

## Poor ovarian responders: to meta-analyse or not, that is the question

Sir,

We have read with great interest the meta-analysis published by Reynolds *et al.* (2013) on the latest issue of *Human Reproduction* concluding that luteal estradiol (LE) priming is associated with decreased cycle cancellation and increased chance of clinical pregnancy in women with poor ovarian response. Although the authors performed a meta-analysis following the most rigorous methodology, it is unfortunate that several parameters related to the primary studies significantly diminish its value.

First of all, we are glad to read that the authors acknowledge the limitation of the diverse definitions used to define poor ovarian responders. This is in complete agreement with our previous work demonstrating the striking variability in the definitions of poor ovarian responders among published randomized controlled clinical trials (RCTs) (Polyzos and Devroey, 2011). The authors have successfully used the random effects model which is indeed most appropriate compared with the fixed effects model for trials with clinical heterogeneity. However, although this can allow comparisons for differences with regard to the stimulation protocol used and the different route of administration and dose of LE, it is unclear whether it can allow meaningful comparisons between populations with totally different potential to respond to treatment. A careful scrutiny of the trials included clearly shows that in several studies women demonstrated an optimal response and surprisingly high pregnancy rates even in the control group in which no LE pretreatment was given (Table I). With a mean number of 11 oocytes retrieved and clinical pregnancy rates reaching 37 in the control group (no LE pretreatment) these patients should be considered normal responders and by no means poor ovarian responders. Consequently, results obtained from this meta-analysis should be interpreted with great caution.

Secondly, although publication bias in the field of reproductive medicine has been reported in the past (Polyzos *et al.*, 2011), no attempt has been made to examine the presence of such a bias in this meta-analysis (Reynolds *et al.*, 2013). Of course, assessment of publication bias might be meaningless when few trials are included (Ioannidis and Trikalinos, 2007) and the authors' choice not to assess is fully justified. Nevertheless, this apparently does not exclude the presence of publication bias. Therefore, considering that trials with positive results in favour of the experimental arm are published more frequently and faster than negative or neutral trials (Polyzos *et al.*, 2011), we cannot exclude that the outcome of this meta-analysis might have been affected by such a bias in such a way that overestimated the actual effect of LE pretreatment.

Finally, the authors' attempt to consider all available data published by including observational studies is indeed an effort to minimize the likelihood of publication bias; nonetheless, it is unclear whether this might have resulted in a more reliable conclusion. By grouping together the results of one randomized and several retrospective cohort studies,

**Table I** Number of oocytes retrieved and pregnancy rates in the control group (no LE priming) in the trials included in the meta-analysis by Reynolds *et al.*

Author (year)	Mean number of oocytes retrieved (mean $\pm$ SD) <sup>a</sup>	Pregnancy rates (%) <sup>b</sup>
Hill <i>et al.</i> (2009)	10.8 $\pm$ 6.2	36.4
Weitzman <i>et al.</i> (2009)	8.9 $\pm$ 4.3	30.3
Elassar <i>et al.</i> (2011)	6.1 $\pm$ 3.0	21.3
DiLuigi <i>et al.</i> (2011)	5.4 $\pm$ 4.7	28.6
Shastri <i>et al.</i> (2011)	8.7 $\pm$ 5.5	24.6
Chang <i>et al.</i> (2012)	3.2 $\pm$ 1.9	10.1
Ata <i>et al.</i> (2011)	7 (4–9) <sup>c</sup>	23.6

<sup>a</sup>As extracted from original trials.

<sup>b</sup>As presented by Reynolds *et al.*

<sup>c</sup>Number refers to median (interquartile range).

this meta-analysis lowers the level of evidence provided. Previous meta-analyses demonstrated that pooled results of low-quality trials may lead to spuriously inflated treatment outcomes in the experimental arm, completely diverse from pooled outcomes of high-quality randomized trials (Polyzos *et al.*, 2010). This might be even more prominent when data from observational studies are included in the pooled estimate as done in the meta-analysis by Reynolds *et al.* (2013). Thus, caution is needed prior to accepting the pooled estimate supporting a beneficial effect of LE pretreatment (Reynolds *et al.*, 2013), while the only RCT included in this meta-analysis did not demonstrate any benefit at all (DiLuigi *et al.*, 2011).

As previously stated *a research finding is less likely to be true when the studies conducted in a field are smaller and where there is greater flexibility in designs, definitions, outcomes and analytical modes* (Ioannidis, 2005). This is indeed the case for several of the retrospective studies included in this meta-analysis and this significantly limits the validity of the results. A simple example is a self-controlled study in which cancellation rates in women treated with LE were compared with cancellation rates in their previous treatment cycle without LE supplementation (Dragisis *et al.*, 2005).

Meta-analysis can indeed be a tool that may promote science when based on high-quality randomized trials; however, it may lose credibility when based on studies of ambiguous quality (Humaidan and Polyzos, 2012). Based on the evidence of the meta-analysis by Reynolds *et al.* we strongly disagree with the statement that *luteal estradiol priming is associated with decreased cycle cancellation and increased chance of clinical pregnancy in women with poor ovarian response*. In addition, we strongly disagree with the statement *Despite its limitations, until the results of an adequately powered, well-designed, multi-centre RCT are available on the effect of LE priming in ART, our systematic review and meta-analysis support the use*

of LE priming prior to COH in poor responders. Instead we believe that until such a randomized trial becomes available it is unclear whether LE priming can offer any benefit in women with poor ovarian response and should not be routinely recommended as an option to increase pregnancy rates. Finally we, again, call for action to postpone any further meta-analysis regarding poor ovarian responders until future trials using a uniform definition become available (Polyzos and Devroey, 2011). Conjoint action by journal editors, reviewers and authors is urgently needed to avoid such a practice.

## Conflict of interest

None declared.

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## Reply: Poor ovarian responders: to meta-analyse or not, that is the question

Dear Sir,

We appreciate the interest in our recent publication, 'Cycle cancellation and pregnancy after luteal estradiol priming in women defined as poor responders: a systematic review and meta-analysis' (Reynolds *et al.*, 2013). Our work was intended to highlight the existing literature regarding the use of luteal estradiol priming to improve outcomes for poor responders—a difficult and often frustrating patient population to treat for whom options are often limited. As with any study, our study has limitations that need to be considered prior to applying the results to clinical practice.

With regard to Drs Polyzos and Tournaye's critique, we do not disagree that a uniform definition for the poor responder among the studies considered in our meta-analysis is indeed lacking. Where we disagree, however, is that this detracts from our findings. On the contrary we consider this a *strength* of our study and believe it highlights the importance of including observational, and perhaps more generalizable, data in meta-analyses intended to inform clinical practice managing heterogeneous patient populations.

Although attempts have been made to better define poor responders (Ferraretti *et al.*, 2011), the fact remains that women with poor ovarian response may be represented by a constellation of poor outcomes in ovarian stimulation and IVF rather than a precise definition. For example, limiting the definition of poor responder to those with low oocyte yield would hardly represent the population of women who may benefit from novel stimulation protocols aimed at improving outcomes for women who have previously failed to conceive with both conservative and aggressive protocols.

Studies included in our meta-analysis were of similar quality, but as pointed out only one study was a randomized controlled trial. To exclude the observational data in this case would therefore exclude