For the next 40 years of in vitro fertilization—let's sharpen our focus on iatrogenic harm reduction

For a relatively nascent field, reproductive medicine has made dramatic strides in improving pregnancy outcomes. The initial studies of *in vitro fertilization* (IVF) conducted in women undergoing natural menstrual cycles yielded on average 0.7 oocytes per retrieval and a 6% per cycle pregnancy rate (1). Forty-two years later, IVF accounts for millions of births worldwide and 1%–3% of all births every year in the U.S. and Europe. A more nuanced understanding of ovarian stimulation, a focus on the importance of the endometrium, and monumental improvements in the embryology lab have afforded our patients a chance at pregnancy that would have been impossible just a generation ago. As we garner data on delivery outcomes from pregnancies conceived through assisted reproductive technology (ART), it has become clear that this treatment modality is not a benign undertaking. While current treatment strategies allow our patients to achieve pregnancy easily than ever before, we must also remain aware of the increased iatrogenic obstetric risks associated with ART.

While the majority of IVF-conceived children are healthy, IVF has been associated with an increased risk of preterm birth, low birth weight, hypertensive disorders of pregnancy, and abnormal placentation (2). It has also become increasingly clear that these adverse outcomes cannot be completely attributed to the underlying infertility and are at least in part caused by discreet ART interventions. Recently, trophectoderm biopsy has been found to be associated with a threefold increase in the odds of preeclampsia, after controlling for relevant ART and maternal level variables (3). Furthermore, hormone replacement frozen embryo transfer cycles are being increasingly scrutinized as the absence of corpora lutea byproducts, such as relaxin, has been implicated in decidual dysregulation with downstream impacts on maternal cardiovascular function, growth restriction, preeclampsia, and abnormal placentation (4). The effects of ART on abnormal placentation are perhaps the most troubling as they are associated with significant morbidity and mortality in patients and neonates alike.

In this edition of *Fertility & Sterility,* Ganer Herman et al. (5) examine the difference in complications of the third stage of labor between spontaneous and ART conceived pregnancies. Utilizing a single center's delivery data, they retrospectively examined 1,264 IVF and 34,166 non-IVF singleton pregnancies for manual removal of the entire placenta, in cases it did not separate, and/or manual exploration of the uterine cavity, in cases of suspected retained products of conception following placental expulsion. They found that in the third stage of labor complications occurred twice as often (5.9 versus 2.8%, $P = .001$) in IVF deliveries as compared to that in spontaneous conceptions. Furthermore, they noted that there were no differences in the third stage of labor complications between pregnancies conceived via fresh versus frozen embryo transfer. While the reasons for these findings are likely multifactorial, the authors suggest that the third stage of labor pathologies in vaginal deliveries likely represent a downstream surrogate endpoint for abnormal trophoblast cell proliferation and invasion.

This study by Ganer Herman et al. (5) adds to a growing body of literature that suggests ART may be associated with increased obstetric complications. It is imperative that we, as a field, pay more attention to not only understanding where these risks are coming along the ART pathway but how we can better mitigate them. Vitrification, trophectoderm biopsy, hormone replacement embryo transfer cycles, and other laboratory techniques may offer small benefits to odds of conception, but at what increased maternal risk? Understanding and better delineating the discrete risks with ART interventions would be valuable not only for obstetricians managing ART conceived pregnancies but also for gestational carriers assuming the risks associated with these interventions. Unfortunately, given the fragmentation between ART centers and obstetric providers, these obstetric outcomes are difficult to ascertain and study. Academic medical centers, such as the one by Ganer Herman et al., are uniquely positioned to answer these important questions at the scale that is required to arrive at a true estimate of effect size. As access and success with ART continue to increase, it is now imperative that we sharpen our focus on better understanding the complications associated with ART interventions so that we can provide patients with the safest treatment options.

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