Assisted reproductive technology and the risk of preterm birth among primiparas

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Objective: To investigate the risk of preterm birth among liveborn singletons to primiparas who conceived with assisted reproductive technology (ART) using four mutually exclusive categories of infertility (female infertility only, male infertility only, female and male infertility, and unexplained infertility) and to examine preterm birth risk along the gestational age continuum.

Design: Retrospective cohort study.

Setting: Not applicable.

Patient(s): Singletons born to primiparas who conceived with or without ART.

Intervention(s): None.

Main Outcome Measure(s): Preterm (<37 weeks' gestation) and preterm/early term birth <39 weeks' gestation).

Result(s): For the male infertility only, female infertility only, combined male and female infertility, and unexplained infertility groups, ART-conceived singletons were significantly more likely than non-ART singletons to be born preterm: adjusted odds ratio (aOR) 1.24 (95% CI, 1.13, 1.37), aOR 1.60 (95% CI, 1.50, 1.70), aOR 1.49 (95% CI, 1.35, 1.64), and aOR 1.26 (1.12, 1.43) respectively. Among infants whose mothers were diagnosed with infertility, the odds of preterm birth were highest between 28–30 weeks [female infertility only, aOR 1.95 (95% CI, 1.59, 2.39); male and female infertility: 2.21 (95% CI, 1.62, 3.00)] compared with infants in the general population. Within the ART population, singletons of couples with female infertility only were more likely to be born preterm than singletons born to couples with other infertility diagnoses.

Conclusion(s): Among singleton births to primiparas, those conceived with ART had an increased risk for preterm birth, even when only the male partner had been diagnosed with infertility. The risk of preterm birth for ART-conceived infants whose mothers were diagnosed with infertility included the earliest deliveries. (Fertil Steril® 2015;103:974–9. ©2015 by American Society for Reproductive Medicine.)

Key Words: Assisted reproductive technology (ART), infertility, preterm birth

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http://dx.doi.org/10.1016/j.fertnstert.2015.01.015

Assisted reproductive technology (ART) is a group of medical procedures for treating infertility in which both male and female gametes are handled outside the body to achieve conception. Since its introduction in 1978, ART has contributed to the birth of more than 5 million infants worldwide (1). In 2009, European registries reported that 109,239 infants were born after ART (2); in the United States, a total

of 61,564 infants were born in 2010, representing, on average, 1.5% of its total births (3).

Although ART may help infertile couples achieve pregnancy, it also presents a public health challenge because of the reported associations with adverse birth outcomes such as preterm birth (PTB), low birth weight, and small for gestational age (GA) (4–6). Multifetal pregnancies are common in pregnancies achieved through ART (3) and are an important risk factor for PTB (7, 8). However, the association between ART and PTB is also observed in singletons (9, 10). Numerous studies have found a twofold risk increase for PTB in ART-conceived compared with non-ART conceived singleton pregnancies (5, 11). The explanation for this ART-PTB association remains unclear; the effect may be fully or partially confounded by other factors such as causes of the underlying infertility. One of the methodologic limitations of previous studies has been the composition of the control group, typically non-ART pregnancies.

The comparison of non-ART pregnancies with ART pregnancies does not provide an opportunity to disentangle effects associated with infertility versus effects of ART treatment. A recent meta-analysis (12) reported that a history of infertility among couples who conceived spontaneously is associated with a moderate risk for PTB, low birth weight, and small for GA. These results reinforce the problem of confounding by fertility-associated factors and demonstrate the need for alternative approaches to try and assess more specifically the effects of ART on adverse birth outcomes.

To elucidate the link of ART to adverse birth outcomes, we used data from the States Monitoring Assisted Reproductive Technology (SMART), a collaborative project of ART surveillance initiated by the Centers for Disease Control and Prevention (CDC) and the Massachusetts, Florida, and Michigan public health agencies. As previously described elsewhere (13), the SMART Collaborative was established to monitor and enhance ART surveillance within states and to study health outcomes among ART users. The SMART data set has been previously described. Briefly, it is a population-based data set of vital records of Massachusetts, Michigan, and Florida probabilistically linked to the National ART Surveillance System (NASS) data of all ART-associated deliveries (14).

The goals of our study were to [1] confirm previous investigations linking increased PTB risk with ART among singleton pregnancies, [2] extend this line of inquiry by considering whether excess PTB risk is confined to couples with female infertility, and [3] examine the ART-related excess risk of PTB across the GA continuum.

MATERIALS AND METHODS

We used a subset of SMART Collaborative data, with all singleton live births to primiparous women occurring in Massachusetts and Florida between the years 2000–2010 and Michigan 2000–2009 to examine GA at birth across study groups. We restricted the data set to primiparous women with singleton deliveries to avoid including multiple live births to the same woman, which would have resulted in correlated, nonindependent data. We excluded deliveries of women younger than 15 years of age and women older

than 60 years because of the lack of comparable ART and non-ART groups, respectively.

Details on infertility diagnosis are part of the NASS data set and were used in the linked data file to create five mutually exclusive groups based on ART status and reason for infertility among ART patients: non-ART (n = 1,804,100), ART female infertility (n = 9,891), ART male infertility (n = 4,819), ART combined (male and female) infertility (n = 3,688), and ART unexplained infertility (n = 2,930). The outcome of interest, GA at birth, was based on the clinical estimate obtained from birth files.

To avoid small cell sizes in contingency tables, our adjusted models included collapsed race/ethnicity and education categories. Race/ethnicity categories of Hispanic and Asian/other were grouped into one, and similarly, both categories of "high school diploma or GED" and "less than high school education" were merged.

Initial analyses were conducted by comparing sociodemographic and pregnancy-relevant factors among the ART and non-ART groups with the purpose of identifying potential confounders. We used basic inferential statistical methods such as t test, chi-square, and linear regression models. In the logistic regression models, odd ratios were calculated for PTB (<37 weeks' gestation) and preterm/early term births (<39 weeks' gestation). Binary logistic regression models compared PTB odds for each ART subgroup with that of non-ART births. The male infertility only group was of particular interest as a means of examining ART outcomes in the absence of female infertility.

To gain more insight into the distribution of PTB risk, we further subclassified GA into five and six categories, with ≥37 and >39 weeks as the referent for PTB and preterm/early term birth, respectively. This strategy recognizes both uncertainties in GA dating and recent concerns for adverse outcomes even among early term births (37–38 weeks' gestation) (15). Recently, the American College of Obstetricians and Gynecologists suggested new definitions for full-term births as ≥39 to <41 gestation weeks (16).

Using multinomial logistic regression models, we next studied the odds of preterm (<37 weeks) versus term (≥37 weeks) birth along the continuum of preterm GA (<28, 28–30, 31–33, and 34–36 weeks) as well as the odds of preterm/early term (<39 weeks) birth along the GA continuum of <28, 28–30, 31–33, 34–36, and 37–38 weeks relative to ≥39 weeks' gestation. Finally, we evaluated the association between the infertility diagnosis and PTB among ART births, using female infertility as the referent. This comparison was of particular interest as a means of assessing the likelihood of PTB according to infertility type among a subfertile population. Crude and adjusted odds ratios and 95% confidence intervals were calculated (SAS 9.3; SAS Institute); all adjusted models included maternal age, education, race, state, and year, which were derived from the birth certificate data. The study received approval from the institutional review boards of Massachusetts, Michigan, Florida, and the CDC.

RESULTS

During the study period there were 21,328 (1.2%) singleton deliveries to primiparous ART users and 1,804,100 (98.8%)