

## Changes in practice make analysis of historical databases irrelevant for comparison between Natural and Stimulated IVF

Sir,

Retrospective analyses of large databases serve a useful function if the data extracted are relevant to the question being addressed. However, the recent study of Sunkara (Sunkara *et al.* 2016) fails to meet this requirement. The study examines the incidence of preterm birth (PTB) and low birth weight (LBW) in infants born following IVF with fresh transfer by comparing 584 835 stimulated cycles with 6168 unstimulated cycles over a 20-year period with the stated purpose of providing 'information for clinicians to counsel patients in their choices'. Thus, the statistical analysis is extended to cover the 'success rates' of the two treatment modalities.

The HFEA database is notable for the paucity of information it contains on vital information on associated risks of stimulation such as FSH dosage and stimulation protocols. However, the authors of this paper were able in a previous publication utilizing this database (Sunkara *et al.*, 2015) to use the number of oocytes collected as a surrogate for amount of stimulation to confirm that ovarian stimulation with the collection of >20 oocytes increased the risk of PTB and LBW. This information reflected other studies (McDonald *et al.*, 2009; Kalra *et al.*, 2011; Mak *et al.*, 2016), showing a link between ovarian stimulation protocols with fresh transfer and both of these complications in singleton births. The question surely is not whether stimulation and fresh transfer is associated with PTB and LBW but at what degree of stimulation and which maternal characteristics contribute to this effect. The study does not attempt to address this issue, which explains the ambiguous conclusion that 'the study cannot exclude the effect of ovarian stimulation on the perinatal outcomes following IVF'.

No one disputes that Stimulated IVF has better success rates than Natural IVF but the data provided in the paper are unlikely to reflect current practice. The authors show a lack of understanding of how Natural IVF has evolved since 1991. In their study, 55% of natural cycles were performed before 2000, which may explain why no oocyte was obtained and no embryo created in 44% and 57% of cycles, respectively. The introduction of indomethacin in Natural Cycle IVF to prevent rupture of the follicle (Nargund *et al.*, 2001) and antagonists to prevent premature LH surge (Oliviennes *et al.*, 2002) both resulted in a significant improvement in the rate of successful oocyte collection and, in our current practice, failure to obtain an oocyte occurs in fewer than 5% of cycles. The evolution of Natural Cycle IVF to the treatment of women with low ovarian reserve (where ovarian stimulation has not been shown to be beneficial) has occurred

since the end of their study in 2006, which explains why there were more women under the age of 35 than over 40 years in the Natural Cycle group. A comparison of the livebirth rates between Natural cycle and Stimulated IVF is now more relevant in women with low ovarian reserve.

The low livebirth rate of 16.9% for Stimulated IVF cycles in their study is also not in keeping with current success rates for this treatment. The incidence of PTB and LBW may also have changed in this group since the end of the study period with vitrification and blastocyst transfer increasing the incentive for higher stimulation protocols.

In summary, we would dispute the authors' claim that this study is of relevance in providing information for clinicians to counsel women in their choices of treatment. The data presented in this paper are more of historical interest than a contemporary assessment of the relative value of Natural and Stimulated IVF in the management of the infertile couple.

Yours sincerely

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