

## Birthweight after assisted reproductive technology: clinical decision-making and patient counseling



The use of assisted reproductive technology (ART) is increasing over time, with >275,000 cycles reported by the Society for Assisted Reproductive Technology in 2018. With improving success rates, there are an ever-increasing number of births conceived through ART, and fertility providers may therefore have the opportunity to impact health outcomes in a significant number of children. In recognition of this, research in the field has expanded to include not only strategies to improve the chance of successful achievement of pregnancy but also interventions that are most likely to result in the optimal outcome—the delivery of a healthy singleton live birth. Adverse obstetric outcomes reported to have an association with the use of ART include preterm birth and small for gestational age (SGA), both of which are highly associated with multiple gestations. Therefore studies such as the one published by Richardson et al. (1) have focused on singleton deliveries to separate the effects caused by multiple gestations and by the actual practices of ART. The inclusion of unassisted conceptions adds an important control group.

A survey of common practices among high-performing fertility clinics in the United States indicated that in 2006–2007, the average number of embryos transferred to women aged <35 years was 2.2 (2), compared with a similar survey of practices 10 years later, in 2016–2017, showing that the percentage of first embryo transfers that were elective single embryo transfers was 85% among women aged <35 years (3). Although these were surveys of a select clinic population, they are indicative of the shift toward single embryo transfers as a whole. Considering the demonstrated correlation between the number of embryos transferred and birthweight (4), this practice trend likely does more to reduce the risk of low birthweight among infants born after ART than any other changes to the protocol we can make. Perhaps, as a result, a recent US population-based study found no increase in the rate of SGA births among singletons born after fertility treatment compared to singleton deliveries that were not derived from fertility treatment, although this study included all fertility treatments and was not focused on ART alone (5).

Nonetheless, there continues to be an unfavorable comparison between the outcomes after ART and those after a natural conception in much of the published literature, and the investigators have provided additional insight into how the mode of conception among patients undergoing ART correlates with these risks. The investigators have confirmed the previous findings of a correlation between the early rise in human chorionic gonadotropin (hCG) levels and birthweight, but they have done it in both natural and ART conceptions. From this, it would appear that events around the time of implantation likely impact the subsequent birthweight. Despite not finding a significant association between the modes of conception and birthweight in this study, the investigators

do show significantly different rates of rise in hCG levels between the modes of conception they included and conclude that the rise in hCG levels is a mediator of the relationship between the mode of conception and subsequent birthweight.

These findings support the hypothesis that interventions such as embryo cryopreservation or biopsy and endometrial preparation technique play a role in determining subsequent birthweight, an outcome associated with multiple health outcomes for offspring. Additional investigation into the mechanisms for this should and certainly will follow. If this trajectory can be identified so early in gestation, it makes chronological sense that the events just before a detectable pregnancy have an impact. I do believe it is important to point out, however, that the mode of conception was not associated with the extremes of birthweight in this study. This finding provides some reassurance that to the extent that large for gestational age and SGA are markers of health in the offspring, the magnitude of impact of different available technologies on birthweight so far is not so clinically significant as to caution us against any of these treatment types. Based on these data, it appears that all are reasonable options that may be chosen when the clinical picture supports them.

Studies such as these certainly add to our knowledge about the interaction between interventions and the pregnancies that are subsequently established. As important as it is to be mindful of potential adverse outcomes in offspring, it is also important to continue to be able to offer the most appropriate treatment in a variety of circumstances, as determined by the provider and patient after a discussion of options, including risks and benefits. When deciding whether to use preimplantation genetic testing for aneuploidies, for example, there are many factors to consider, including the age of the patient, the magnitude of benefit that they are likely to receive from this additional information for embryo selection, patient preference, the accuracy of results, risk of embryo failure to survive cryopreservation, and so on. And as we learn more about the risk to offspring, these data contribute information to provide in risk discussions. Many of these considerations are also important when deciding whether to do a fresh transfer or freeze all protocol with subsequent frozen embryo transfer cycle. One size may not fit all, as suggested again by the abovementioned survey of high-performing clinics, most of whom report offering both fresh and frozen transfer cycles.

With the increasing use of ART for conception and improved live birth rates, the efforts to learn more about the health of the pregnancies we create are more important than ever. Promoting single embryo transfer in most, if not all, cases has likely contributed the most to decreased obstetric complications. However, continuing to learn more about how our treatment protocols impact birth outcomes can help drive best practices going forward as well.

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