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). Joint action by journal editors, reviewers and authors is urgently needed to avoid such a practice.

Conflict of interest
None declared.

References


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...
the bulk of the existing data regarding the use of luteal estradiol priming. Given our use of observational data we made every effort to minimize the faults of the individual studies included in our manuscript, using rigorous methodology and the random effects model to minimize the inter-study differences and improve the applicability of our results to all populations of poor responders across the spectrum from mild to severe. It is because of this heterogeneity that we chose a random effects model (DerSimonian and Laird, 1986) to minimize the intrinsic effects of population variation and increase the generalizability of our results. In doing so we believe that the results of our analysis can be applied to patients on both ends of the spectrum—patients with only a mild degree of poor ovarian response and those with a response so consistently poor that they are repeatedly cancelled prior to retrieval. By incorporating studies that included both mild and severe ends of the poor ovarian response spectrum as highlighted by Drs Polyzos and Tournaye, this strengthens our findings by improving the applicability of our results instead of isolating the findings to a more severe phenotype.

Drs Polyzos and Tournaye question the effect of publication bias on our findings. We appreciate this comment, and we do agree that there may be some degree of publication bias included in our analysis, as could be found in any meta-analysis. Our systematic review included studies with both positive and negative findings, and we incorporated all of these results into our analysis. In truth, one of our primary goals in performing this analysis was to improve the body of literature evaluating treatment of the poor responder, and if the results of our analysis lead to increased publications describing a neutral or negative effect of the luteal estradiol protocol in poor responders, this achieves our goal in improving available data which we welcome greatly.

As with any study, we do agree with Drs Polyzos and Tournaye that our findings should be interpreted with caution as cited in our paper as these findings are limited by the body of literature currently available. As the poor responder lacks a concrete definition, there is some heterogeneity to these results, which merits caution when applying our findings to individual patients. Furthermore, the increased clinical pregnancy rate demonstrated when using the LE protocol may be principally related to the decreased cycle cancellation rate. Despite these limitations, the vigilant physician can use our findings to improve their knowledge of possible treatment options for the poor responder. It is our hope that the findings of our study will increase enthusiasm for designing more robust research strategies evaluating definitions and management of the poor responder, leading to improved outcomes for this difficult and deserving patient population.

References


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Comment on ‘Recombinant LH supplementation to a standard GnRH antagonist protocol in women of 35 years old or older undergoing IVF/ICSI: a randomized controlled multicentre study’

Sir,

I have enjoyed the lecture of the study recently published in your journal by König et al. (2013), where authors conclude that LH supplementation in GnRH antagonist cycles does not show any benefit in terms of pregnancy rate in patients 35 years old or more.

These findings could seem to be in discrepancy with those published by our group (Bosch et al., 2011). We observed that LH administration in antagonist cycles in patients aged 36–39 was associated with a significantly better implantation rate. Nevertheless, an analysis in detail of the differences between both studies draws interesting and complementary conclusions about the possible role of LH in the treatment of this particular population.

The methodological differences that may explain the inconsistency of the results are the use of a contraceptive pill (CP) the cycle prior to stimulation, and the substitution of 75 IU of recombinant (r) FSH by 75 IU of rLH from the first day of stimulation in the study group. These differences are reflected in the synthesis of estradiol (E2) and progesterone (P), and in the oocyte yield.

Although in our study hormonal determinations before starting stimulation were not available, it is very likely that after one cycle of CP all values were lower than in the present study. In this scenario, LH may help for a better steroidogenesis, promoting the synthesis of androgens as substrate for their later aromatization to estrogens. This is observed particularly in older patients, in whom basal androgens are decreased (Davison et al., 2005) and there is an impaired capability to produce androstenedione in response to rFSH (Welt et al., 2006).

The administration of rLH from the beginning of stimulation could be related to the lower P levels observed on the day of hCG. Through its action at the theca layer, LH enhances the conversion from pregnenolone to androstenedione, while FSH enhances its conversion into P in the granulosa cells. This P cannot be converted into androgens (Yding Andersen et al., 2011), so if its production is excessive it is delivered into the circulation (Fleming and Jenkins, 2010). In a multivariate analysis