The influence of assisted reproductive technologies on obstetric and perinatal outcomes: the chicken, the egg, or both?

Safety and efficacy have been the overriding concerns for the assisted reproductive technologies (ART) since their inception over 40 years ago. Adverse obstetric and perinatal outcomes were recognized as inherent risks early on, but much of this excess risk stemmed from the high multiple pregnancy rates attributed to ART. With the advent of successful single embryo transfer (SET), that risk was substantially mitigated, and with significant improvements in pregnancy rates with SET, largely due to advances in the laboratory, it now is feasible to contemporaneously assess the true risk of ART more precisely with smaller populations of patients in a shorter timeframe. An unresolved question is how much of the recognized additional maternal and neonatal risk is due to the technology itself vs. the underlying risk conferred with the diagnosis of infertility.

These two confounding variables are inextricably linked, and novel study designs are necessary to assess their relative contribution to the problem. To this end, Dr. Ganer Herman and colleagues (1) examined obstetric and perinatal outcomes in a cohort of women from a single center with successive singleton spontaneous and autologous ART conceived pregnancies, such that each woman served as her own control. A centralized electronic medical records review was undertaken to exclude maternal confounding factors, including body mass index, smoking, müllerian anomalies, pregestational diabetes, and hypertension. The main outcome was the rate of preterm delivery (PTD), for which the study was adequately powered to detect a 5% absolute increase by including 544 serial discordant conception method pregnancies in 532 women. The authors did not find a difference in the PTD rate among the groups, even when subanalyzed separately for the order of conception method (i.e., spontaneous/ART and ART/spontaneous) and use of frozen and fresh embryo transfer. However, the authors did note a lower birthweight in the ART neonates, which was statistically significant but likely clinically insignificant, compared to spontaneously conceived neonates (ART: 3,164 g $\pm$ 530 vs. spontaneous: 3,213 g $\pm$ 490; $P = .042$). The finding that no difference was found between the 2 groups in the rate of small for gestational age neonates supports this conclusion.

The study was not adequately powered to address rarer outcomes, such as placenta previa and the need for blood transfusion (associated with abnormalities of placentation). Significant differences were not found, although a trend was reported, in the rate of placental abruption (ART: 1.8% vs. spontaneous: 0.7% $P = .08$) and gestational diabetes (ART: 7.9% vs. spontaneous: 5.9%; $P = .06$).

Placental abnormalities, including placenta previa, placental abruption, and morbidly adherent placenta, have been reported to be higher among singleton ART than spontaneously conceived pregnancies and are likely due to potential genetic and/or epigenetic factors (2, 3). Some of these findings are consistent with a previous ART sibling study (4), which used population-based data and reported that women who conceived with ART following a first spontaneous birth had small differences in birthweight. They also had higher rates of gestational diabetes, abruptio placenta/placenta previa, small for gestational age neonates, and a higher rate of PTD than the national average (4).

Limitations of this study, which limit more general application, include the ART population studied, comprised of approximately 30% male factor cases and 70% fresh embryo transfers with an unspecified stage of embryo development. In addition, the same paternity could not be confirmed among the studied pregnancies. The high proportion of male factor cases requiring ART does create a potential confounding variable. However, the study's conclusions offer additional support for the notion that a history of parental subfertility increases the risk of obstetric and perinatal complications, which has been consistently reported in the literature.

While their study was underpowered to assess the risk of placental abnormalities and gestational diabetes with ART adequately, their findings do not refute the risk suggested by previous literature (2). It is biologically plausible that abnormal implantation and subsequent placentation driven by genetic and/or epigenetic factors arising from the parents or the ART process could lead to short- and long-term adverse maternal, fetal and/or childhood outcomes. The question is, how much is each contributing to the observed outcome? Unique study models that might further illuminate this quandary could include couples undergoing ART with autologous oocytes for non-infertility indications, such as for preimplantation genetic testing for monogenic disorders or structural rearrangements, sex selection through preimplantation genetic testing for aneuploidy, and women without a male partner requiring ART. Furthermore, women who have conceived both naturally and with the help of ART, as in this study, offer an exceptional opportunity to study the effects of assisted conception on obstetrical and perinatal outcomes while controlling for maternal factors.

Whether it is the chicken, the egg, or both, it is essential to identify potential contributing factors and discern obstetrical and perinatal differences and the lifelong impact they may have on future offspring through the developmental origins of adult disease (Barker) hypothesis. For example, besides the more common subtle differences in weight and fetal growth trajectories that have been reported, fetal cardiovascular changes that persist into infancy, with a yet-unknown

adult long-term impact, also have been described (5). However, after over 40 years into the ART era, we can take solace that, overall, ART has become a very safe and effective treatment, although much work remains to elucidate the true magnitude and source of risk.

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