Unlocking the cause of increased adverse singleton pregnancy outcomes: the role of the assisted reproductive technology derived embryo

The ultimate goal of an assisted reproductive technology (ART) cycle is a healthy baby. Much has been written about a variety of maternal and neonatal adverse outcomes associated with in vitro fertilization (IVF). Clearly multiple pregnancies are the major culprit; however, singleton pregnancies after IVF also appear to be associated with more unfavorable outcomes than those singletons that are naturally conceived. Many factors appear to be involved including the underlying infertility, laboratory manipulation and, potentially, an abnormal endometrial development leading to a less than favorable implantation (1).

In this issue Woo et al. (2), have attempted to isolate the impact of the ART derived embryo by analyzing pregnancy outcomes of women who had offspring via gestational surrogacy, using the carrier's own naturally conceived pregnancies as a control. This is an exciting article that forwards a nice model in an attempt to evaluate the impact of the ART embryo and perinatal outcomes. Woo and colleagues (2) reported several adverse outcomes including a lower gestational age at delivery (38.8 vs 39.7 WGA), higher rate of preterm delivery (10.7 vs 3.1%) and a lower birth weight (105 g lower) in those children delivered after gestational surrogacy. These differences are minimal but reached significance. The authors also found an increase in adverse maternal outcomes including gestational diabetes and hypertension.

These increased adverse events are important to note, but the design of the study preclude definitively concluding that they exist solely due to ART-derived embryos as opposed to a naturally conceived pregnancy. Rather, it should be a springboard for proposing a large, multi-center prospective trial. Importantly, the authors replaced the embryos in an artificially programmed cycle when the women underwent gestational surrogacy. While the authors state that the preparation was designed to mimic the natural cycle, it clearly is different from a natural cycle and one cannot assume that this doesn't play a role in the increased adverse effects they found in these ART-derived pregnancies as compared to naturally conceived pregnancies. Implantation is a complex interplay between maternal and embryonic cytokines/growth factors and the hormonal milieu does affect the endometrial expression of various cytokines. Thus, it is not fair to state that the artificially created replacement cycle is equivalent to the natural cycle.

Another issue that may be a confounder is the impact of the number of embryos replaced in these surrogate cycles. The authors do not provide this data, but given that almost one-third of the surrogate pregnancies were twins, I suspect that most patients had more than 1 embryo replaced. It has previously been shown that in favorable prognostic women transferring fewer embryos was associated with a more favorable perinatal outcome including gestational age and birth weight (3).

In addition, Woo et al. (2) describe a rate of vanishing twins of only 1 %. This appears to be much lower than normal averages. Some studies have reported up to 10% of all IVF singleton deliveries are the result of vanishing twin pregnancies (4). It is well described that vanishing twin pregnancies are associated with increased adverse outcomes. Perhaps this is related to the retrospective collection of date and the possibility that some vanishing twin pregnancies were missed in the initial data collection. The authors do not report when the initial pregnancy ultrasounds were obtained and by whom.

Another potential issue is the number of years that this study encompassed with a variety of different lab techniques. How many different labs were used? Could the impact of the replacement of an ART-derived embryo be related to specific practices in the 1990s and not from more recent lab procedures and techniques? As the authors only included natural pregnancies that occurred before the surrogate cycle; how did they account for complications that are increased with aging? Both gestational diabetes and hypertension are associated with advancing maternal age and one has to wonder what role maternal age may have played. What was the time eclipsed between the natural pregnancies and surrogate pregnancies? Could the patients have gained weight before becoming surrogates and been more likely to develop diabetes or hypertension? Again, this data is missing. Given that this was a retrospective study; the interpretations of the pregnancy outcomes must be considered carefully. There is no description of why the preterm deliveries occurred. Do the Obstetricians treat the surrogate pregnancy different that a natural conception?

All in all, this is a very interesting study that proposes to separate out a very important concept in trying to understand why ART pregnancies may be associated with more adverse perinatal events. The authors are to be congratulated on nicely working with what information they have. However, because of the retrospective nature of the design and the utilization of artificial cycles, the study falls short of completely isolating the impact of the utilization of ART derived embryos as the cause of the increase in adverse outcomes that were seen. However, it does generate a nice hypothesis and a platform for a more comprehensive prospectively performed study. I hope to see this group take that step.

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