Adverse pregnancy and birth outcomes associated with underlying diagnosis with and without assisted reproductive technology treatment

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Objective: To compare the risks for adverse pregnancy and birth outcomes by diagnoses with and without assisted reproductive technology (ART) treatment to non-ART pregnancies in fertile women.
Design: Historical cohort of Massachusetts vital records linked to ART clinic data from Society for Assisted Reproductive Technology Clinic Outcome Reporting System.
Setting: Not applicable.
Patient(s): Diagnoses included male factor (ART only), endometriosis, ovulation disorders, tubal (ART only), and reproductive inflammatory disorders (non-ART only). Pregnancies resulting in singleton and twin live births from 2004 to 2008 were linked to hospital discharges in women who had ART treatment (n = 3,689), women with no ART treatment in the current pregnancy (n = 4,098), and non-ART pregnancies in fertile women (n = 297,987).
Intervention(s): None.
Main Outcome Measure(s): Risks of gestational diabetes, prenatal hospitalizations, prematurity, low birth weight, and small for gestational age were modeled using multivariate logistic regression with fertile deliveries as the reference group adjusted for maternal age, race/ethnicity, education, chronic hypertension, diabetes mellitus, and plurality (adjusted odds ratios [AORs] and 95% confidence intervals [CIs]).
Result(s): Risk of prenatal hospital admissions was increased for endometriosis (ART: 1.97, 1.38–2.80; non-ART: 3.34, 2.59–4.31), ovulation disorders (ART: 2.31, 1.81–2.96; non-ART: 2.56, 2.05–3.21), tubal factor (ART: 1.51, 1.14–2.01), and reproductive inflammation (non-ART: 2.79, 2.47–3.15). Gestational diabetes was increased for women with ovulation disorders (ART: 2.17, 1.72–2.73; non-ART: 1.94, 1.52–2.48). Preterm delivery (AORs, 1.24–1.93) and low birth weight (AORs, 1.27–1.60) were increased in all groups except in endometriosis with ART.
Conclusion(s): The findings indicate substantial excess perinatal morbidities associated with underlying infertility-related diagnoses in both ART-treated and non-ART-treated women. (Fertil Steril® 2015;103:1438–45. ©2015 by American Society for Reproductive Medicine.)
Key Words: ART, endometriosis, ovulatory disorder, pregnancy outcome, preterm delivery, low birth weight

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Assisted reproductive technology (ART) has been used to assist couples to have children for more than 3 decades. In recent years, evidence has emerged that ART pregnancies are at an increased risk of adverse outcomes. Demonstrated risks have included increased rates of prematurity and low birth weight as well as an increase in infants born small for

gestational age (1–3). ART-assisted pregnancies have been shown to have increased risk of preeclampsia, gestational diabetes, and bleeding disorders (4–6). Much of the increased risk with ART results from multiple gestation (7), however, risks are increased even in singleton pregnancies (2). The reasons for the increase in adverse outcomes with ART are not known. One hypothesis is that they result from the ART procedure itself and are caused by medications used to stimulate multiple ovulations, manipulations of gametes, in vitro culture, transfer of multiple embryos, or other treatment-related phenomena. Another strong possibility is that underlying infertility-related diagnoses of the women who undergo ART contribute directly to the adverse outcomes. Distinguishing between these possibilities is complicated by the fact that many studies compare ART pregnancies with those of fertile women rather than with those of infertile women who did not undergo ART.

We addressed the question of whether adverse ART outcomes arise from ART treatment or underlying infertility-related diagnoses using data from the Massachusetts Outcome Study of Assisted Reproductive Technology (MOSART) that uses linked data from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) database and the Pregnancy to Early Life Longitudinal (PELL) data system, a vital statistics data system. The goal of this study was to compare the risks for adverse pregnancy and birth outcomes by infertility-related diagnoses with and without ART treatment to pregnancies in a fertile population.

METHODS

Study Design and Setting

This historical cohort study included 305,774 pregnancies resulting in singleton and twin live-birth deliveries that took place between July 1, 2004, and December 31, 2008, in Massachusetts. To identify ART pregnancies, ART cycles from the SART CORS were linked to Massachusetts vital records in the PELL data system.

Data Sources

The SART CORS. The SART CORS database is used by SART to collect national ART data under the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102-493) and to report these data to the CDC. SART CORS data include patient demographic information, cycle-specific treatment data, and outcome data. Data are validated annually through review by SART and the Centers for Disease Control and Prevention (CDC).

The PELL data system. Birth certificate data and hospital discharge data were obtained from the PELL data system. The PELL database was developed as a collaborative effort between the Massachusetts Department of Public Health, the CDC, and Boston University School of Public Health and links vital records from birth and fetal death certificates, hospital discharges, and program data from child health and development programs.

MOSART. The MOSART is a project developed to link data from the SART CORS to PELL with the goal of evaluating pregnancy, child health, and women's health outcomes on a population basis. Before performing the linkage, a Memorandum of Understanding was executed between SART and the three entities that participate in the PELL project. Human subjects approval was obtained from all entities and participating universities. The study had the approval of the SART Research Committee.

Participants

Pregnancies resulting in live-birth deliveries between July 1, 2004, and December 31, 2008, to women and men older than age 18 were classified as ART if the birth certificate linked to a SART CORS outcome using mother's first and last name, mother's date of birth, father's name, race of both parents, date of delivery, and number of babies born per delivery. Methods for linkage have been described elsewhere (8) and resulted in a linkage rate of 89.7% overall and 95.0% for deliveries in which both ART cycle patient zip code and treatment clinic were located in Massachusetts. The linkage yielded deliveries identified for this study as ART deliveries. The linkage identifies live births and fetal deaths but could not identify early pregnancies within the PELL data system. The fetal deaths were not included as they represented less than 1% of deliveries and suppression rules required for use of vital records data in Massachusetts would have prevented us from distinguishing the fetal deaths from the live births in the data set.

Diagnosis groups for ART-treated deliveries were identified through the diagnosis fields reported to SART CORS and included male factor (n = 1,901), endometriosis (n = 406), ovulatory disorders (n = 676), and tubal disease (706). Of those with tubal disease, 7% had tubal ligation, 7% had hydrosalpinx, and the rest had other forms of tubal disease. Diagnosis groups for women who did not undergo ART were identified from Massachusetts deliveries. Women whose deliveries were not linked to SART CORS were included in the non-ART group if they had one or more hospital encounters (admissions, observational stays, or emergency room visits) of endometriosis (ICD-9 codes 617.0, 617.1, 617.2, 617.3, 617.9; n = 590), ovulatory disorders (ICD-9 codes 256.1, 256.39, 256.4, 256.8, 256.9, 626.4, 626.8; n = 833), or reproductive inflammation, a category in which we included both reproductive tract (uterus, fallopian tube, ovary) and pelvic inflammatory conditions (ICD-9 codes 614.0, 614.1, 614.2, 614.3, 614.4, 614.5, 614.8, 614.9; n = 2,675). Patients were included in one of the above ART-treated and non-ART treated groups if they had a single diagnosis only; patients with multiple infertility-related diagnoses were excluded. Deliveries to fertile women (n = 297,987) were identified as not being in either of the two above groups and not having been included in a previously defined subfertile group (9). All groups were limited to singleton and twin deliveries of $\geq$20 weeks' gestation with birth weights between 350 g and 8,165 g to mothers age 18 or older with a single diagnosis.

Variables

The pregnancy and birth outcomes analyzed included maternal morbidity (pregnancy hypertension and gestational diabetes), prenatal hospital utilization (emergency room visits, observational stays, and hospital admissions), delivery