

## **Preimplantation Genetic Diagnosis: Is it right for you?**

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### **What is Preimplantaion Genetic Diagnosis (PGD)?**

**PGD** is a general term referring to the testing of fertilized eggs (embryos) for genetic abnormalities prior to transferring the embryos into the uterus for implantation.

To obtain embryos for screening, PGD must be done in conjunction with **IVF** (in vitro fertilization). With IVF, eggs are extracted from a woman and combined with sperm in the lab to achieve fertilization outside of the body ('in vitro' or literally 'in glass' fertilization, that is, fertilization in the lab). An egg that has been successfully fertilized by a sperm is called a preembryo or simply an "embryo." An embryo starts out as one cell; by the third day after fertilization it is typically 8 cells. **The most popular method of PGD is to take one or two cells (blastomeres) from an 8-cell embryo for analysis.** The analysis takes time, almost 2 days. If the analysis is normal and the embryo continues to grow in the lab, it is now about 100 cells and called a **blastocyst** and ready to transfer to the uterus.

### **What are the potential indications for PGD?**

Well over 100,000 IVF cycles are performed in the USA per year. Only a relatively small number of these cycles involve PGD, the exact number is unknown but is growing. PGD was first reported in 1989 and involved determining the gender of embryos to avoid an X-linked genetic disorder [1]. For many years the focus of PGD was on screening the embryos of couples known to be at risk for a specific disease caused by a single gene defect (for example, cystic fibrosis). Because couples with this issue are relatively rare, PGD was performed at relatively few centers in the USA.

The recent growing popularity of PGD is a result of it being used to screen for "**chromosomal aneuploidies.**" The genetic or DNA blueprint of a person, namely the ~100,000 genes from each parent, is organized into 23 paired thread-like structures called chromosomes. As a woman ages, especially after the age 35, it is known that the eggs she produces has a higher chance of having an extra or missing chromosome, this is called a chromosomal aneuploidy. By screening embryos for chromosomal aneuploidies prior to transferring the embryos into the uterus, PGD is potentially a means to improve the outcome

of IVF in older women, women who have failed multiple IVF cycles, and some women with recurrent pregnancy loss. A recent meta-analysis and review concluded there is still insufficient data to indicate if PGD improves IVF live birth rates in older women [2, 4].

### **What genetic abnormalities can be screened by PGD?**

PGD can detect embryos with an abnormal number of chromosomes or chromosomal aneuploidy. For example, an extra chromosome 21 is Down Syndrome, a missing X chromosome is Turner Syndrome. Chromosomal aneuploidy is detected by a lab method called fluorescent in situ hybridization (FISH). FISH can detect the presence and absence of the X and Y-chromosomes and thus can determine the gender of an embryo. PGD can also detect abnormalities in chromosome structure (for example, translocations and inversions). A common PGD probe, the so-called “5-probe” screens for abnormalities in chromosomes 13, 18, 21, and X, Y. There is also a 9 and 10-probe. Note however that there are a total of 23 chromosome pairs (22 autosomes and X,Y). Current PGD screening with FISH thus only screens for a portion of potential chromosome aneuploidies; it is estimated that the 9 and 10 probes detect about 70% of the most common aneuploidies found in miscarriages [3]. Furthermore, smaller or partial aneuploidies of the chromosomes probed may go undetected. There is also the issue of mosaicism; embryos are not infrequently mosaic, that is, all of the 8 blastomeres do not have the same chromosomal makeup. Therefore with the analysis of a mosaic embryo, the analysis of a given blastomere may be correct but not reflective of the rest of the embryo. Other errors can be introduced by the inherent limitations in the FISH technique itself by events such as nuclear fragmentation. All of these limitations lead to an error rate estimated to be about 10%. Therefore, in a conception following IVF and PGD, standard prenatal genetic screening considerations including amniocentesis are still in effect.

New techniques, such as comparative genomic hybridization & blastocyst (trophectoderm) biopsy are being developed to improve current PGD limitations.

### **Summary:**

- PGD screens embryos for genetic abnormalities prior to transferring the embryos back to the uterus for implantation (“Preimplantation Genetic Diagnosis”).

- PGD requires IVF, with removal of one or two cells from an 8-cell embryo, and transferring the embryo into the uterus, about 2 days later if the embryo tests normally and continues to grow.
- PGD has been a clinical tool for over a decade. The recent popularity of PGD for screening chromosomal aneuploidy is driven by the hopes that it can improve the pregnancy rate in older women undergoing IVF, women with repeated IVF failure, and some women with recurrent miscarriage, these hopes have not been proven by studies yet [2, 4].
- PGD for screening chromosomal aneuploidy is a very promising tool that would be ideal if it tested for aneuploidy in all the chromosomes and was 100% accurate. In reality, it has a small but real error rate, and is potentially taxing to the embryo (requiring removal of one or two cells from the embryo, and necessitating the embryo grow in the lab for 1-2 more days while awaiting results). Ideally, it is performed on a couple that can produce many embryos with IVF, not always the case in women over 35. Like many new procedures in medicine, PGD is an amazing procedure with significant promise; on closer reflection, there are indications and some limitations that should be fully understood if you decide to undergo this advanced procedure.

[1] Handyside A, Pattinson JK, Penketh RJ. Biopsy of human preimplantation embryos and sexing by DNA amplification. *Lancet* 1989;1:347-9.

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[3] Munne S, Magli C, Bahce M, et al. Preimplantation diagnosis of the aneuploidies most commonly found in spontaneous abortions and live births: XY, 13, 14, 15, 16, 18, 21, 22. *Prenat Diagn* 1998;18:1459.

[4] Donoso P, Staessen C, Fauser BC, Devroey P. Current value of preimplantation genetic aneuploidy screening in IVF. *Hum Reprod Update*. 2007 Jan-Feb;13(1):15-25.