Low-technology assisted reproduction and the risk of preterm birth in a hospital-based cohort

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Objective: To estimate the risk of preterm birth in singleton infants conceived through low-technology assisted reproduction (intrauterine insemination and/or ovulation induction/stimulation).
Design: Hospital-based cohort study.
Setting: University-affiliated hospital.
Patient(s): Singleton babies born between 2001 and 2007 to 16,712 couples with no reported infertility (reference category), 378 babies conceived with low-technology treatment; 437 conceived with high-technology treatment; and 620 conceived naturally after a period of infertility.
Intervention(s): None. Treatment data were obtained from couples undergoing standard infertility investigation and care.
Main Outcome Measure(s): Preterm birth, defined at three clinical endpoints: <37, <35, and <32 weeks of completed gestation.
Result(s): After adjustment for age, parity, education, smoking, alcohol/drug use, and body mass index, the risk ratios and 95% confidence intervals (CI) of preterm birth for low technology were: 1.49 (CI: 1.12–2.00); 2.02 (CI: 1.30–3.13); and 2.93 (CI: 1.63–5.26) at <37, <35, and <32 weeks gestation, respectively, not dissimilar from the estimates for in vitro fertilization. Restricting the analysis to primiparas strengthened the association between treatment and preterm birth at the lower gestational endpoints. The increased risk persisted when the untreated group was used as the reference category, although the estimates were attenuated.
Conclusion(s): In this large hospital-based cohort study, low-technology assisted reproduction appeared to be a moderately strong predictor of preterm birth, with similar associations observed in the high-technology treatment group. After adjusting for confounders, as well as the shared characteristics of infertile couples, associations were attenuated but remained significant, suggesting that part of the risk is likely attributable to the treatment. (Fertil Steril® 2015;103: 81–8. ©2015 by American Society for Reproductive Medicine.)
Key Words: Assisted reproduction, infertility, intrauterine insemination, ovulation induction, preterm birth

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Worldwide, nearly 5 million babies have been born through assisted reproductive technology (ART) since 1978, representing between 1% and 4% of all births (1, 2). Although many more infants are conceived with non-ART procedures, such as ovulation induction and intrauterine insemination (IUI), the population surveillance is uncommon, and the full extent of their use is unknown (3). It has, however, been estimated that ovulation induction alone accounts for two to six times more births than ART in the United States (3), making medically assisted reproduction an important public health issue.

Extensive research has been performed on the health of ART-conceived children over the last two decades. Findings have consistently shown that babies born as a result of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) are at increased risk of adverse outcomes, including preterm birth (4–18). Although more recent studies suggest that the overall risks associated with ART have declined in younger cohorts (14), singleton pregnancies remain at a higher risk of

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complication (7, 10, 13, 14, 17–19). Furthermore, a substantial body of evidence suggests that couples conceiving naturally after a long time to pregnancy (TTP) are also at increased risk of preterm birth (14, 20). Most research has focused on IVF-based technologies, but studies examining the risk of infertility itself by examining the naturally conceived pregnancies have not always been able to rule out non-IVF based treatment, and in particular, the use of pharmacotherapeutic ovulation induction agents prescribed outside a reproductive clinic setting (3, 14, 20).

"Low" technology treatments, such as ovulation induction or ovarian stimulation protocols (OS), alone or combined with IUI, are extensively relied upon as first-line methods in assisted reproduction (21, 22). Considering their widespread use and the number of babies born as a result of these procedures (3), there is comparatively little research examining their effect on pregnancy outcomes (14).

In this study, we estimate the risk of preterm birth in singleton infants conceived after different categories of treatment exposure compared with a reference group with no reported infertility. In particular, we investigate the risk associated with low-technology assisted reproduction (IUI and/or OS) as fewer studies exist on their potential effect on perinatal outcomes such a preterm birth.

MATERIALS AND METHODS

Study Population and Data

We assembled a hospital-based cohort of births from women residing in Montreal, Canada, who delivered at a large tertiary-care hospital from April 2001 to September 2007. Data were based on the hospital's extensive maternal and neonatal database (MOND) with virtually complete records for all live births and stillbirths (the latter recorded only if >500 g). The MOND included 25,198 records during the study period. We used a priori exclusion and inclusion criteria to reduce bias and confounding due to the hospital-based design. We excluded the following: high-risk referral pregnancies and births, women residing outside the city, women ≤20 and ≥45 years of age, and those with comorbidities known to be associated with both ART and preterm birth (see Supplemental Fig. 1, available online, for cohort formation). Twins and higher order multiples were also excluded, as preterm birth is very common among twins.

To complement the infertility information in MOND, we identified those women who had attended the hospital's reproductive clinic and had given birth within 36 months of their initial clinic appointments. We only requested a sample of charts (908 of 1,382) as the primary objective of the selection process was to obtain only those charts whereby we had missing information on the underlying cause of infertility in MOND. We obtained 839 of the requested medical charts, resulting in 1,050 births, and we abstracted information on diagnosis and treatment blindly with respect to the outcome (see Supplemental Fig. 2, available online, for medical chart identification and the abstraction process).

The final cohort comprised 18,147 singleton pregnancies. The reference group (n = 16,712) consisted of all pregnancies for which we had no indication of infertility based on either the MOND or the reproductive clinic data. The infertility exposed group (n = 1,435) comprised pregnancies conceived after a period of infertility, either naturally or after treatment. The study was approved by the McGill University Health Centre Institutional Ethics Review Board.

Classification of Exposure Status

We determined the infertility status for each pregnancy by using all relevant variables in MOND, complemented with the data collected from the medical chart. Time to pregnancy (TTP) was only available for women attending the infertility clinic and whose chart was obtained, so we relied on the infertility variable in MOND to determine eligibility in the exposed group. Among pregnancies with recorded TTP, those conceived after at least 12 months of trying were included as part of the infertile group. Those with <12 months and no record of treatment were included in the reference group (n = 14). Instances where we did not have TTP were classified in the reference group if there was no record of infertility or treatment in MOND (n = 268).

To determine treatment status, we first estimated the date of conception (calculated by subtracting gestational age from the infant's birth date). Based on this, a pregnancy was considered positive for treatment if the last recorded clinic cycle listed any form of treatment or if treatment was reported in MOND.

We separated pregnancies by type of treatment: low-technology (IUI or OS, alone or in combination) and high-technology (IVF, ICSI, or other procedures whereby gametes were manipulated in vitro). If present, the treatment information reported in the medical chart was considered as the gold standard in the event of discrepancies between the clinic and MOND data. When only the MOND data were available, these were considered valid. A pregnancy was considered naturally conceived if it was conceived within 90 days of the last recorded cycle and no treatment was indicated in either MOND or the clinic chart, or if it was conceived after 90 days of the last recorded/available cycle and there was no indication of treatment in MOND.

Outcome Definition

Preterm birth was defined as any pregnancy that ended between 20 and <37 gestational weeks, either as a live- or stillbirth. Pregnancies ending before 20 weeks were considered miscarriages and were excluded from the analysis (see Supplemental Fig. 1). Gestational age at birth in the hospital's database was estimated by an algorithm based on the first day of the last known menstrual period when confirmed by early ultrasound within ± 10 days. In cases where the last known menstrual period and early ultrasound estimates differed by more than 10 days, the latter was used. When the last known menstrual period was unknown, gestational age was based on ultrasound alone. We examined preterm birth at three clinical end points: [1] overall preterm birth: <37 weeks versus ≥37 weeks; [2] moderate preterm birth: <35 weeks versus ≥37 weeks; [3] very preterm birth: <32 weeks versus ≥37 weeks.