Letter to the Editor

Individualized FSH dosing improves safety and reduces iatrogenic poor response while maintaining live-birth rates.

Sir,

We read with interest the trials published by the OPTIMIST trial group (Oudshoorn, et al., 2017, van Tilborg, et al., 2017, van Tilborg, et al., 2017). These three papers collectively suggest that the individualization of FSH dosing according to a baseline antral follicle count is not effective. We are concerned that this conclusion is driven by excessive reliance on live-birth rates, rather than outcomes which are directly modifiable by ovarian stimulation. Recognition of non-inferiority for live-birth rates, but the distinct advantages of fewer poor responses and improved patient safety with respect to a reduced risk of ovarian hyperstimulation syndrome (OHSS) have been reported in other trials examining individualization of ovarian stimulation (Allegra, et al., 2017, Nyboe Andersen, et al., 2017). We would suggest that the data from the OPTIMIST trials in fact confirms the benefits of individualized FSH dosing, and it is notable that these advantages were achieved despite the very limited stratification of doses (100, 150, 225 and 450IU) that were initially assessed.

Specifically, the authors demonstrate that for the potential poor responder patient (van Tilborg, et al., 2017), individualization with increased doses of FSH reduces cycle cancellations (cancellation due to inadequate follicular response 30% in the 150IU arm as compared to 8% for 225IU or 4.4% for 450IU) and increases oocyte yield by one or two oocytes in the first treatment cycle (9.2 v 7.3 and 6.4 v 5.3 oocytes). The authors are to be commended for retaining as many women in the trial, however, this experience is not universal and cycle cancellation is known to contribute to discontinuation of treatment, particularly if maximal stimulation has been used (Troude, et al., 2014). To examine live-birth rates, a much larger sample size would have been required. For example to show a relative 25% increase in live-birth rates from 20% to 25% for that first cycle in women with an AFC<10, over 2000 women would be required to be randomized. That there is a consistent linear association with live-birth rates in this range of oocytes (Steward, et al., 2014), particularly when fresh and frozen embryos are accounted for, would further support the need for a much larger trial, prior to definitively concluding that there is no benefit of increased doses on live-birth rates from that first treatment cycle.

Likewise in (Oudshoorn, et al., 2017), cycle cancellation was increased with 100IU suggesting that at these low doses, additional factors like bodyweight that are inversely associated with FSH exposure need to be taken into account (Howles, et al., 2006, Ledger, et al., 2011) and confirms the need for robust modelling of dose selection prior to commencing an RCT examining individualised FSH doses. At the other extreme of ovarian response and the anticipated hyper-responder, the customization of therapy for the first treatment cycle results in a significant reduction in the rate of hyper-response (11.6% v 38.3%) as well as a reduced incidence of ovarian hyperstimulation syndrome (OHSS)(4.7% v 14.7%), while maintaining both fresh live birth rates (25.7% v 25.2%) and cumulative live birth rates (36.0% v 39.1%).

We are somewhat surprised that, in light of these findings, the authors suggest that clinicians should use a standard dose of 150 units for all women entering an IVF programme regardless of their antral follicle count. We propose an alternative interpretation of the data, that individualization of ovarian stimulation reduces the variability of the number of oocytes recovered, increases the number of oocytes recovered in the poor responder and reduces the number of oocytes in the hyper responder. It reduces the proportion of women who have a poor or hyper-response, reduces the risk of cancellation of the cycle, increases the number of patients who reach embryo transfer and reduces the incidence of OHSS. Furthermore, it achieves all of this while maintaining live-birth rates. That some patients did not have an optimal outcome would suggest that alternative algorithms and biomarkers should be considered to individualize clinical dosing (Allegra, et al., 2017, Nyboe Andersen, et al., 2017). We would suggest that individualization of the dose of FSH is definitively superior to "a one-size fits all", and when combined with data from other recent trials, individualization of gonadotropin dosing should now be the standard of care.

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