ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Perinatal outcomes among singletons after assisted reproductive technology with single-embryo or double-embryo transfer versus no assisted reproductive technology

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Objective: To examine outcomes of singleton pregnancies conceived without assisted reproductive technology (non-ART) compared with singletons conceived with ART by elective single-embryo transfer (eSET), nonelective single-embryo transfer (non-eSET), and double-embryo transfer with the establishment of 1 (DET −1) or ≥2 (DET ≥2) early fetal heartbeats.
Design: Retrospective cohort using linked ART surveillance data and vital records from Florida, Massachusetts, Michigan, and Connecticut.
Setting: Not applicable.
Patient(s): Singleton live-born infants.
Intervention(s): None.
Main Outcome Measure(s): Preterm birth (PTB <37 weeks), very preterm birth (VPTB <32 weeks), small for gestational age birth weight (<10th percentile), low birth weight (LBW <2,500 g), very low birth weight (VLBW <1,500 g), 5-minute Apgar score <7, and neonatal intensive care unit (NICU) admission.
Result(s): After controlling for maternal characteristics and employing a weighted propensity score approach, we found that singletons conceived after eSET were less likely to have a 5-minute Apgar <7 (adjusted odds ratio [aOR] 0.33; 95% CI, 0.15–0.69) compared with non-ART singletons. There were no differences among outcomes between non-ART and non-eSET infants. We found that PTB, VPTB, LBW, and VLBW were more likely among DET −1 and DET ≥2 compared with non-ART infants, with the odds being higher for DET ≥2 (PTB aOR 1.58; 95% CI, 1.09–2.29; VPTB aOR 2.46; 95% CI, 1.20–5.04; LBW aOR 2.17; 95% CI, 1.24–3.79; VLBW aOR 3.67; 95% CI, 1.38–9.77).
Conclusion(s): Compared with non-ART singletons, singletons born after eSET and non-eSET did not have increased risks whereas DET −1 and DET ≥2 singletons were more likely to have adverse perinatal outcomes. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Assisted reproductive technology, double-embryo transfer, elective single-embryo transfer, in vitro fertilization, perinatal outcomes

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Several studies have found singletons born to women with infertility after use of assisted reproductive technology (ART) to have worse perinatal outcomes than singletons conceived without ART, even after controlling for potential confounding variables such as maternal age, body mass index (BMI), tobacco use, and parity (1–4). Among ART singletons, risks of growth restriction and preterm birth have been shown to increase with an increasing number of embryos transferred and number of fetal heartbeats established (5–7). Furthermore, there have been studies demonstrating an increased risk of growth restriction and preterm birth after early fetal loss of a cotwin (8, 9).

If adverse outcomes among singleton gestations after ART are partly due to the transfer of more than one embryo or a vanishing twin, we would expect adverse perinatal outcomes among singletons after double-embryo transfer (DET) to be increased compared with singletons in the general population conceived without ART. Furthermore, we would expect singletons born after single-embryo transfer (SET) to be similar to those conceived in the general population without ART. Studies that have compared non-ART to SET infants are limited. Studies from Finland and Sweden have suggested a modest increased risk of preterm birth and low birth weight for singletons born after SET compared with singletons in the general population (10, 11).

Single-embryo transfer can be elective (eSET), defined as the transfer of only one embryo when more than one high-quality embryo is available, or nonelective, the transfer of only one embryo because only one embryo is available. This distinction is important as the nonelective SET group likely represents a population in which the poor response to ovarian stimulation or inability to grow more than one acceptable embryo for transfer may represent an underlying pathology that predisposes these women and their fetuses to worse outcomes. Although the distinction between elective and nonelective SET is not always made in the existing literature, there is some evidence to suggest that eSET singletons also have an increased risk of preterm birth (11, 12) and low birth weight (12) compared with those conceived spontaneously.

We compared perinatal outcomes among singletons born without the use of ART (non-ART) to singletons born after eSET, after single-embryo transfer that was not considered elective (non-eSET), and after DET with the establishment of one early fetal heartbeat (DET −1) or two or more early fetal heartbeats (DET ≥2). We hypothesized that risk of adverse perinatal outcomes will be similar between non-ART and eSET but will increase in a stepwise fashion for each of the following groups: non-eSET, DET −1, and DET ≥2, respectively.

MATERIALS AND METHODS

We performed a retrospective cohort analysis of data from the States Monitoring Assisted Reproductive Technology (SMART) collaborative database that has been described previously elsewhere (13). Briefly, the SMART collaborative was formed to examine ART-related health outcomes in infants and mothers. Data from the National ART Surveillance System (NASS) are linked with states' vital records files and hospital discharge data with a probabilistic linkage methodology using the mother's date of birth, infant's date of birth, plurality, gravidity, and zip code. This method has been validated and found to be both accurate and efficient with a linkage rate of 90.2% for SMART data (13). At the time of this analysis, Connecticut, Florida, Massachusetts, and Michigan were the states included in the SMART database with data ready to analyze. This study was approved by the institutional review boards of the Centers for Disease Control and Prevention (CDC) and the Massachusetts Department of Public Health. The study was reviewed by the Michigan Department of Health and Human Services and was determined not to be human subjects research because all data are deidentified. Connecticut and Florida do not require state-specific institutional review board approval of studies using data contained within the CDC.

All singleton live births in SMART were identified using birth certificates from Connecticut, Florida, Massachusetts, and Michigan between 2000 and 2010. Deliveries were considered non-ART if they could not be linked to the NASS database, suggesting they were not conceived with ART. To minimize confounding, ART deliveries were restricted to fresh, nondonor cycles, and gestational carriers were excluded. All fresh, nondonor cycles were included, regardless of whether preimplantation genetic screening or diagnosis was performed.

We defined eSET as having one embryo transferred and ≥1 embryo cryopreserved from the same cycle as reported in NASS. We compared the demographics among women who delivered a singleton conceived without ART (non-ART) with the women who underwent eSET, non-eSET, DET −1, and DET ≥2 including maternal age, race/ethnicity, tobacco use, history of chronic hypertension, education, marital status, maternal BMI, history of prior live birth, state of delivery, and year of delivery. Demographic variables were obtained from birth certificates and the NASS database for ART deliveries. Because maternal BMI was poorly recorded on birth certificates in Connecticut and was not recorded in Florida before 2005, Michigan before 2008, or Massachusetts before 2011, the BMI data in Table 1 are restricted to Florida and Michigan, 2008 to 2010.

Among ART deliveries we also compared infertility diagnosis, number of prior ART cycles, number of oocytes retrieved, number of embryos cryopreserved, and stage of embryo transfer. The comparisons of the distribution of these characteristics were made using chi-square and Fisher exact tests. The primary outcomes included preterm birth (<37 weeks), very preterm birth (<32 weeks), small for gestational age (<10 percentile), low birth weight (<2,500 g), very low birth weight (<1,500 g), 5-minute Apgar score <7, and admission to the neonatal intensive care unit (NICU). The NICU admissions were not collected in Connecticut or Massachusetts, and were not collected in Florida and Michigan before 2005. Therefore, the results for admission to the NICU are only among deliveries in Florida and Michigan, 2005 to 2010.

In this study, we employed a weighted propensity score approach to correct for estimation bias (14), which was