

## Time to think about neonatal outcome in assisted reproductive technology



Assisted reproductive technology (ART), originally called in vitro fertilization (IVF), has been with us for forty years. During all this time efforts have mainly been targeted at increasing outcome, first expressed as pregnancy rates and more recently, as overall ART yield or live-birth rates. Of all the steps taken for improving ART outcome, the introduction of ovarian stimulation (OS) nearly from the inception of ART has been the single most effective measure ever implemented. Originally, fears existed that OS might alter oocyte quality, as it leads to recuperate, and inseminate, oocytes bound for atresia. Yet, we now know that this fear did not materialize, as embryo euploidy rates are not affected by the number of oocytes obtained (1). Unexpectedly however, the danger came from where it was least expected, the impact of OS on the endometrium and in turn the quality of placentation with possible consequences on neonatal outcome. It is about time therefore that we now expend our interest beyond the mere issue of pregnancy rates, or even live-birth rates, to also focus on the neonatal outcome of the pregnancies generated by ART.

In this issue, Palmsten et al. (2) are focusing precisely on obstetrical outcome with a report indicating that extreme inter-pregnancy intervals (IPI), short or long, are associated with increased pre-term birth (PTB) risks. These findings seen in ART women constitute an amplification of what is encountered in naturally conceived pregnancies (2). There are no clear explanations for the results reported by Palmsten et al. (2), nor the fact that short IPIs also affect the risk of PTB and small for gestational age (SGA) in natural conceptions.

One striking element in the article by Palmsten et al. (2) lies in the methodology used: computerized pairing of ART registries and birth record data. This approach offers promising means for studying the still too neglected topic of the obstetrical outcome of ART babies.

Overall, there are converging reports indicating that ART is by itself generally associated with increased obstetrical complications including PTB and SGA (3). In this context, our interest has been attracted by the role possibly played by the quality of placentation in the risk for PTB and SGA seen in ART (3). Indeed, the lower risk of PTB and SGA in frozen (de-vitrified) embryo transfers (FETs), as compared to fresh transfers, points at a likely origin of the phenomenon in the quality of placentation. In a recent meta-analysis of the literature, Maheshwari et al. (4) confirm the lower incidence of PTB, low birth-weight and SGA in FET as compared to fresh pregnancies (4). According to these authors, the difference between FET and fresh transfers has remained stable over the past 5 years (4). This strongly suggests that the hormonal imbalances caused by OS alter obstetrical outcomes encountered in fresh-transfer ART babies by disrupting the quality of placentation. Could short IPI also alter the quality of placentation by an imperfect

post-delivery recovery of endometrial function, and be further amplified in ART as compared to the natural conception population?

One of the most puzzling neonatal alterations encountered in ART is the higher incidence of post-date and large babies seen following FETs (4). At first glance, the endometrial preparation achieved by E2 and progesterone cycles used in FETs avoid the presumed culprit of altered placentation, the high E2 levels of OS, and thus, is presumed safe. Yet the fact that the quality of placentation is highly vulnerable with too shallow placentation capable of affecting obstetrical outcome leads to query whether the opposite might not also be true. Could excessive progesterone impregnation, that is possibly due to the so-called first uterine pass effect reported with vaginal progesterone administration, result in excessively deep placentation? Could this in turn lead to large babies and delayed parturition in FETs? The recent report of higher miscarriage rates in women receiving vaginal as compared to intramuscular progesterone in their FET treatment might lend credence to this concept (5).

The methodology used in the article by Palmsten et al. (2), the electronic pairing of ART registries and birth record databases, should be employed for further delineating the causes of the obstetrical outcome alterations encountered in FETs. For example, one would like to know whether the type of progesterone, dose, and route of administration used might play a role in the depth of placentation and its possible consequence, large babies.

It is about time that we center our interest on the obstetrical outcome of ART pregnancies in order to optimize our treatments accordingly. A recent report indicated that a freeze-all, deferred-transfer and FET provide superior results in polycystic ovary syndrome. This will likely lead to offers of freeze-all and deferred embryo transfers to polycystic ovary syndrome patients. Ultimately it would be better to identify the treatments that optimize obstetrical outcome and let that latter parameter dictate our therapeutic choices rather than remaining guided by the sole differences, at time small, in pregnancy rates.

Finally, the question of whether all risks, or slight differences in risks, ought to be exposed to patients should be debated. While these are issues of public health concern, with the impact of the quality of placentation on obstetrical outcome in ART being one, not all is good to share with patients. Certain differences in outcome are too minimal to be of clinical concern for single individuals. Should infertile patient be exposed to all minor differences in outcome that are observed in different circumstances? Exposing patients to the possibility of marginal differences in risk may lead to more harm by the stress generated than the actual risk or difference in risk. One easily convenes that patients should be exposed to the consequences of twin pregnancies when discussing the number of embryos to be transferred because the issue at stake is of consequential magnitude. Differences in obstetrical outcome linked to IPI may not be sufficiently relevant clinically to force exposing infertile couples to those data and risking to have them lose perspective. For example, there are differences in accident rates between major airlines that can

reach statistical significance. Yet it may not be relevant to expose passengers to such differences, as in all cases driving to the airport is still riskier than flying on any of these airlines. The debate on what needs to be shared with patients ought to be held, as the ART community starts being preoccupied about the obstetrical outcome of ART pregnancies. We thank Palmsten et al. (2) for sowing seeds that are fueling this debate.

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## REFERENCES

1. Barash OO, Hinckley MD, Rosenbluth EM, Ivani KA, Weckstein LN. High gonadotropin dosage does not affect euploidy and pregnancy rates in IVF PGS cycles with single embryo transfer. *Hum Reprod* 2017;32:2209–17.
2. Palmsten K, Homer MV, Zhang Y, Crawford S, Kirby RS, Copeland G, et al. In vitro fertilization, interpregnancy interval, and risk for adverse perinatal outcomes. *Fertil Steril* 2018;109:840–8.
3. Henningsen AK, Pinborg A, Lidegaard Ø, Vestergaard C, Forman JL, Andersen AN. Perinatal outcome of singleton siblings born after assisted reproductive technology and spontaneous conception: Danish national sibling-cohort study. *Fertil Steril* 2011;95:959–63.
4. Maheshwari A, Pandey S, Amalraj Raja E, Shetty A, Hamilton M, Bhattacharya S. Is frozen embryo transfer better for mothers and babies? Can cumulative meta-analysis provide a definitive answer? *Hum Reprod Update* 2018;24:35–58.
5. Devine K, Richter KS, Widra EA, McKeeby JL. Vitified blastocyst transfer cycles with the use of only vaginal progesterone replacement with Endometrin have inferior ongoing pregnancy rates: results from the planned interim analysis of a three-arm randomized controlled noninferiority trial. *Fertil Steril* 2018;109:266–75.