Excessive fetal growth in frozen embryo transfer: false alarm or clinical concern?

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Letter to the Editor

Dear Editor,

Maheshwari *et al*. recently adjourned their previous meta-analysis on the impact of frozen embryo transfer on pregnancy outcome (Maheshwari *et al*., 2012; Maheshwari *et al*., 2018). They actually confirmed with more robust data and increased precision the reduction in the risk of Small for Gestation Age (SGA) newborns (RR=0.62, 95%CI: 0.56-0.65) but also highlighted an increased risk of Large for Gestational Age (LGA) (RR=1.54, 95%CI: 1.48-1.61). To note, these results (mainly obtained from observational studies) are in line with those emerging from two recent RCTs (excluded from the meta-analysis) on the effectiveness of the "freeze all" strategy (Shapiro *et al*., 2016; Chen *et al*., 2016).

Interpretation of associations emerging from observational studies is always challenging because of the risk of confounders (Grimes and Schulz, 2012). Nonetheless, some hypotheses can be formulated. In particular, Maheshwari *et al*. (2018) interpreted the reduction in SGA as a direct benefit of the frozen embryo transfer strategy on the endometrium. The hyperestrogenism associated with ovarian hyperstimulation could indeed cause "*abnormal endometrial angiogenesis leading to (…) abnormal placentation*". On the other hand, they remained vague on the interpretation of the increased risk of LGA. They mentioned to the hypothesis by Pinborg *et al*. (2014) who interpreted this effect as an overgrowth guided by epigenetics alterations at early embryonic stages. The freezing and thawing procedures could perturb the epigenetic processes causing overgrowth of the fetus. This view is also supported by the higher risk of LGA after frozen embryo transfer emerging from comparisons with the general population (Pinborg *et al*., 2014; Luke et al., 2017; Spijkers et al., 2017), an epidemiological comparison that is however exposed to relevant confounders, of those the most critical being the specific surrounding cause of infertility, the socio-economical status and the psychological condition associated to infertility (Pandey *et al*., 2012; Siristatidis *et al*., 2013). Overall, the theory of a iatrogenic perturbation at the embryonic

stages is plausible and fascinating but inevitably fuels concerns and alarmism among physicians and patients.

We herein suggest an alternative interpretation of the findings, i.e. the simple shift of the distribution curve of the newborns weights (Figure 1). In other words, if frozen embryo replacement consents a more physiological placentation, one could expect a better fetal growth for all fetuses, not only for those who would have been SGA in fresh conditions. A significant proportion of embryos whose destiny was to be SGA if transferred in fresh conditions could be Appropriate for Gestational Age (AGA) using the frozen approach and, similarly, a significant proportion of embryos whose destiny was to be AGA in fresh conditions could be LGA using the frozen approach. To note, in the study from Maheshwari *et al*., (2018), the magnitude of the reduction of the risk of SGA and the increase in the risk of LGA are specular and very similar (-48% and +54%, respectively). If true, our interpretation would be extremely reassuring since it would support the view that frozen embryo transfer consents normalization of fetal growth rather than causing overgrowth. Future well-designed observational studies comparing pregnancies from frozen embryo transfer and from natural conception may shed more light on this issue. An in-depth collection of patients' characteristics is however warranted to allow for a reliable adjustment.

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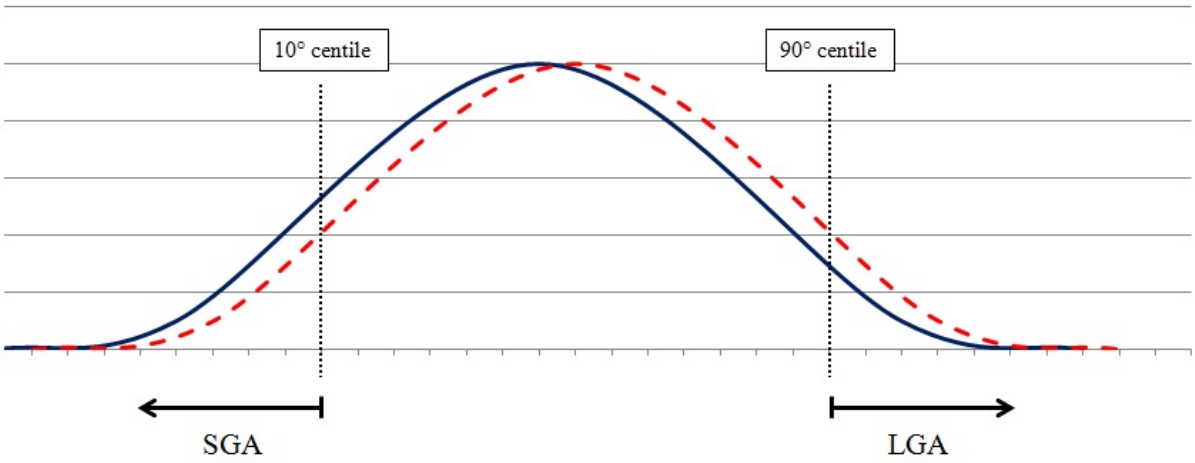
Figure legend

Figure 1: Shifting of the curve of newborn weights from fresh embryo transfer (straight blue line) to frozen embryo transfer (dotted red line). SGA: Small for Gestational Age. LGA: Large for Gestational Age. The distribution is assumed to be normal just for clarity.


10° centile
90° centile
SGA
LGA