ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Preimplantation genetic diagnosis: a national multicenter obstetric and neonatal follow-up study

Bjorn Bay, Ph.D.,[a,b] Hans Jakob Ingerslev, D.M.Sc.,[a] Josephine Gabriela Lemmen, Ph.D.,[c] Birte Degn, Ph.D.,[a] Iben Anne Rasmussen, Ph.D.,[d] and Ulrik Schiøler Kesmodel, Ph.D.[a,e]

[a] The Fertility Clinic and Center of Preimplantation Genetic Diagnosis, Department of Obstetrics and Gynecology, Aarhus University Hospital, Aarhus; [b] The Fertility Clinic, Department of Obstetrics and Gynecology, Institute of Clinical Medicine, Aarhus University, Regionshospitalet, Horsens; [c] The Fertility Clinic, Rigshospitalet, Copenhagen; [d] The Fertility Clinic, Department of Gynecology and Obstetrics, Odense Universitetshospital, Odense; and [e] The Fertility Clinic, Department of Gynecology and Obstetrics, Herlev and Gentofte Hospital, Herlev, Denmark

Objective: To study whether women conceiving after preimplantation genetic diagnosis (PGD) and their children have greater risks of adverse pregnancy and birth outcomes compared with children conceived spontaneously or after IVF with or without intracytoplasmic sperm injection (ICSI).
Design: Historical cohort study.
Setting: Not applicable.
Patient(s): All deliveries following PGD treatment for single gene and sex-linked disorders or structural chromosomal aberrations (n = 126 deliveries/149 children), IVF/ICSI treatment (n = 30,418 deliveries/36,115 children), and spontaneous conception (n = 896,448 deliveries/909,624 children).
Intervention(s): None.
Main Outcome Measure(s): Adverse obstetric and neonatal outcomes, such as pre-eclampsia, preterm primary rupture of membranes, placenta previa, abruption of placenta, preterm birth, low birth weight, malformations, and neonatal admission.
Result(s): Compared with spontaneously conceived pregnancies, PGD pregnancies were at significantly increased risk of placenta previa (adjusted odds ratio [ORa] 9.1; 95% confidence interval [95% CI] 3.4, 24.9), cesarean section (ORa 2.0; 95% CI 1.3, 2.9), preterm birth (ORa 1.6; 95% CI 1.0, 2.7), shorter gestation (mean difference −3.4 days; 95% CI −5.7, −1.1 days), and longer neonatal admission (mean difference 21 days; 95% CI 15, 28 days). The risks were comparable to that of pregnancies following IVF/ICSI. In subanalyses, adverse outcomes were only present in children conceived by PGD owing to parental monogenetic disorder and comparable to those of children born to parents with monogenic disorders conceiving without PGD, except for a higher risk of placenta previa.
Conclusion(s): In this cohort study, the risk of adverse obstetric and neonatal outcomes was mainly related to the underlying parental condition rather than the PGD procedure. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Assisted reproduction, neonatal outcomes, obstetric outcomes, PGD

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Worldwide, more than 5 million children have been born after assisted reproductive technology (ART) (1). With the continuous advancement of the techniques, the obligation to monitor the safety remains an important issue. It has been established that IVF and intracytoplasmic sperm injection (ICSI) are associated with a small but increased risk of adverse obstetric and neonatal outcomes (2, 3). Studies have suggested that more invasive treatments, such as ICSI, in which a single spermatozoa is injected directly into the oocyte, may pose the largest risk for the developing embryo (4–6). With preimplantation genetic diagnosis (PGD), in vitro embryos are biopsied and tested for genetic aberrations, to avoid inheritable diseases present in the parents. Such intervention may be considered the most invasive procedure in ART and has been an object of concern (7). Yet very few studies have investigated the risk associated with this procedure. Preimplantation genetic diagnosis includes hormonal stimulation of the

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Reprint requests: Bjørn Bay, Ph.D., The Fertility Clinic, Department of Obstetrics and Gynecology, Institute of Clinical Medicine, Aarhus University, Regionshospital Horsens, Denmark (E-mail: bjornbay@me.com).

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women to develop several mature ovarian follicles containing oocytes that can be retrieved by ultrasound-guided transvaginal aspiration. The oocytes are fertilized by IVF in case of X-linked disease and structural chromosomal abnormalities, or in the case of monogenetic disorders by ICSI, to avoid contamination from other cells. Subsequently, one or two blastomeres are aspirated from the embryos, usually at the six- to eight-cell stage (cleavage stage), through a small opening in the zona pellucida using either acid or a laser. The genetic diagnosis is performed on the extracted cell(s) with polymerase chain reaction or fluorescence in situ hybridization, depending on the nature of the genetic disorder. Eventually, one to two unaffected embryos are transferred to the uterus, and any surplus embryos may be cryopreserved.

We conducted a cohort study including all children born after PGD since its introduction in Denmark in 1999 and compared obstetric and neonatal outcomes with those of children born after IVF/ICSI or spontaneous conception.

MATERIALS AND METHODS

This study was designed as a historical cohort study including all children born in Denmark from January 1, 1999 to December 31, 2013. The cohort was established on the basis of data from the Danish Medical Birth Registry, which contains information on all children born in Denmark since 1968 (8). With the use of the unique person identification number assigned to all Danish citizens, we cross-linked individual-level information obtained from the Danish Health Registers and medical records in all children born after gestational week 21+6.

PGD, IVF, and ICSI Treatment

Information about PGD treatments was obtained from each of the three University Hospital centers performing PGD in Denmark. At each center the biologist responsible for PGD treatments files extensive information on all PGD cycles. For each treatment resulting in a confirmed pregnancy, we validated the treatment protocol and the birth of a child in the medical records. From the Danish national IVF register we assessed information about exposure to other types of fertility treatment (IVF or ICSI). The IVF register contains information on each woman's personal identification number, type of treatment, as well as information on pregnancy outcomes and the personal identification number of the resulting children (9). Children born after IUI were excluded. A total of 945,888 children born between January 1, 1999 and December 31, 2013 in Denmark were divided into three groups: children born after PGD, children born after IVF/ICSI, and children born after spontaneous conception. The study did not include pregnancies following preimplantation genetic screening (PGS), which was not available in Denmark during the study period.

Obstetric and Neonatal Outcomes

Information about obstetric and neonatal outcomes was obtained from the Medical Birth Registry. This register contains information about the pregnancy, the birth, and the newborn, as reported electronically by the physicians and midwifes attending the pregnancy and birth. Additionally, individual-level data from the Danish National Patient Register are transferred to the specific records in the Birth Register when appropriate, for example in the case of malformations discovered during the first years of the child's life. Only major malformations were included as categorized by the European Surveillance of Congenital Anomalies (10).

Statistical Analysis

Data from the medical records and the national health registers were cross-linked using the personal identification number. Multiple logistic and linear regressions were performed to compare obstetric and neonatal outcomes between the exposure groups (PGD or IVF/ICSI) and the control group (spontaneously conceived children). All analyses were conducted while adjusting for multiplicity (singleton/multiples), child gender (boys/girls), maternal prepregnancy body mass index (BMI [kg/m^2]), maternal age (years), parity (nulliparous/parous), and smoking during pregnancy (yes or quit during pregnancy/no), as reported in the Medical Birth Registry. Subsequently, we performed secondary analyses comparing the neonatal and obstetric outcomes in children conceived after PGD with those of the children conceived after IVF/ICSI. Further, we performed subanalyses stratifying the PGD group into two groups based on PGD indication. Because fertilization is performed by standard IVF in case of structural chromosomal aberrations, and by ICSI in case of monogenetic disorders diagnosed by polymerase chain reaction, we performed analyses comparing these two groups with children conceived after IVF or ICSI, respectively, in addition to the comparison with spontaneously conceived children.

All the above-mentioned analyses were based on an a priori determined analysis plan. Families carrying or suffering from genetic disorders have a range of choices when considering having a child. Although PGD is one option, others choose to conceive naturally and subsequently seek prenatal diagnostics to determine the genetic status of the fetus. Information on all prenatal diagnostic investigations performed owing to risk of monogenetic disorders in the study period (chorion villus biopsy or amniotic fluid sample) was obtained from the Danish Central Cytogenic Register. Beside the date and reason for the procedure, the register also contains information on the result of the diagnostic test. Thus, we conducted subanalyses comparing obstetric and perinatal outcomes between children born by parents with monogenetic disorders (autosomal and X-linked) conceiving naturally or after PGD, respectively. Because the nature of PGD is likely to have changed over time, we additionally estimated the risk adjusted for birth year. Finally, sensitivity analyses with robust standard errors were performed, to account for any correlations between siblings.

The statistical analyses were conducted using Stata/SE 12 (11). Results are based on complete case analyses and