

## Over a decade of experience with preimplantation genetic diagnosis: a multicenter report

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**Objective:** To review a 12-year experience of the world's three largest preimplantation genetic diagnosis (PGD) centers.

**Design:** Multicenter analysis of the clinical outcome of PGD.

**Setting:** In vitro fertilization programs at the Reproductive Genetics Institute, Chicago, Illinois; Saint Barnabas Medical Center, West Orange, New Jersey; and SISMER, Bologna, Italy.

**Patient(s):** Poor-prognosis IVF patients, patients carrying balanced chromosomal translocations, and couples at risk for producing children with Mendelian disorders.

**Intervention(s):** In vitro fertilization, intracytoplasmic sperm injection, polar body removal, blastomere biopsy, and ET.

**Main Outcome Measure(s):** DNA or chromosomal analysis of biopsied polar bodies or blastomeres, implantation and clinical pregnancy rates, and live-born pregnancy outcome.

**Result(s):** A total of 754 babies have been born as a result of 4,748 PGD attempts, which shows the expanded application and the practical relevance of PGD for single-gene disorders, chromosomal aneuploidies and translocations, late-onset diseases with genetic predisposition, and nondisease testing in couples at need for human leukocyte antigens-matched offspring for treatment of affected siblings.

**Conclusion(s):** Preimplantation genetic diagnosis is evolving to become a clinical option for couples at risk for producing offspring with Mendelian diseases, has a positive numerical impact in standard assisted reproduction practices through aneuploidy testing, and reduces by at least fourfold the spontaneous abortion rate in couples carrying translocations. (Fertil Steril® 2004;82:292-4. ©2004 by American Society for Reproductive Medicine.)

**Key Words:** Preimplantation genetic diagnosis, aneuploidy testing, IVF efficiency, chromosomal translocation, preimplantation HLA testing, live-born pregnancy outcome

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Introduced only in 1990 as an experimental procedure (1, 2), preimplantation genetic diagnosis (PGD) is now becoming an established clinical option in reproductive medicine. The estimated number of apparently healthy children born after PGD worldwide has surpassed 1,000, which validates that there is no ostensible evidence of any incurred adverse effect (3-5).

Used at first only for preexisting Mendelian diseases, such as cystic fibrosis and X-linked disorders, PGD initially did not seem to be practical. Only a few babies were born during the first 3 years of work, and several misdiag-

noses were reported, including those mentioned in Table 1 (3, 4). However, after the introduction of fluorescent in situ hybridization (FISH) analysis in 1993-94 for PGD of chromosomal disorders, the number of PGD cycles began to double annually, yielding more than 100 unaffected children within the next 2 years.

Application of PGD increased further when the ability to detect translocations became possible in 1996, first using locus-specific FISH probes and then more widely available subtelomeric probes. Because many carriers of balanced translocations have a poor chance of having an unaffected pregnancy, PGD has a

**TABLE 1**

Babies born and clinical pregnancies with different indications for preimplantation genetic diagnosis (PGD). Total experience of the three most active centers.

|                      | Aneuploidy       | Single gene disorders | Translocations | Total            |
|----------------------|------------------|-----------------------|----------------|------------------|
| PGD cycles           | 3,747            | 532                   | 469            | 4,748            |
| ETs                  | 3,099            | 466                   | 356            | 3,921            |
| Clinical pregnancies | 722 <sup>a</sup> | 142                   | 123            | 987              |
| % Pregnancies per ET | 23.3             | 30.5                  | 34.6           | 25.2             |
| Babies born          | 564              | 108 <sup>b</sup>      | 82             | 754 <sup>c</sup> |

<sup>a</sup> Three misdiagnoses with trisomy 21.

<sup>b</sup> Two misdiagnoses: one cystic fibrosis and one fragile-X syndrome.

<sup>c</sup> Two hundred seven pregnancies are still ongoing.

Verlinsky. *Preimplantation genetic diagnosis. Fertil Steril* 2004.

clear advantage over the traditional prenatal diagnosis in assisting these couples in achieving an unaffected pregnancy and delivering a child free from unbalanced translocations (5, 6).

Further expansion of PGD occurred in 1999, when it was applied for late-onset diseases with genetic predisposition, a novel indication never previously considered for the traditional prenatal diagnosis (7, 8).

This article presents the overall outcome data of the world's three most active PGD centers, the Reproductive Genetics Institute, in Chicago, Illinois; Saint Barnabas Medical Center, West Orange, New Jersey; and SISMER, Bologna, Italy. The work in each center was approved by the Institutional Review Board. These centers are the major contributors to the estimated first 1,000 babies born after PGD worldwide.

## PRESENT EXPERIENCE

A total of 754 babies have been born from 4,748 PGD attempts in our three centers, with 207 pregnancies still ongoing (Table 1). In the aggregate, these cases may encompass approximately three quarters of the cases worldwide (3–5). Preimplantation genetic diagnosis has allowed hundreds of at-risk couples not only to avoid producing offspring with genetic disorders, but more importantly, to have unaffected healthy babies of their own without facing the risk of pregnancy termination after traditional prenatal diagnosis. Without PGD, it is likely that few of these children would have been born.

The natural extension of PGD's ability to allow transfer of euploid embryos is its positive impact on the live-born pregnancy outcome (9–11). This is especially applicable to poor-prognosis IVF patients (prior IVF failures, maternal age over 37). Using commercially available five-color

probes, 3,747 clinical cycles have been performed by the three centers listed above for aneuploidy testing (Table 1). This has resulted in the birth of 564 children, including three with misdiagnosis, which suggests the continued need for improving the accuracy of FISH analysis.

The overall pregnancy rate per transfer is 23.3%, much higher than the rate in IVF patients in the comparable age group (average age, >39 years) without PGD, which does not exceed 20%. Although randomized controlled studies will still be required to further quantify the clinical impact of preselection of aneuploidy-free zygotes for ET, the present results suggest that it does have clinical relevance. Widespread confirmation of these results would indicate that the current IVF practice of transferring embryos based solely on morphological criteria is inefficient and in need of revision, given that half these embryos are chromosomally abnormal and would compromise outcome.

The 469 PGD cycles for translocations accumulated by the three centers (Table 1) demonstrated at least a fourfold reduction of spontaneous abortion in these couples compared with their experience before PGD (5, 6).

For patients with an inherited pathological predisposition, PGD provided a realistic reason for achieving pregnancy, with a reasonable chance of producing unaffected offspring, so prospective parents at such risk should be aware of this emerging option. The use of PGD for testing for genetic cancers, which are often autosomal dominant, and other late-onset diseases with a genetic predisposition has recently been summarized (7, 8).

Another unique option that can now be considered, although it involves ethical debate, concerns human leukocyte antigens (HLA) typing during PGD. This option cannot be considered with traditional prenatal diagnosis, but with PGD, it offers not only preventative technology to avoid affected offspring, but a new method for treating (older) siblings with congenital or acquired bone marrow diseases.

This approach was first applied to couples desiring an unaffected (younger) child free from the disorder in the older sibling (12). In addition to a diagnosis ensuring a genetically normal embryo, HLA-matched unaffected embryos were replaced. At delivery, cord blood (otherwise to be discarded) was gathered for stem cell transplantation. This approach can also be used without testing of the causative gene for the sole purpose of finding a matching HLA progeny for a source of stem cell transplantation for affected siblings with congenital or acquired bone marrow disease or cancer (5).

## DISCUSSION

The 12-year PGD experience demonstrates considerable progress. It may be estimated that more than 6,000 clinical cycles have been performed worldwide, resulting in the birth of at least 1,000 children. The birth prevalence of congenital malformations in the majority of these children, reported

previously to be in the range 5%–6%, was not different from population prevalence (3–5). With the highly improved accuracy of genetic analysis and indications expanding well beyond those for prenatal diagnosis, approximately 1,000 PGD cycles are performed annually. The incidence of testing during the last 2 years may have resulted in the birth of nearly the same number of children as during the entire preceding decade since the introduction of PGD (4, 5).

Preimplantation genetic diagnosis offers special advantages not possible with traditional prenatal diagnosis. One is to avoid clinical pregnancy termination (4). This is especially attractive for couples carrying translocations (6), couples at risk for producing offspring with common diseases of autosomal-dominant or recessive etiology, and, finally, for couples wishing to have not only an unaffected child, but an HLA-compatible cord blood donor for treatment of an older moribund sibling with a congenital disorder (12). Yet the greatest numerical impact of PGD is in standard assisted reproduction practices (9–11), where improved IVF efficiency through aneuploidy testing is surely evolving to become the standard.

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