Association of birth defects with the mode of assisted reproductive technology in a Chinese data-linkage cohort

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Objective: To evaluate the impact of assisted reproductive technology (ART) on the offspring of Chinese population.
Design: Retrospective, data-linkage cohort.
Setting: Not applicable.
Patient(s): Live births resulting from ART or natural conception.
Intervention(s): None.
Main Outcome Measure(s): Birth defects coded according to ICD-10.
Result(s): Births after ART were more likely to be female and multiple births, especially after intracytoplasmic sperm injection (ICSI). ART was associated with a significantly increased risk of birth defects, especially, among singleton births, a significantly increased risk in fresh-embryo cycles after in vitro fertilization (IVF) and frozen-embryo cycles after ICSI. Associations between ART and multiple defects, between ART and gastrointestinal malformation, genital organs malformation, and musculoskeletal malformation among singleton births, and between ART and cardiac septa malformation among multiple births were observed.
Conclusion(s): This study suggests that ART increases the risk of birth defects. Subgroup analyses indicate higher risk for both fresh and frozen embryos, although nonsignificantly for frozen embryos after IVF and for fresh embryos were presented with low power. Larger sample size research is needed to clarify effects from fresh- or frozen-embryo cycles after IVF and ICSI. (Fertil Steril® 2018;109:849–56. ©2018 by American Society for Reproductive Medicine.)
Key Words: Assisted reproductive technology (ART), in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), birth defect, congenital malformation

Assisted reproductive technology (ART), which includes procedures used to achieve pregnancy in infertile couples, has been in use for more than three decades in China. For the city of Shanghai, one of the megacities in China, with more than 14 million registered inhabitants, a number of factors, including lifestyle changes, living conditions, and the two-child policy, which now allows parents of single children to have one more child, have led to an increasing number of couples resorting to ART for conception.

Many studies have shown that infants born after ART have poorer birth outcomes than spontaneously conceived infants (1–5). However, few large population-based studies to assess the risk of birth defects associated with ART have been carried out in China, owing to the lack of complete records in the birth registry in many regions. Most studies of ART in China do not include comparisons with spontaneous-conception populations or are limited by small numbers of participants. Furthermore, research suggests that there is a difference between

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women who have and have not received ART in sociodemographic characteristics, pregnancy-related complications, medical conditions, and psychologic pressure (6, 7), as well as the likelihood of multiple births after ART (8, 9). There is still a dispute about whether extra risk of birth defects after ART may be attributable to sterility-related characteristics (10) or to the treatment itself (11), and whether the risk is similar across different modes of ART and related therapies (12).

In consideration of previous study results, the hypothesis that factors from ART procedures as well as the couple's own risk factors for birth defects contribute to an increased risk of birth defects after an ART procedure was assumed in this study. The purpose of the present study was to analyze the association between birth defects and ART and to examine the excess risk of birth defects across different methods for infertility treatment. The risk of birth defects associated with spontaneous pregnancy among women after assisted reproductive treatment was also assessed; the risks of main categories of birth defects were evaluated as well.

METHODS

Data Sources

Birth data. The earliest birth registry system in China was established by the Shanghai Municipal Center for Disease Control and Prevention (CDC) in 2003. The system covers all hospitals with authorized delivery services in Shanghai and has collected records of all babies born after January 1, 2004. As of 2016, more than two million births had been collected in this system. These births were not limited by gestational age or birth weight, with the earliest gestational age at birth being 20 weeks.

The birth information includes date of birth, baby's sex, weight, length, and gestational age at birth, birth defects, embryo number, mode of delivery, parity, previous live births of the mother, previous miscarriages of the mother, and sociodemographic characteristics of the parents. Birth defects detected at birth or during the early neonatal period (within 7 days after birth) are reported by the physicians. Birth defects were coded according to the International Classification of Diseases, 10th edition, by staffs at Shanghai district-level CDCs.

Infertility data. Details of treatment with the use of ART were provided by the Shanghai Ji Ai Genetics and IVF Institute, the first ART center in Shanghai, which was formed by the Obstetrics and Gynecology Hospital of Fudan University and American Genetics and IVF Institute (GIVF) in 1997. This center was registered to provide infertility treatment, such as artificial insemination from husband, artificial insemination from donor, in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), preimplantation genetic diagnosis, and embryo freezing, recovery, and implantation. This center provided data for infertility treatments from January 2005 through April 2016. The data include sociodemographic characteristics of couples, embryo transfer date, and ART treatment type.

Unique National Identification numbers of parents were applied to link the records of parents with a history of ART treatment to the birth registry. Embryo transfer date, birth date, and gestational age were applied to verify whether the births had resulted from ART or not. Spontaneous births after previous ART treatment were also identified.

The study was approved by the Ethics Review Committee of the Shanghai Municipal CDC.

Statistical Analysis

Birth characteristics, including the growth and development indexes of newborns, such as birth weight, gestational age at birth, and birth defects, were divided into singleton and multiple (twins and higher order) births because multiple births are strongly associated with both ART and birth defects (13, 14). Higher-order multiple births were not frequent in Shanghai, even for births resulting from ART, so they were not separated from multiple birth for analysis. Chi-square test was used to compare birth characteristics in births after assisted conception and tin he total population (including all births in Shanghai). Fisher exact test was applied to assess the significance of the difference in these groups when the expected number in any of the cells was less than five.

The prevalence of birth defects was compared among the following groups: births as a result of each mode of ART; births as a result of spontaneous conception in women with a history of ART; and the total population.

Crude relative risk (RR) were calculated to compare the prevalence of birth defects among groups, with the use of two-tailed P values in SAS statistical software, version 9.4. The adjusted analysis included a priori confounders of maternal and paternal age (categorized in 5-year age groups), maternal and paternal education level, parity, baby's sex, previous miscarriages, and year of birth, and the effect of clustering of births within women in a Poisson generalized linear mixed model (15). Evaluation of the model fit proved that there was no evidence of overdispersion and that the Poisson variance assumption was adequate. Subgroup analyses were also applied to test the effects of each treatment method (including fresh vs. frozen embryos) and each subcategory of birth defects with the same analytic strategy.

RESULTS

Parental and Birth Characteristics

During 2005–2016, The birth registry database included a total of 2,326,506 live births. Births to parents younger than 20 years were excluded from this study because none had resulted from assisted conception. In the end, there were 2,243,125 births for analysis, with 6,372 births resulting from ART: 3,375 births had resulted from IVF, 40.39% (1,363 births) of which had undergone fresh-embryo cycles, and 2,997 births had resulted from ICSI, where the proportion of fresh-embryo cycles (35.47%, 1,063 births) was lower than that of IVF (Table 1).

Compared with the total population, parents who used ART were older and tended to be more highly educated. Women in the IVF group were more likely to have a history of abortion, and the opposite was true for the ICSI group (Table 1). In addition, births after ART were more likely to be female and to be multiple births, especially in the ICSI