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


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
of more than 4000 cycles, we observed that P elevation is significantly related to the daily dose of FSH, but not of LH (Bosch et al., 2010).

The impact of LH on ovarian stimulation seems to be more patent when its administration is started at the beginning of the cycle than when given from the sixth day of stimulation, when follicular recruitment is already completed. In this case, only a modest increase in E2 and testosterone levels is observed, but probably too late to have an impact on ovarian response and cycle outcome. Indeed, no differences in follicular growth and oocyte yield are observed, while in our study, patients who received LH obtained less overall oocytes, but more metaphase II, reflecting a selective role of LH in ovarian response. This, together with lower P levels the day of hCG, may explain the better outcome of these patients when rLH is administered from stimulation Day 1.

In summary, the present study shows that LH supplementation from stimulation Day 6 in GnRH antagonist cycles does not improve cycle outcome in patients 35 years and older. This reinforces the concept that the possible beneficial effect of LH requires that its administration commences on the first day of stimulation to achieve optimal steroidogenesis and a better oocyte competence. This role may be especially needed when a CP is given on the previous cycle for programming. Further studies comparing both LH supplementation protocols may be necessary for an optimal address of this issue.

References

Ernesto Bosch*
IVI Valencia, Valencia, Spain

*Correspondence address. E-mail: ernesto.bosch@ivi.es
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Reply: Comment on ‘Recombinant LH supplementation to a standard GnRH antagonist protocol in women of 35 years or older undergoing IVF/ICSI: a randomized controlled multicentre study’

Sr,
We highly appreciate the interest and comments made by the group of Bosch et al. regarding our recent publication on recombinant LH supplementation to a standard GnRH antagonist IVF/ICSI protocol in women of 35 years or older (König et al., 2013). We agree that there are a few methodological differences between our study and the study of Bosch et al. (2011) which might explain discrepancies in reported results. These differences generate some interesting questions on the mechanism of a possible beneficial effect of LH administration in a specific group of older women seeking IVF/ICSI treatment receiving a specific treatment protocol. Although we agree with some of the comments that are made, a number of raised questions are hypothetical and open to debate.

Our study showed no beneficial effect of recombinant (r)LH supplementation from stimulation Day 6 on ongoing pregnancies in women of advanced age receiving a short (no oral contraceptive pill pretreatment) GnRH antagonist protocol. However, Bosch et al. found a beneficial effect of LH on implantation rates, which could be explained by lowering basal LH levels after oral contraceptive pill pretreatment. The clinical implication of this could be questioned, since the use of oral contraceptive pills prior to a GnRH antagonist protocol is controversial and much debated (Smulders et al., 2010). There is evidence that suggests that oral contraceptive pill pretreatment adversely affects the IVF outcome in GnRH antagonist cycles (Nardo et al., 2013).

In contrast to our findings of no effect of rLH on progesterone levels, Bosch et al. found lower progesterone levels on the day of hCG. This could be explained by a possible effect of LH administration on stimulation Day 1 by the action of LH on the theca layer in the early follicular phase. However, in the late follicular phase FSH also stimulates the granulosa cell to produce progesterone. Since Bosch et al. reduced the amount of rFSH in patients randomized to rLH administration, this effect of FSH on the granulosa cell cannot be ruled out. Furthermore, the relation of progesterone levels on pregnancy rates is still a matter of debate (Venetis et al., 2013).

LH supplementation from stimulation Day 6 onwards does not seem to be beneficial. However, we agree that there might be a potential beneficial effect of LH supplementation from stimulation Day 1 in an antagonist cycle especially with pretreatment of oral contraceptives in this specific group of older women. Further studies are indeed necessary to address this issue.

References
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