OBSTETRICS

Pregnancy, birth, and infant outcomes by maternal fertility status: the Massachusetts Outcomes Study of Assisted Reproductive Technology

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BACKGROUND: Births to subfertile women, with and without infertility treatment, have been reported to have lower birthweights and shorter gestations, even when limited to singletons. It is unknown whether these decrements are due to parental characteristics or aspects of infertility treatment.

OBJECTIVE: The objective of the study was to evaluate the effect of maternal fertility status on the risk of pregnancy, birth, and infant complications.

STUDY DESIGN: All singleton live births of ≥22 weeks' gestation and ≥350 g birthweight to Massachusetts resident women in 2004—2010 were linked to hospital discharge and vital records. Women were categorized by their fertility status as in vitro fertilization, subfertile, or fertile. Women whose births linked to in vitro fertilization cycles from the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System were classified as in vitro fertilization. Women with indicators of subfertility but not treated with in vitro fertilization were classified as subfertile. Women without indicators of subfertility or in vitro fertilization treatment were classified as fertile. Risks of 15 adverse outcomes (gestational diabetes, pregnancy hypertension, antenatal bleeding, placental complications [placenta abruptio and placenta previa], prenatal hospitalizations, primary cesarean delivery, very low birthweight [<1500 g], low birthweight [<2500 g], small-for-gestation birthweight [z-score ≤−1.28], large-for-gestation birthweight [z-score ≥1.28], very preterm [<32 weeks], preterm [<37 weeks], birth defects, neonatal death [0—27 days], and infant death [0—364 days of life]) were modeled by fertility status with the fertile group as reference and the subfertile group as reference, using multivariate log binomial regression and reported as adjusted risk ratios and 95% confidence intervals.

RESULTS: The study population included 459,623 women (441,420 fertile, 8054 subfertile, and 10,149 in vitro fertilization). Women in the

subfertile and in vitro fertilization groups were older than their fertile counterparts. Risks for 6 of 6 pregnancy outcomes and 6 of 9 infant outcomes were increased for the subfertile group, and 5 of 6 pregnancy outcomes and 7 of 9 infant outcomes were increased for the in vitro fertilization group. For 4 of the 6 pregnancy outcomes (uterine bleeding, placental complications, prenatal hospitalizations, and primary cesarean) and 2 of the infant outcomes (low birthweight and preterm) the risk was greater in the in vitro fertilization group, with nonoverlapping confidence intervals to the subfertile group, indicating a substantially higher risk among in vitro fertilization—treated women. The highest risks for the in vitro fertilization women were uterine bleeding (adjusted risk ratio, 3.80; 95% confidence interval, 3.31—4.36) and placental complications (adjusted risk ratio, 2.81; 95% confidence interval, 2.57—3.08), and for in vitro fertilization infants, very preterm birth (adjusted risk ratio, 2.13; 95% confidence interval, 1.80—2.52), and very low birthweight (adjusted risk ratio, 2.15; 95% confidence interval, 1.80—2.56). With subfertile women as reference, risks for the in vitro fertilization group were significantly increased for uterine bleeding, placental complications, prenatal hospitalizations, primary cesarean delivery, low and very low birthweight, and preterm and very preterm birth.

CONCLUSION: These analyses indicate that, compared with fertile women, subfertile and in vitro fertilization—treated women tend to be older, have more preexisting chronic conditions, and are at higher risk for adverse pregnancy outcomes, particularly uterine bleeding and placental complications. The greater risk in in vitro fertilization—treated women may reflect more severe infertility, more extensive underlying pathology, or other unfavorable factors not measured in this study.

Key words: adverse pregnancy outcomes, assisted reproductive technology, infertility, subfertility

The outcomes of pregnancies to subfertile women, with and without infertility treatment, have been reported to have more complications, lower birthweights, and shorter

gestations, even when limited to singleton births.[1-8] There is continued scientific debate regarding the role of parental characteristics, including the etiology of the subfertility[9-12] vs the effect of specific infertility treatments[13-23] in suboptimal outcomes in these women.

In addition, an acknowledged drawback of prior in vitro fertilization (IVF) research in the United States has been the self-reported nature of the outcomes data, which are typically provided by the patient herself or by her obstetrical provider.

This study seeks to overcome these limitations by linking the Society for Assisted Reproductive Technology (SART) Clinic Outcomes Reporting System (CORS) data to birth certificate and hospital utilization data as well as accounting for fertility status. This analysis is part of a larger population-based study of IVF in Massachusetts.[11,24-39]

The first analysis of perinatal outcomes from the Massachusetts Outcome Study of Assisted Reproductive Technology (MOSART) was based on singleton and twin births in 2004—2008

and examined 4 adverse outcomes: preterm birth, low birthweight, small for gestational age, and perinatal death.[30]. In this analysis, based on births in 2004—2010, we have increased the sample size by nearly 50% (singleton births from 320,135 to 459,623), expanded the number of adverse outcomes from 4 to 15 (6 maternal and 9 infant), and separated the analysis by plurality, with the results in singletons presented in this paper and the results for twins (further divided by like sex and unlike sex pairs) in a subsequent paper.[40]

This analysis was repeated and expanded to clarify associations and to further identify factors that may be in the pathway between fertility status, treatment, and perinatal outcomes. The objective of this current analysis was to evaluate the effect of maternal fertility status (fertile, subfertile, or IVF) on the pregnancy and birth outcomes in singleton live births.

Materials and Methods
Study design and setting
This longitudinal cohort study included all women with singleton live births of ≥22 weeks' gestation and ≥350 g birthweight in Massachusetts from July 1, 2004, through Dec. 31, 2010. As a project within the Massachusetts Department of Public Health, the Pregnancy to Early Life Longitudinal (PELL) system links records from birth certificates, hospital discharges, and program data from child health and development programs.

Data sources
The PELL data system
The PELL system has linked information on more than 99% of all births and fetal deaths in Massachusetts from 1998 through 2010 to the corresponding hospital utilization data (hospital admissions, observational stays, and emergency room visits) for individual women and their children, including 1,004,320 deliveries. The Massachusetts Department of Public Health and the Massachusetts Center for Health Information and Analysis are the custodians of the PELL data system, composed of individual databases linked together by randomly generated unique identifications for mother and infant.

The Society for Assisted Reproductive Technology Clinic Online Data Reporting System
The data source for IVF data for this study was the SART CORS, which contains comprehensive data from more than 83% of all clinics performing IVF and more than 91% of all IVF cycles in the United States.[41] Data are collected and verified by SART and reported to the Centers for Disease Control and Prevention in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102-493).

SART maintains the Health Insurance Portability and Accountability Act—compliant business associates agreements with reporting clinics. In 2004, following a contract change with Centers for Disease Control and Prevention, SART gained access to the SART CORS data system for the purposes of conducting research. The national SART CORS database for 2004—2010 contains 930,957 IVF treatment cycles. The data in the SART CORS are validated annually,[42] with some clinics having on-site visits for chart review based on an algorithm for clinic selection.

Massachusetts Outcome Study of Assisted Reproductive Technology
The MOSART project links data from the SART CORS with the PELL data system to evaluate pregnancy and child health outcomes on a population basis. Human subjects approval was obtained from Boston University, Massachusetts Department of Public Health, Dartmouth College, and Michigan State University. The study also had the approval of the SART Research Committee.

We constructed the MOSART database by linking the SART CORS and PELL data systems for all Massachusetts births to Massachusetts resident women between July 1, 2004, and Dec. 31, 2010. The starting date was chosen based on the availability of SART CORS data (Jan. 1, 2004) to allow us to capture any births associated with IVF, and the end date reflected the latest available linked data of the SART CORS to PELL.

A deterministic 5 phase linkage algorithm methodology was implemented[24] using the mother's first and last name, the mother's date of birth, the father's name, the race of both parents, the date of delivery, and the number of babies born per delivery. Linked files were later identified by the use of a linkage identification from which identifiers were removed. The linkage rate was 89.7% overall and 95.0% for deliveries in which both ZIP code and clinic were located in Massachusetts. The linkage yielded pregnancies and deliveries identified for this study as the IVF group.

We identified a subfertile group as previously described.[26] Briefly, all Massachusetts deliveries were reviewed for the answer to 2 questions on the Massachusetts birth certificate about use of fertility drugs and assisted reproduction. Those who answered yes to either or both of these questions and had not been identified in the SART CORS linkage were included as subfertile.

In addition, any woman who at delivery, or in the 5 years previous to delivery, had been hospitalized with a discharge code of female infertility (International Classification of Diseases, ninth revision [ICD-9] diagnosis code 628.0; infertility-anovulation, 628.2; infertility-tubal origin, 628.3; infertility-uterine origin, 628.8; female infertility of other specified origin, 628.9; female infertility of unspecified origin or Current Procedural Terminology procedural code V230; pregnancy with diagnosis of infertility) was also included as part of the subfertile group if they were not in the SART CORS linkage. Deliveries not in either the subfertile or IVF groups were listed as fertile.

Variables
Independent variables included parental ages, race and ethnicity, education, and payor status at delivery; parity (nulliparous and parous), smoking, maternal prepregnancy medical conditions (chronic hypertension and diabetes mellitus); and repeat cesarean delivery and infant sex (Table 1).