ORIGINAL ARTICLE: ENVIRONMENT AND EPIDEMIOLOGY

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

Jeani Chang, M.P.H., Sheree L. Boulet, Dr.P.H., Gary Jeng, Ph.D., Lisa Flowers, M.P.A., and Dmitry M. Kissin, M.D., M.P.H.

Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia

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

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/changj-ivf-pgd-united-states/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

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,

Received June 17, 2015; revised October 14, 2015; accepted October 17, 2015.
J.C. has nothing to disclose. S.L.B. has nothing to disclose. G.J. has nothing to disclose. L.F. has nothing to disclose. D.M.K. has nothing to disclose.
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Reprint requests: Jeani Chang, M.P.H., Division of Reproductive Health, Centers for Disease Control and Prevention, 4770 Buford Highway NE, Mailstop F-74, Atlanta, Georgia 30341 (E-mail: jchang@cdc.gov).

Fertility and Sterility® Vol. ■, No. ■, ■ 2015 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.10.018

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

Institute), and $P<.05$ was considered statistically significant for all values. The study was approved by the CDC's institutional review board.

RESULTS

A total of 229,096 fresh autologous ART cycles performed in 2011 and 2012 were reported to NASS; among these, 10,407 (4.5%) reported use of PGD. In 2011, 440 (98%) of 451 ART clinics reported at least one PGD cycle; in 2012, all reporting ART clinics (n = 456) performed PGD cycles. After limiting our study to cycles that took place in clinics that performed at least one PGD cycle in 2011 or 2012 and cycles with retrieval of at least one oocyte and transfer at blastocyst stage, the final data set was composed of 106,902 ART cycles, including 9,833 PGD cycles (about 94% of the original 10,407 reported). Among these 9,833 PGD cycles, the majority (55.6%, n = 5,471) were performed for aneuploidy screening, followed by other reasons (29.1%, n = 2,859) and genetic testing (15.3%, n = 1,503) (Table 1). Among cycles where PGD was used for other reasons, only 2% (n = 68) provided further information on specific reasons for PGD use, which mostly included gender selection (n = 63).

Table 1 presents patient demographic and clinical characteristics for fresh, nondonor PGD cycles (by PGD reason) and non-PGD cycles. The percentage of all cycles with PGD performed decreased from 4,697 (9.5%) of 49,359 cycles in 2011 to 5,136 (8.9%) of 57,543 cycles in 2012. An increase in PGD use was only detected among cycles with PGD for aneuploidy screening (see Table 1). Clinical characteristics, such as pregnancy history, number of prior ART cycles, and factors related to oocyte and embryo quality, varied across the PGD groups. For example, the proportion of women with one or more prior miscarriages was higher in the PGD Aneuploidy group compared with women in the PGD Other group and the PGD Genetic group (53.8% vs. 30.6% and 29.6%, respectively). Of all PGD cycle groups, the PGD Genetic group had the highest number of oocytes retrieved (43.7% had 16 or more oocytes retrieved) and the highest number of embryos transferred (45.1% of cycles resulted in the transfer of ≥ 2 embryos). Compared with women who did not use PGD, a greater proportion of women who used PGD for the prevention of genetic disorders or for other reasons were younger than 35 years or aged 35–37 years. In contrast, more than half of women (50.9%) undergoing PGD for aneuploidy screening were >37 years, compared with 32.8% of women who did not use PGD. Approximately 74.6% of PGD Genetic and 73.9% of PGD Other cycles resulted in the transfer of one or more embryos as compared with 62.1% of non-PGD cycles; however, the non-PGD group had the highest percentage of embryos cryopreserved.

Table 2 presents the odds ratios for the association of age-specific treatment outcomes and use of PGD according to indication after adjusting for confounding factors (infertility diagnosis, pregnancy history, prior ART cycles, and factors related to oocyte and embryo quality). Among cycles with women <35 years involving transfer of at least one embryo, odds of clinical pregnancy and live birth per transfer were lower for all types of PGD cycles than non-PGD cycles. Among live-birth deliveries, those resulting from PGD Genetic cycles had significantly reduced odds than those resulting from non-PGD cycles to be low-birth-weight infants (aOR 0.73; 95% CI, 0.54–0.98). In contrast, PGD Aneuploidy cycles were associated with significantly higher odds of low-birth-weight delivery per live birth compared with cycles without PGD (aOR 1.25; 95% CI, 1.01–1.54).

For women 35–37 years, the adjusted odds of clinical pregnancy and live birth tended to be lower for PGD Genetic and PGD Other cycles compared with non-PGD cycles, although most associations were not statistically significant (aOR for PGD Genetic 0.85; 95% CI, 0.65–1.12, and 0.78; 95% CI, 0.59–1.04, respectively; aOR for PGD Other 0.83, 95% CI, 0.69–1.01, and 0.77; 95% CI, 0.63–0.93, respectively). Notably, PGD for aneuploidy screening was statistically significantly negatively associated with miscarriage (aOR 0.62; 95% CI, 0.45–0.87). Although PGD for genetic and other reasons had increased odds for miscarriage, the CI for the association with PGD Genetic included the null value (aOR 1.56; 95% CI, 0.95–2.57, and 1.49; 95% CI, 1.05–2.12, respectively).

Among women >37 years of age, PGD Aneuploidy was positively associated with 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), and negatively associated with miscarriage (aOR 0.55; 95% CI, 0.43–0.70), compared with non-PGD cycles. When we restricted the analysis to clinics with high PGD use (that reported at least 10 IVF cycles and had PGD rates of >25%), the results were not different than those for all clinics with at least one cycle of PGD performed (data now shown).

DISCUSSION

The findings from this national study of PGD cycles performed in 2011 and 2012 indicate that the most commonly reported indication for PGD was aneuploidy screening, followed by other reasons and the detection of genetic disorders. Among embryo transfer cycles, use of PGD was not associated with improved clinical pregnancy or live-birth rates for women aged <35 years, regardless of the indication. However, PGD for aneuploidy screening was associated with lower odds of miscarriage per pregnancy relative to cycles without PGD among women aged ≥ 35 years. Furthermore, among women aged >37 years, PGD for aneuploidy screening was associated with a higher likelihood of having a live-birth delivery per transfer, but these live-birth deliveries were also more likely to be multiple births, compared with cycles where PGD was not used.

Consistent with other studies (15–17), we found that the majority of women using PGD for the prevention of genetic disorders were younger than 35 years with no prior miscarriages; in contrast, PGD for aneuploidy screening was performed more often among women older than 37 years and those with one or more prior miscarriages. Because the majority of embryos among women older than 37 years are chromosomally abnormal (18, 19), it is recommended that these women undergo PGD to screen for aneuploidies and thereby improve pregnancy rates. We found that the percentage of cycles resulting in the transfer of at least one

TABLE 1

Characteristics of patients with fresh, nondonor ART cycles, with and without use of preimplantation genetic diagnosis, United States, 2011–2012.

Characteristic	PGD cycles: Genetic, n = 1,503 (15.3%)	PGD cycles: Aneuploidy, n = 5,471 (55.6%)	PGD cycles: Other, n = 2,859 (29.1%)	Non-PGD cycles, n = 97,069
Data, y[a]				
2011	797 (53.0)	2,418 (44.2)	1,482 (51.8)	44,662 (46.0)
2012	706 (47.0)	3,053 (55.8)	1,377 (48.2)	52,407 (54.0)
Patient age, y[a]				
<35	930 (61.9)	1,518 (27.8)	1,427 (49.9)	45,077 (46.4)
35–37	314 (20.9)	1,166 (21.3)	783 (27.4)	20,177 (20.8)
>37	259 (17.2)	2,787 (50.9)	649 (22.7)	31,815 (32.8)
Infertility diagnosis[b]				
Tubal factor[a]	65 (4.3)	443 (8.1)	175 (6.1)	12,884 (13.3)
Endometriosis[a]	42 (2.8)	307 (5.6)	108 (3.8)	8,272 (8.5)
Uterine factor[a]	39 (2.6)	314 (5.7)	83 (2.9)	5,235 (5.4)
Ovulatory dysfunction[a]	119 (7.9)	614 (11.2)	280 (9.8)	14,952 (15.4)
DOR[a]	124 (8.3)	1,436 (26.3)	313 (11.0)	22,829 (23.5)
Male factor[a]	247 (16.4)	1,416 (25.9)	645 (22.6)	32,893 (33.9)
Other factor[a]	1,246 (82.9)	2,475 (45.2)	1,825 (63.8)	19,648 (20.2)
Unexplained[a]	50 (3.3)	480 (8.8)	178 (6.2)	12,110 (12.5)
No. of prior pregnancies[a]				
0	502 (33.4)	1,291 (23.6)	551 (19.3)	46,868 (48.3)
1	439 (29.2)	1,141 (20.9)	538 (18.8)	24,257 (25.0)
≥2	561 (37.3)	3,027 (55.3)	1,735 (60.7)	25,646 (26.4)
Missing	1 (0.1)	12 (0.2)	35 (1.2)	298 (0.3)
No. of prior miscarriages[a]				
0	1,058 (70.4)	2,527 (46.2)	1,985 (69.4)	68,889 (71.0)
1	281 (18.7)	1,188 (21.7)	525 (18.4)	17,659 (18.2)
≥2	164 (10.9)	1,756 (32.1)	349 (12.2)	10,521 (10.8)
No. of prior live births[a]				
0	791 (52.6)	3,191 (58.3)	844 (29.5)	71,992 (74.2)
1	501 (33.3)	1,462 (26.7)	658 (23.0)	18,519 (19.1)
≥2	207 (13.8)	768 (14.0)	1,154 (40.4)	6,031 (6.2)
Missing	4 (0.3)	50 (0.9)	203 (7.1)	527 (0.5)
No. of prior ART cycles[a]				
0	732 (48.7)	2,696 (49.3)	1,779 (62.2)	58,052 (59.8)
1	339 (22.6)	1,035 (18.9)	542 (19.0)	16,502 (17.0)
≥2	432 (28.7)	1,738 (31.8)	538 (18.8)	22,511 (23.2)
Missing		2 (<0.1)		4 (<0.1)
No. of oocytes retrieved[a]				
1–10	443 (29.5)	1,948 (35.6)	868 (30.4)	38,079 (39.2)
11–15	403 (26.8)	1,401 (25.6)	787 (27.5)	22,885 (23.6)
≥16	657 (43.7)	2,122 (38.8)	1,204 (42.1)	36,105 (37.2)
No. of embryos transferred[a]				
None	382 (25.4)	2,005 (36.7)	746 (26.1)	36,768 (37.9)
1	444 (29.5)	1,518 (27.8)	983 (34.4)	12,499 (12.9)
≥2	677 (45.1)	1,948 (35.6)	1,130 (39.5)	47,802 (49.2)
No. of embryos cryopreserved[a]				
0	791 (52.6)	3,075 (56.2)	1,424 (49.8)	34,842 (35.9)
≥1	707 (47.0)	2,362 (43.2)	1,421 (49.7)	62,055 (63.9)
Missing	5 (0.3)	34 (0.6)	14 (0.5)	172 (0.2)

Note: Missing values were <1% for all variables. Cycles were restricted to [1] clinics that performed at least one PGD cycle in any given reporting year, [2] retrieval of at least one oocyte, and [3] blastocyst transfer among transfer cycles (days 5–6). DOR = diminished ovarian reserve; PGD = preimplantation genetic diagnosis.

[a] Pearson's chi-square $P < .05$ comparing the distribution of characteristic in each PGD category with non-PGD group.

[b] Percentages do not add up to 100 because the groups are not mutually exclusive (one patient may have multiple diagnoses).

Chang. IVF with PGD. Fertil Steril 2015.

embryo among PGD cycles was higher than that of non-PGD cycles. We also found that fewer embryos were cryopreserved among PGD cycles compared with non-PGD cycles. These findings may reflect the detection and elimination of chromosomally abnormal and aneuploid embryos after PGD, thereby leaving fewer available for cryopreservation.

Among women aged <35 years we found the adjusted odds of clinical pregnancy and live birth were lower compared with cycles where PGD was not used, irrespective of the reported indication for PGD. While there is no sufficient evidence to explain the reasons for the lack of beneficial outcomes of PGD among younger women (<35 years), it is possible that this group of women has more complex infertility problems that were developed at earlier age and cannot be easily overcome by the use of PGD. When PGD was performed for aneuploidy screening among women 35–37 years,

TABLE 2

Reproductive outcomes for cycles with preimplantation genetic diagnosis, by reason for use, versus those without preimplantation genetic diagnosis, stratified by patient age, United States, 2011–2012.

	PGD cycles									Non-PGD cycles
	Genetic (n = 1,503)			Aneuploidy (n = 5,471)			Others (n = 2,859)			Referent (n = 97,069)
Outcome	n (%)	OR (CI)	aOR (CI)[a]	n (%)	OR (CI)	aOR (CI)[a]	n (%)	OR (CI)	aOR (CI)[a]	n (%)
<35 y										
CP (per transfer)	398 (54.3)	0.78 (0.68–0.91)	0.89 (0.76–1.04)	606 (51.5)	0.70 (0.63–0.79)	0.82 (0.72–0.93)	597 (52.1)	0.72 (0.64–0.81)	0.74 (0.65–0.84)	20,479 (60.2)
LB delivery (per transfer)	336 (45.8)	0.76 (0.65–0.88)	0.87 (0.74–1.02)	512 (43.5)	0.69 (0.61–0.78)	0.82 (0.72–0.93)	521 (45.4)	0.75 (0.66–0.84)	0.77 (0.68–0.88)	17,954 (52.8)
SAB (per pregnancy)	54 (13.6)	1.34 (1.00–1.79)	1.20 (0.88–1.64)	78 (12.9)	1.26 (0.99–1.60)	1.09 (0.84–1.40)	67 (11.2)	1.08 (0.83–1.39)	1.06 (0.80–1.41)	2,154 (10.5)
MB delivery (per LB)	96 (28.6)	0.79 (0.62–1.00)	0.97 (0.73–1.28)	165 (32.2)	0.94 (0.78–1.13)	1.13 (0.91–1.40)	120 (23.0)	0.59 (0.48–0.72)	0.76 (0.60–0.97)	6,055 (33.7)
PT delivery (per LB)	79 (23.5)	0.77 (0.60–0.99)	0.93 (0.70–1.22)	144 (28.2)	0.98 (0.81–1.19)	1.09 (0.88–1.35)	113 (21.7)	0.69 (0.56–0.85)	0.87 (0.69–1.10)	5,133 (28.6)
LBW delivery (per LB)	59 (17.6)	0.63 (0.47–0.83)	0.73 (0.54–0.98)	138 (27.0)	1.08 (0.89–1.32)	1.25 (1.01–1.54)	96 (18.4)	0.66 (0.53–0.83)	0.87 (0.67–1.13)	4,563 (25.4)
35–37 y										
CP (per transfer)	106 (44.9)	0.69 (0.54–0.90)	0.85 (0.65–1.12)	430 (50.3)	0.86 (0.75–0.99)	1.01 (0.87–1.17)	278 (47.7)	0.77 (0.66–0.91)	0.83 (0.69–1.01)	7,088 (54.1)
LB delivery (per transfer)	83 (35.2)	0.65 (0.50–0.86)	0.78 (0.59–1.04)	376 (44.0)	0.95 (0.82–1.09)	1.13 (0.97–1.31)	219 (37.6)	0.72 (0.61–0.86)	0.77 (0.63–0.93)	5,949 (45.4)
SAB (per pregnancy)	22 (20.8)	1.60 (1.00–2.58)	1.56 (0.95–2.57)	46 (10.7)	0.73 (0.54–1.00)	0.62 (0.45–0.87)	53 (19.1)	1.44 (1.06–1.96)	1.49 (1.05–2.12)	995 (14.0)
MB delivery (per LB)	20 (24.1)	0.74 (0.45–1.22)	1.03 (0.58–1.83)	98 (26.0)	0.82 (0.64–1.03)	1.08 (0.83–1.42)	44 (20.1)	0.58 (0.42–0.82)	0.79 (0.53–1.17)	1,792 (30.1)
PT delivery (per LB)	21 (25.6)	0.98 (0.60–1.61)	1.16 (0.68–1.98)	80 (21.3)	0.77 (0.60–0.99)	0.84 (0.64–1.10)	44 (20.1)	0.72 (0.51–1.00)	0.86 (0.59–1.25)	1,547 (26.0)
LBW delivery (per LB)	13 (15.7)	0.63 (0.35–1.14)	0.82 (0.44–1.51)	62 (16.5)	0.67 (0.50–0.88)	0.76 (0.56–1.02)	40 (18.3)	0.76 (0.53–1.07)	0.99 (0.66–1.47)	1,359 (22.8)
>37 y										
CP (per transfer)	69 (40.8)	0.93 (0.69–1.27)	1.20 (0.87–1.66)	601 (40.6)	0.92 (0.83–1.03)	1.18 (1.05–1.34)	166 (41.1)	0.94 (0.77–1.15)	0.98 (0.78–1.22)	5,662 (42.5)
LB delivery (per transfer)	51 (30.2)	0.99 (0.71–1.38)	1.22 (0.86–1.71)	493 (33.3)	1.14 (1.02–1.28)	1.43 (1.26–1.62)	136 (33.7)	1.16 (0.94–1.43)	1.14 (0.90–1.43)	4,046 (30.4)
SAB (per pregnancy)	17 (24.6)	0.93 (0.54–1.61)	0.93 (0.53–1.63)	101 (16.8)	0.57 (0.46–0.72)	0.55 (0.43–0.70)	26 (15.7)	0.53 (0.35–0.81)	0.65 (0.42–1.03)	1,473 (26.0)
MB delivery (per LB)	11 (21.6)	0.93 (0.48–1.82)	1.46 (0.71–3.00)	105 (21.3)	0.91 (0.73–1.15)	1.98 (1.52–2.57)	29 (21.3)	0.92 (0.60–1.39)	1.56 (0.95–2.56)	923 (22.8)
PT delivery (per LB)	11 (22.0)	0.91 (0.46–1.78)	1.13 (0.57–2.27)	96 (19.4)	0.78 (0.61–0.98)	1.05 (0.81–1.36)	20 (14.8)	0.56 (0.35–0.91)	0.74 (0.44–1.24)	956 (23.7)
LBW delivery (per LB)	9 (17.7)	0.83 (0.40–1.71)	1.22 (0.57–2.58)	92 (18.6)	0.88 (0.69–1.12)	1.27 (0.97–1.65)	25 (18.4)	0.87 (0.56–1.35)	1.12 (0.64–1.95)	832 (20.6)

Note: aOR = adjusted odds ratio; CI = confidence interval; CP = clinical pregnancy; LB = live birth; LBW = low birthweight; MB = multiple birth; OR = odds ratio (unadjusted); PGD = preimplantation genetic diagnosis; PT = preterm; SAB = spontaneous abortion (miscarriages).

[a] Models were adjusted for infertility diagnosis, prior SAB, prior LB, prior ART, number of oocytes retrieved, number of embryos transferred, and embryos cryopreserved.

Chang. IVF with PGD. Fertil Steril 2015.

the rate of miscarriage was significantly lower compared with women of the same age who did not undergo PGD. In addition, among women aged >37 years, PGD for aneuploidy screening was associated with reduced odds of miscarriage and improved likelihood of having a live-birth and a multiple live-birth delivery, thereby suggesting that more viable or euploid embryos were transferred after screening. Thus, PGD for aneuploidy screening may be beneficial in reducing the risk of miscarriage for women aged ≥35 years and for improving the chance of having a live birth in women aged >37 years.

Although NASS does not collect information on PGD methods, newer techniques of array comparative genomic hybridization (CGH) were likely used during 2011–2012. As such, our findings are consistent with a number of randomized studies using array CGH, indicating the benefit of aneuploidy screening among women with advanced maternal age (20–22). Additionally, our findings support the counseling criteria and guidelines which recommend the use of PGD for aneuploidy testing among women >37 years as a means of improving their likelihood of ART success (14, 23).

Our report is among the first to assess PGD use and associated pregnancy outcomes using national data on nearly all ART cycles performed in the United States (13). In addition, we were able to evaluate a variety of outcomes according to the reason for PGD use among various age strata and limited to blastocyst transfers, thus reducing the potential impact of bias due to patient selection. However, several limitations should be recognized in the interpretation of our findings. Although the NASS collects data on PGD use and reasons for PGD, reporting of reasons for use of PGD may be imprecise and vary by physicians and clinics, particularly among PGD cycles for other reasons. For example, the characteristics of patients undergoing PGD for other reasons vary, making it difficult to interpret the results for this heterogeneous group. The non-PGD group may also have included cycles with known genetic disorders or chromosomal abnormalities that did not undergo PGD for various reasons, such as financial burden and possible false-negative results due to mosaicism (24). Moreover, NASS does not collect information on whether PGD use is intended for a particular treatment cycle, and some IVF cycles for which PGD is intended may not have embryos available for biopsy. Furthermore, we limited our analysis to cycles where at least one blastocyst embryo was transferred, which represents a selected population of good-prognosis patients. Another important limitation is the lack of information on the embryo morphology in NASS, which does not allow for evaluation or comparison of embryo viability among PGD cycles and non-PGD cycles. Finally, due to the retrospective study design used for our analysis, it is possible that selection bias affected our findings, particularly for the association between PGD for aneuploidy screening and miscarriage, as women with recurrent pregnancy loss may be more likely to undergo PGD.

Due to the complexity of PGD techniques, the efficacy of PGD depends on many different factors associated with the patient's characteristics and embryo's quality in addition to the type of PGD method used (6). The fact that NASS does not collect information on biopsy type, the protocol used to select chromosomal abnormalities, embryo-specific morphology or quality, including number of embryos available for biopsy, number of embryos biopsied, number of embryos discarded after PGD (e.g., chromosomally abnormal or aneuploidy embryos), and their diagnostic results, limited our ability to assess the effectiveness of the PGD procedure. Furthermore, comparing pregnancy results from PGD use can be challenging because different PGD methods may yield different results. Whereas the current method of chromosomal screening by array CGH has been found to improve pregnancy rates when used as part of a comprehensive screening program (20–22), older methods such as fluorescent in situ hybridization (FISH) have not been shown to improve outcomes (12). It is also possible that clinics with high rates of PGD performed had better outcomes than clinics that only performed a few PGD cycles. However, the results of our sensitivity analysis indicated that clinics with high (>25%) PGD rates did not have better treatment outcomes than clinics with lower rates. Although NASS collects information on the number of previous IVF cycles, it does not include information on previous PGD cycles or the availability of euploid embryos, particularly for two consecutive PGD cycles, which has been associated with improved pregnancy and implantation rates (25). Finally, as with any clinical diagnostic test, misdiagnosis of embryos can occur in PGD because of the technical difficulty of handling delicate cells and the fact that the cells can only be tested once; potential errors can occur and may result in the transfer of chromosomally abnormal or aneuploidy embryos (2, 19, 25–27).

Using data from a national population-based surveillance system with sufficient numbers to examine treatment outcomes for IVF cycles where PGD use was reported, we did not find the use of PGD to be associated with improved rates of clinical pregnancy or live birth among women aged ≤37 years, irrespective of the indication. However, PGD for aneuploidy screening of embryos improved the likelihood of having a live birth among women >37 years. This improved pregnancy outcomes among women with advanced maternal age is likely due to the enhanced PGD technique of array CGH with 24-chromosome analysis (20–22). Therefore, identifying euploid embryos presents the most effective opportunity for elective single-embryo transfer to achieve optimal live-birth delivery rate, even among women with advanced maternal age.

While preimplantation genetic testing can improve outcomes in certain patient populations, particularly those with a previous genetically affected child or a family history of chromosomal abnormality, the potential risks and benefits of the procedure should be considered in an effort to optimize both the safety and effectiveness of IVF treatments (26). Furthermore, collecting accurate information on PGD indication, PGD methods, and the outcomes of biopsied embryos with morphology information is critical as part of the national ART surveillance to better understand the effectiveness of PGD. Well-designed prospective, randomized studies are needed to effectively evaluate the efficacy of PGD.

Acknowledgments: The authors thank Michael Mersol-Barg, M.D., for his thorough review and suggestions.

REFERENCES

1. Kuliev A, Verlinsky Y. Place of preimplantation diagnosis in genetic practice. Am J Med Genet 2005;134A:105–10.
2. Baruch S, Kaufman D, Hudson KL. Genetic testing of embryos: practices and perspectives of US in vitro fertilization clinics. Fertil Steril 2008;89:1053–8.
3. Handyside AH. Clinical evaluation of preimplantation genetic diagnosis. Prenat Diagn 1998;18:1345–8.
4. Kokkali G, Traeger-Synodinos J, Vrettou C, Stavrou D, Jones GM, Cram DS, et al. Blastocyst biopsy versus cleavage stage biopsy and blastocyst transfer for preimplantation genetic diagnosis of B-thalassaemia: a pilot study. Hum Reprod 2007;22:1443–9.
5. Kearns WG, Pen R, Graham J, Han T, Carter J, Moyer M, et al. Preimplantation genetic diagnosis and screening. Semin Reprod Med 2005;22:336–46.
6. Munné S, Wells D, Cohen J. Technology requirements for preimplantataion genetic diagnosis to improve assisted reproduction outcomes. Fertil Steril 2010;94:408–30.
7. Adashi EY, Wyden R. Public reporting of clinical outcomes of assisted reproductive technology programs: implications for other medical and surgical procedures. JAMA 2011;306:1135–6.
8. Munné S, Fischer J, Warner A, Chen S, Zouves C, Cohen J, et al. Preimplantation genetic diagnosis significantly reduces pregnancy loss in infertile couples: a multicenter study. Fertil Steril 2006;85:326–32.
9. Munné S, Bahce M, Schimmel T, Sadowy S, Cohen J. Case report: chromatid exchange and predivision of chromatids as other sources of abnormal oocytes detected by preimplantation genetic diagnosis of translocations. Prenat Diagn 1998;18:1450–8.
10. Kuliev A. Preimplantation testing for chromosomal disorders improves reproductive outcome of poor-prognosis patients. Reprod Biomed Online 2005;11:219–25.
11. Gleicher N, Kushnir VA, Barad DH. Preimplantation genetic screening (PGS) still in search of a clinical application: a systematic review. Reprod Biol Endocrinol 2014;12:1–8.
12. Mastenbroek S, Twisk M, van der Veen F, Repping S. Preimplantation genetic screening: a systematic review and meta-analysis of RCTs. Hum Reprod Update 2011;17:454–66.
13. Centers for Disease Control and Prevention. American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. 2012 Assisted reproductive technology fertility clinic success rates report. Atlanta: U.S. Department of Health and Human Services; 2014.
14. Tempest HG, Simpson JL. Role of preimplantation genetic diagnosis (PGD) in current infertility practice. Int J Infertil Fetal Med 2010;1:1–10.
15. Ginsburg E, Baker V, Racowsky C, Wantman E, Goldfarb J, Stern JE. Use of preimplantation genetic diagnosis and preimplantation genetic screening in the United States: a Society for Assisted Reproductive Technology Writing Group paper. Fertil Steril 2011;96:865–8.
16. Simpson J. Preimplantation genetic diagnosis at 20 years. Prenat Diagn 2010;30:682–95.
17. Harper JC, Wilton L, Traeger-Synodinos J, Goossens V, Moutou C, SenGupta SB, et al. The ESHRE PGD Consortium: 10 years of data collection. Hum Reprod 2012;18:234–47.
18. Munné S, Alikani M, Tomkin G, Grifo J, Cohen J. Embryo morphology, developmental rates and maternal age are correlated with chromosome abnormalities. Fertil Steril 1995;64:382–91.
19. Marquez C, Sandalinas M, Bahçe M, Alikani M, Munné S. Chromosome abnormalities in 1255 cleavage-stage human embryos. Reprod Biomed Online 2000;1:17–26.
20. Yang Z, Liu J, Collins GS, Salem SA, Liu X, Lyle SS, et al. Selection of single blastocysts for fresh transfer via standard morphology assessment alone and with array CGH for good prognosis IVF patients: results from a randomized pilot study. Mol Cytogenet 2012;5:24.
21. Schoolcraft WB, Katz-Jaffe MG. Comprehensive chromosome screening of trophectoderm with vitrification facilitates elective single-embryo transfer for infertile women with advanced maternal age. Fertil Steril 2013;100:615–9.
22. Forman E, Hong K, Ferry K, Tao X, Taylor D, Levy B, et al. In vitro fertilization with single euploid blastocyst transfer: a randomized controlled trial. Fertil Steril 2013;100:100–7.
23. Simpson JL. Preimplantation genetic diagnosis to improve pregnancy outcomes in subfertility. Best Pract Res Clin Obstet Gynaecol 2012;26:805–15.
24. Collins SC. Preimplantation genetic diagnosis: technical advances and expanding applications. Curr Opin Obstet Gynecol 2013;25:201–6.
25. Pagidas K, Ying Y, Keefe D. Predictive value of preimplantation genetic diagnosis for aneuploidy screening in repeated IVF-ET cycles among women with recurrent implantation failure. J Assist Reprod Genet 2008;25:103–6.
26. Practice Committee of the Society of Assisted Reproductive Technology and Practice Committee of the American Society of Reproductive Medicine. Preimplantation genetic testing: a practice committee opinion. Fertil Steril 2008;90(Suppl):S136–43.
27. Wilton L, Thornhill A, Traeger-Synodinos J, Sermon KD, Harper JC. The causes of misdiagnosis and adverse outcomes in PGD. Hum Reprod 2009;24:1221–8.