

## Taking a second look at obstetrical outcomes after assisted reproductive technologies



The authors of the Declaration of Independence held certain truths to be self-evident, including that all men are created equal, that they are endowed by their Creator with certain unalienable rights, among these are Life, Liberty, and the pursuit of Happiness. Likewise, in the world of assisted reproduction, we have long held many truths to be self-evident, including the fact that pregnancies achieved with in vitro fertilization (IVF) cannot have the same outcomes as unassisted pregnancies. For many years it has been accepted that pregnancies after assisted reproduction carry increased risks of premature delivery, low birth weight, preeclampsia, placental abruption, and other complications (1). Much of this risk stemmed from the high rates of multiple pregnancies that resulted from multiple embryo transfers. These iatrogenically induced twin and triplet pregnancies resulted in prematurity, low birth weight, and other third trimester complications that gave IVF a negative connotation that persists today. Nevertheless, the association of poor obstetrical outcome and IVF persisted when analyses were limited to singleton pregnancies (2). Thus, it has remained unclear whether these increased risks are a product of Assisted Reproductive Technologies (ART) or merely the patients who require ART treatments (3). Furthermore, many patients with infertility are older with medical comorbidities and potential oocyte and sperm quality issues. Most importantly, many of the studies were performed when IVF technologies were considerably less mature, focusing on the transfer of multiple cleavage-stage embryos into a hyperstimulated uterine environment without the benefit of preimplantation genetic testing. Is it fair to say that this applies to modern ART practices?

Today's IVF focuses on extended embryo culture, preimplantation genetic testing, and freeze-all cycles. Superior culture systems and time-lapse embryo imaging have improved the efficiency of the IVF laboratory. Intracytoplasmic sperm injection is used more frequently for nonmale factor indications. Single embryo transfers have become de rigueur and should be considered as first-line therapy for most patients. Vitrification of oocytes and embryos has allowed for fertility preservation, and frozen embryo transfers have become the mainstay. Moreover, recent data suggest that natural cycle frozen embryo transfer cycles may have reduced risks of preeclampsia when compared with synthetic frozen embryo transfers (4). All of this begs the question of whether today's modern IVF carries the same pregnancy risks as fresh, cleavage-stage embryo transfers. Is it fair to hold today's ART guilty for the past crimes of a nascent field that was just coming to maturity when many of the studies we hold as gospel were written?

In this month's issue, Glatthorn et al. (5) present an intriguing look at the rate of small for gestational age infants after ART. Using a large, administrative database from the

National Center for Health Statistics of the Centers for Disease Control and Prevention, they offer a first glimpse into how modern ART practices may result in improved perinatal outcomes over prior treatments. In their study, a cohort of over 16 million singleton births from 2015 to 2019 were examined for the prevalence of ART treatments, and then the rates of small for gestational age infants were calculated. Using elegant statistical methods, the investigators attempted to control for misclassification bias, missing data, and confounding. The extremely large sample size carries significant statistical power. Glatthorn et al. (5) found that infertility treatments were associated with a 27% reduced risk of small for gestational age infants. It is unclear whether this is a causative effect or merely an association. This protective effect may be counterintuitive and requires further validation. However, it may be a reflection of how modern ART seeks to find the most viable embryos and give them the best environment in which to flourish.

There are limitations to their work, and much remains unanswered. There was a low prevalence of infertility treatments, less than 2%, which seems implausible given that infertility affects 1 in 8 couples. There is also no way to determine exactly what infertility treatments were used as the database relies on patient self-report and clinical data collection by the hospital staff at the time of delivery. Finally, there is no information about contributing factors and other maternal medical conditions which may have played a role in these findings. Nevertheless, the investigators should be commended for performing their study and opening our eyes to question what we thought was once dogma. Given the striking changes in modern ART practice, this highlights the fact that we should be reexamining many long-held assumptions that were found when our field was quite different.

Modern ART practice involves improved embryo culture and selection. While animal studies have raised concerns about the epigenetic effects of prolonged embryo culture, modern global media and time-lapse incubators have not been studied in the same way. Although we lack definitive markers for metabolic competence, ongoing research may soon make it possible to better understand which euploid embryos have the best chance for sustained implantations. The use of preimplantation genetic testing for aneuploidy has become widespread and offers the opportunity to select out euploid embryos and gives clinicians the impetus to move toward universal single embryo transfer. Finally, the refinement of vitrification techniques has made synchronous frozen embryo transfer a key component of ART that seeks to improve endometrial receptivity. Unfortunately, there is little data to suggest how these modern approaches to ART may change previous findings regarding obstetrical outcomes.

Prospective studies looking at obstetrical and neonatal records for children born after IVF should be the standard by which we all hold ourselves accountable. After all these years, there is still no registry for ART children in the United States for long-term follow-up. As physicians, we are bound by the Hippocratic oath of "do no harm," and it is true that the

vast majority of children born after ART are healthy. It is clear today that many of the prior studies were performed when ART was still in its infancy and far less efficient at achieving the outcome of one healthy baby at a time. We should celebrate how far our techniques have evolved and give ourselves a new opportunity to revisit these truths that we once held self-evident. Perhaps we will find that modern ART treatments are not only safer but also may offer advantages that we did not previously consider possible.

**Thomas A. Molinaro, M.D., M.S.C.E.**

Reproductive Medicine Associates of New Jersey, Basking Ridge, New Jersey

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