The text is difficult to interpret, but did Pundir et al. notice the apparent inconsistency?

Professor Coomarasamy has had the recent experience of being led astray by a similar systematic review of prostogens to prevent miscarriage in which an implausibly large benefit observed in multiple small unregistered trials was later refuted by his own well-conducted, and registered, large trial.

We would question the need to waste precious research funds every time a few poor-quality studies suggest that a dietary supplement has a miraculous effect.

**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

**Table S1.** All the reported outcomes from each primary trial.

**Table S2.** The first outcome reported in the abstract, main paper methods and main paper results. We have added the term “primary” or “main” where used.

**References**


Rachel Hibberd, Nick Raine-Fenning, & Jim Thornton
University of Nottingham, Nottingham, UK
Accepted 19 September 2017.
DOI: 10.1111/1471-0528.14991

**Authors’ reply**

Sir,

We are grateful to Hibberd and colleagues for their interest in our systematic review on myo-inositol.

In particular, they appear to be concerned about the following: choice of primary outcomes in the included studies and perceived selective
reporting in our review, limitations in the quality and reporting of the included studies, and finally the need for a primary trial.

First, the primary outcome in a well-conducted systematic review is usually the one that is considered to be most clinically important, reflective of the greatest therapeutic benefit of the intervention. Whereas, in primary trials, the primary outcome is often the one chosen to satisfy sample size requirements, mostly surrogate measures, which may or may not be of utmost clinical relevance. Such trials usually provide secondary outcomes, which may be more important to clinical practice than their primary outcomes. A systematic reviewer is then faced with two choices: either choose to only meta-analyse outcomes that have been clearly reported as ‘primary’ in the studies, or prespecify a priori certain clinically relevant outcomes to be ‘primary outcomes’. We took the latter approach, to avoid bias by selectively reporting only published primary outcomes in trials as selectively only reporting arbitrarily designated primary outcomes in individual trials negates the point of a systematic review and meta-analysis.3

Second, we have clearly specified in our discussion the limitations of the primary studies; their qualities have been assessed and reported in detail, and we have highlighted the heterogeneity in the population, intervention and outcomes reported. It is precisely because of these factors, that we have avoided recommending use of myo-inositol in clinical practice, or even an Individual Participant Data meta-analysis of relevant outcomes. Our methodology followed the PRISMA checklist and Cochrane reporting guidelines to provide objective rationale for approaches used.

Third, we disagree with the argument of Hibberd et al. that a well-conducted, randomised trial, which aims to provide definitive information on the effects of myo-inositol on the most clinically important measure, i.e. live births, is not required. There is a physiological plausibility to use myo-inositol because it is involved in the second messenger pathway of insulin signalling and we observed consistent evidence that appears to favour the metabolic and reproductive profiles of participants. In our survey of clinicians, 90% (61/68) were willing to offer myo-inositol as first-line agent for ovulation induction if it were found effective in a randomised controlled trial on women with anovulatory polycystic ovary syndrome (PCOS) and 67% (47/70) were keen to recruit women in such a trial. Given the easy availability of the supplement over the counter, and its relatively low cost, and the support for it among clinicians, we consider it reasonable to undertake a definitive trial in this area.

If found to be beneficial, myo-inositol use will transform the management of women with PCOS and sub-fertility. If found to be ineffective, it will avoid inappropriate prescriptions that provide false hopes on successful fertility outcomes. We hope that Hibberd et al. will join us in developing this much needed multicentre randomised trial on myo-inositol in women with PCOS to improve live birth rates and other outcomes of interest, which will be prospectively registered and adequately powered. The need for such trials has also been recommended by others.4,5

References


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Re: Insights from outside BJOG. Research Snippets

Further evidence of serious harm of early cord clamping

Sir,

Athol Kent1 has reviewed the need for research into early versus delayed cord clamping. He considers that there is already enough evidence to show that the intervention is against the infant’s best interests and it is therefore unethical behaviour. If this applies to research then