As the use of assisted reproductive technology has increased over time, there is increased attention on associated adverse obstetric outcomes. Some of these outcomes can be attributed to high rates of multiple gestation in pregnancies conceived with in vitro fertilization (IVF) as well as the fact that the maternal age of women pursuing IVF is, on average, older. In JAMA Network Open, Wang et al provide a thought-provoking comparison of obstetric and neonatal risks between singleton and twin pregnancies conceived with and without IVF in China, including more than 16 million pregnancies from 2013 to 2018 identified using a Hospital Quality Monitoring System. Of these pregnancies, 1.6% were conceived with IVF. The twin pregnancy rate was 32.1% in the IVF group (vs 1.5% in the non-IVF group). The authors reported rates of maternal adverse outcomes as well as neonatal complications, stratifying according to maternal age, singleton vs twin gestation, and whether IVF was used to achieve pregnancy.

Conception with IVF in and of itself was associated with increased rates of almost all reported adverse maternal and neonatal outcomes, including hypertensive diseases of pregnancy, gestational diabetes, placental disorders, cesarean delivery, and low birth weight deliveries. These risks persisted in IVF twin pregnancies, and, not surprisingly, rates were higher than in the singleton pregnancies. Rates of stillbirth were highest in non-IVF twin pregnancies and lowest in IVF singleton pregnancies. Compared with non-IVF users, a higher proportion of women of advanced maternal age were IVF users (28.8% vs 13.7%). The authors elegantly point out that almost all the obstetric and neonatal risks were compounded by increasing maternal age (illustrated in their Figure 2). Cesarean delivery rates were high in all groups, with 66.5% of singleton and 88.8% of twin pregnancies conceived via IVF resulting in cesarean delivery. The higher twin pregnancy rates with IVF use described in this study is likely due to transfer of multiple embryos, although this study was not able to report the number of embryos transferred. A recent national report on IVF cycles in China, encompassing the years 2013 to 2016, noted a mean of 1.87 embryos transferred in 2016. Many countries have implemented voluntary recommendations for elective single embryo transfer (eSET) in younger women or with preimplantation genetic testing of embryos. Higher rates of eSET adherence result in lower rates of multiple pregnancy. In the US, since the implementation of national recommendations, multiple rates have decreased. Japan has an enviable eSET rate of 82%, with a singleton live birth rate of 97%. As Wang et al point out in their discussion, no such guidelines or regulations exist in China.

There are significant health care costs associated with multiple pregnancy. In the US, twin births are approximately 5 times more expensive than singleton births owing to increased use of cesarean delivery and longer hospital stays for both the mother and the infants. It is an important public health message that many adverse outcomes and increased health care costs can be avoided with use of eSET.

Notably, there were still increased obstetric risks among singletons conceived with IVF compared with non-IVF pregnancies. Some of this risk is due to higher rates of chronic disease before pregnancy in women who conceived with IVF (eg, chronic hypertension, diabetes) and that more women were of advanced maternal age who conceived with IVF. However, these same risks persisted even in young women without chronic diseases. Therefore, although increasing eSET use will mitigate many obstetric and neonatal risks, questions remain about why risk persists with IVF alone. Of note, the authors were not able to report whether the transferred embryos were transferred in a fresh or frozen cycle or the type of endometrial preparation (eg, natural unmedicated cycle or
medicated cycle with exogenous hormone preparation). Increasing data suggest that the uterine environment in which embryos are transferred is responsible for some of the obstetric risks,\(^6\) with hormone-stimulated cycles imparting higher risks of preterm delivery, low-birth-weight infants, and hypertensive disorders of pregnancy.

Another important finding was the high cesarean delivery rate among all groups described in this study: 88.8% in the twin IVF group, 80.3% in the twin non-IVF group, 66.5% in the singleton IVF group, and 43.6% in the singleton non-IVF group.\(^1\) Globally, China has one of the highest rates of cesarean delivery, especially in urban areas, where the tertiary hospitals contributing to this study population are located. One prior study\(^7\) found a significant proportion of cesarean deliveries were performed without medical indication (eg, 14.9% on maternal request). Because cesarean deliveries have higher morbidity and longer associated hospital stays than vaginal deliveries, these rates of nonindicated cesarean delivery pose another health care challenge.

Although this study's large sample size and elegantly presented data are impressive, there are a couple of important limitations to discuss. As noted above, the study was limited in not being able to report the number of embryos transferred, whether the embryos were transferred in a fresh or a frozen cycle, and whether preimplantation genetic testing for aneuploidy was performed. Twin chorionicity and oocyte source (eg, donor or autologous) were also not reported; these are both potential contributors to obstetric and neonatal morbidity. In addition, only patients who delivered at tertiary hospitals in China were considered, and non-Chinese women and women living in Hong Kong, Macao, and Taiwan were excluded in the analysis. These exclusions potentially limit the generalizability of the findings, because high-risk patients and those with worse obstetric complications are more likely to be seen in a tertiary hospital. Further studies on an expanded patient population with the inclusion of additional IVF-specific data points would help improve our understanding of maternal and neonatal risks associated with IVF, twin pregnancies, and cesarean deliveries.

**ARTICLE INFORMATION**


Open Access: This is an open access article distributed under the terms of the CC-BY License. © 2021 Diego D et al. JAMA Network Open.

**Corresponding Author:** Heather S. Hipp, MD, Division of Reproductive Endocrinology and Infertility, Department of Gynecology and Obstetrics, Emory University School of Medicine, 550 Peachtree St, Ste 1800, Atlanta, GA 30308 (hhipp@emory.edu).

**Author Affiliations:** Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta, Georgia (Diego); Division of Reproductive Endocrinology and Infertility, Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta, Georgia (Hipp).

**Conflict of Interest Disclosures:** None reported.

**REFERENCES**


