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Outcomes of in vitro fertilization with preimplantation genetic diagnosis: an analysis of the Unites States Assisted Reproductive Technology Surveillance Data, 2011–2012

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Objective: To assess the characteristics of IVF cycles for which preimplantation genetic diagnosis (PGD) was used and to evaluate indications for PGD and treatment outcomes associated with this procedure as compared with cycles without PGD with the data from the U.S. National ART Surveillance System.
Design: Retrospective cohort study.
Setting: None.
Patient(s): Fresh autologous cycles that involved transfer of at least one embryo at blastocyst when available.
Intervention(s): None.
Main Outcome Measure(s): PGD indications and age-specific reproductive outcomes.
Result(s): There were a total of 97,069 non-PGD cycles and 9,833 PGD cycles: 55.6% were performed for aneuploidy screening (PGD Aneuploidy), 29.1% for other reasons (PGD Other), and 15.3% for genetic testing (PGD Genetic). In comparison to non-PGD cycles, PGD Aneuploidy cycles showed a decreased odds of miscarriage among women 35–37 years (adjusted odds ratio [aOR] 0.62; 95% CI, 0.45–0.87) and women >37 years (aOR 0.55; 95% CI, 0.43–0.70); and an increased odds of clinical pregnancy (aOR 1.18; 95% CI, 1.05–1.34), live-birth delivery (aOR 1.43; 95% CI, 1.26–1.62), and multiple-birth delivery (aOR 1.98; 95% CI, 1.52–2.57) among women >37 years.
Conclusion(s): Aneuploidy screening was the most common indication for PGD. Use of PGD was not observed to be associated with an increased odds of clinical pregnancy or live birth for women <35 years. PGD for aneuploidy was associated with a decreased odds of miscarriage for women >35 years, but an increased odds of a live-birth and a multiple live-birth delivery among women >37 years. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: Aneuploidy, chromosomal abnormality, genetic, in vitro fertilization, preimplantation genetic diagnosis

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Preimplantation genetic diagnosis (PGD) is a procedure used to identify genetic or chromosomal abnormalities in developing oocytes or embryos during a cycle of in vitro fertilization (IVF). Preimplantation genetic diagnosis was first introduced in the late 1980s as a viable alternative to prenatal diagnosis that would assist couples in avoiding pregnancy terminations due to fatal or debilitating diseases when one or both parents are affected by specific genetic abnormalities (1–4). Since that time, technological advances in biopsy methods and genetic analysis have improved the accuracy of the techniques and contributed to an expanding list of indications for its use. Common indications for PGD include Huntington disease,

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hemophilia, and cystic fibrosis (3). Studies have also indicated that PGD may help select good-quality embryos and improve infertile couples' chances to conceive and deliver a healthy baby, especially among women of advanced age, or with previous IVF failure or recurrent pregnancy loss (1, 2, 5–10).

Since its introduction, PGD has been increasingly used to test for genetic defects in embryos and to screen for chromosomally abnormal embryos before transfer to the woman's uterus, despite ongoing debate regarding its clinical benefits in achieving live-birth deliveries (5, 6, 8, 10–12). About 4% of IVF cycles (6,099 out of 176,247) reported use of PGD during 2012 in the United States (13). Although there is evidence of increasing use of PGD for certain indications in the United States (14, 15), studies have not been conducted at the national level that focus on patient and treatment characteristics associated with PGD use, and pregnancy outcomes of ART cycles that involve PGD, including miscarriages and live-birth deliveries. Our study describes the characteristics of IVF cycles for which PGD was used and evaluates the pregnancy outcomes associated with these procedures using U.S. assisted reproductive technology (ART) surveillance data for 2011–2012.

MATERIALS AND METHODS

In 1992, Congress passed the Fertility Clinic Success Rate and Certification Act (FCSRCA), which requires each medical center in the United States that performs ART procedures to report data to the Centers for Disease Control and Prevention (CDC) on every ART procedure initiated, where ART is defined as any procedure in which oocytes or embryos are handled in the laboratory for the purpose of establishing a pregnancy. All ART data are reported annually to the CDC's Web-based National ART Surveillance System (NASS) (7, 13). The data collected in NASS include patient demographics, medical history, infertility diagnoses, clinical information pertaining to the ART procedure, and information regarding resultant pregnancies. The data file is organized with one record per ART cycle performed. Because nonreporting clinics (7% of clinics in operation in 2012) tend to be smaller and perform fewer cycles, the CDC estimates that NASS contains information on over 95% of all ART procedures performed in the United States (13).

The collection of information for NASS on the use of PGD and the reason for its use started in 2004 and has been revised over time; consistent reporting of these data began after 2010. For the current study, the cycles with use of PGD and the reported reason for use were categorized into three mutually exclusive groups based on the indication for PGD use: [1] PGD for genetic disorders or chromosomal abnormality (PGD Genetic), [2] PGD for aneuploidy screening of the embryos (PGD Aneuploidy), and [3] PGD for other or unknown reasons (PGD Other, including gender preference, history of infertility, elevated follicle-stimulating hormone [FSH] levels, obesity, etc.). We also examined the reported reasons for ART use, which included free-text entries ("other specify") for reasons for use; in some cases, this information was used to reclassify indication for PGD using a hierarchical system. For example, when cycles for which "aneuploidy screening of the embryos" (PGD Aneuploidy) was reported as the reason for PGD but "genetic disease" was listed as the reason for ART, we reclassified the report for the indication for PGD use to "PGD Genetic." Similarly, if "recurrent miscarriage" was the reason for ART but "other screening for embryos" was reported as the reason for PGD (PGD Other), we reclassified the PGD indication to "PGD Aneuploidy." Cycles without reported use of PGD were categorized as non-PGD cycles for the purpose of comparison with PGD cycles.

Because information on PGD use is not consistently collected for frozen cycles and PGD is often used for routine screening of donor cycles, which often have different outcomes than fresh autologous cycles, we restricted our study to fresh, autologous ART cycles performed in 2011 and 2012 (the latest data available with consistent PGD reporting information). Because PGD procedures are not offered at all ART clinics, we further limited our study to cycles performed in clinics that reported at least one PGD cycle in either 2011 or 2012. Cycles cancelled before oocyte retrieval were excluded. We further restricted our study to cycles with a blastocyst stage embryo available for transfer because PGD nearly always requires culture of the embryo to blastocyst stage (5–6 days after fertilization) and only 1% of the transfers occurred at the cleavage stage.

For cycles with and without use of PGD, we examined the distribution of the following patient characteristics: patient age, infertility diagnosis, number of prior ART cycles, number of prior miscarriages, number of prior pregnancies, number of oocytes retrieved, number of embryos transferred, and number of embryos cryopreserved. Patient age at the time of the ART procedure was grouped into three categories, <35, 35–37, and >37 years. The infertility diagnoses assessed included tubal factor, ovulatory dysfunction, diminished ovarian reserve, endometriosis, uterine factor, male factor, and unexplained factor; because more than one diagnosis could be reported, the diagnosis categories were not mutually exclusive. The number of oocytes retrieved was categorized as 1–10, 11–15, and ≥ 16, and the number of embryos transferred was categorized as no transfer, 1, and ≥ 2. The number of embryos cryopreserved was classified as none and ≥ 1. We used two-tailed Pearson's chi-square tests to compare the distribution of patient characteristics (demographic and clinic) for PGD cycles, by PGD category, versus cycles without PGD.

The treatment outcomes we assessed were rate of clinical pregnancy and live-birth delivery per transfer; rate of miscarriage (pregnancy loss) per pregnancy, and rate of multiple birth delivery, preterm delivery, and low birth weight delivery per live birth. We calculated age-specific rates of these treatment outcomes for each category of PGD reason and for cycles without use of PGD. Multivariable logistic regression models were developed to calculate unadjusted and adjusted odds ratios (aOR) and 95% confidence intervals (CI) for the association between the treatment outcomes and the reason for PGD, stratified by age group; non-PGD cycles were the referent. In addition, a subanalysis was conducted of data from 24 clinics that performed at least 10 IVF cycles and had PGD rates of $>25\%$ to test whether these clinics have better treatment outcomes than those of all clinics. Statistical analyses were conducted using SAS, version 9.3 (SAS