Regulating Preimplantation Genetic Diagnosis (PGD)

Preimplantation Diagnosis (PGD)—A European Clinician's Point of View

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This paper describes the current status of preimplantation diagnosis from the viewpoint of an experienced clinician specialized in reproductive medicine. Current progress and international experiences with different applications and techniques are being reviewed on the basis of the literature. Particular interest is focused on possible advantages of routinely diagnosing major chromosome aneuploidies in preimplantation-embryos of patients undergoing in vitro fertilization and embryo transfer. Last but not least, a short survey of the international guidelines and legislation is compared to the situation in the author's country, Austria, where it is currently unclear whether preimplantation diagnosis is allowed or not.

KEY WORDS: Preimplantation diagnosis; in vitro fertilization; assisted reproductive technology; infertility; polar body; aneuploidy; genetic and chromosomal disorders.

Internationally, there is consensus that PGD should be performed in all sufficiently large IVF centers with good pregnancy rates (1). Depending on the case there are different approaches which are suggested for PGD:

- 1) PGD for diagnosis of genetic diseases
- 2) Polar body-analysis for PGD
- 3) PGD as routine method to eliminate aneuploidy in IVF
- 4) Scientific aspects

PGD FOR DIAGNOSIS OF GENETIC DISEASES

The amount of diseases where PGD is indicated is steadily increasing and readers should refer to the appropriate articles in the literature (1–5). For people with heritable diseases, PGD is the method of choice to avoid pregnancies with genetically defect embryos. For those couples, the only possibility was so far prenatal diagnosis through chorionic villi sampling or am-

niocentesis with an abortion as a consequence of revealed genetic disorders. Keeping in mind that there are patients who went through two or three abortions due to such indications, the possibility of PGD in such cases provides progress and blessing.

POLAR BODY-ANALYSIS FOR PGD

In 1990, the group of Y. Verlinsky (6,7) described and realized the removal of the first and second polar-body to reveal chromosomal misarrangements of human oocytes. It is important to mention that this group was, for a long time, the only one worldwide that analyzed aneuploidies through this method while most other groups did this analysis on embryos after biopsies of 1–2 blastomeres (2,8,9).

In countries with legal restrictions, in regard to embryo biopsy (see last paragraph of this paper), polar body diagnosis is however the only option for the investigation of chromosomal aneuploidies in oocytes. Following a long research period, a group in Germany has started to offer polar body diagnosis for aneuploidy screening of chromosomes 13, 16, 18, 21, and 22, and published recently their excellent results reporting a 18.5% implantation rate and the first

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live birth following polar body diagnosis in Germany (10,11).

It is very important to notice that male genetic factors cannot be diagnosed by polar body-analysis. This is a great disadvantage compared to embryo biopsy. An additional limitation of polar body-analysis arises at the examination of monogenic diseases. Moreover, the second polar body has to be analyzed obligatorily to diagnose the heritage of monogenic diseases (10). For these reasons, such examinations have to be carried out by specialized units with adequate know-how only.

PGD AS ROUTINE METHOD TO ELIMINATE ANEUPLOIDY IN IVF

The raise of pregnancy rates through selection for viable embryos or elimination of aneuploidies respectively is one of the newest and most important goals for the application of preimplantation diagnosis. This goal only can be achieved by preferably large bandwidth of chromosomes, which are analyzed on a single preembryo. Furthermore, the risk of abortion can be reduced through this method. There are some hospitals in the United States that carry out PGD routinely, especially for older women, e.g., above 38 years of age (12).

Indications and Targets for PGD in IVF

It has to be outlined that this is not eugenic indication, as discussed in many ethical debates on the subject of PGD, but primarily a powerful method to eliminate nonviable embryos with aneuploidies of the first chromosomes.

According to recent publications, about 70% of all embryos of women older than 38 years are chromosomally damaged and are transferred "blind" hence they look normal in standard light microscopy. This explains why pregnancy rates in this age group remain at relatively low levels (12–16).

Through selection of chromosomally normal and therefore viable embryos, it would be possible to enhance the pregnancy rates for these women and to reduce costs and useless IVF attempts. Additionally to age indication, PGD would be a great hope for women with frequent early abortions, because this risk could be reduced significantly.

The third indication group includes patients with multiple failed IVF-attempts due to the fact that one can assume that many nonviable embryos will be produced or transferred.

SCIENTIFIC ASPECTS

The observation of mosaïque formation in dividing embryos is one of the most interesting scientific subjects of the present, because it offers an insight in early human preembryonal development. Because of first insights, one can observe that certain additions to culture media and enhancement of culture conditions reduce and control respectively the percentage of mosaïque formation (1). Therefore, it is very interesting from the scientific point of view to observe pathological diagnosed embryos or oocytes in further development through PGD.

LEGAL LIMITATIONS ON PGD IN EUROPE

International legal practice ranges from explicit legalization (e.g., the Netherlands, United Kingdom, France, Spain) over more or less "lawless control" (e.g., Italy, Belgium, and more) to legal prohibition through restrictive laws, as for instance in Germany or Switzerland. However, even in these countries, there is a tendency to ease such legal restrictions.

As the author asserts, there is no interdiction of PGD in his country Austria, neither through the law on Reproductive Medicine nor through the law on Genetic Engineering, unless the polar body or blastomere biopsy would be misinterpreted as "interference in the germ cell lineage" which, according to paragraph 9 passage 2 of the Austrian Act on Reproductive Medicine (17), would be prohibited.

The research on embryos, as well as their use for other purposes than assisted reproduction is strictly forbidden in Austria. Here again, it would be a great mistake equating diagnostic methods with research. Furthermore, there are attempts to interpret passage 1 of paragraph 1 as prohibition (18) where it is written that developmentally potent oocytes can be analyzed and treated only if it is for the purpose of causing a pregnancy (17). Perhaps one can interpret this as a prohibition through the so-called "eugenic indication" for PGD. If it is acknowledged today that PGD already serves the creation of pregnancies through exclusion of nonviable aneuploidies and selection of capable oocytes, then the application of PGD would, in the objective point of view, meet with the interests of the legislator. In the legal consideration it is essential to differentiate between polar body-analysis and PGD in the eight-cellular embryo. In Germany, for instance, the former method is allowed whereas the latter is forbidden. How Austrian law has to be

interpreted within this discrimination still remains a subject of further discussion. However, it would be possible to argue that polar body-analysis is legal within the Austrian legislature. The uncertainties within Austrian law still pose a great drawback on PGD in our country, and one is worried about more concrete prohibitions to come, a fact that still prevents clinics from purchasing the expensive and complex equipment for this technique. Existing prenatal diagnostic institutes could yet upgrade their laboratories to the modern diagnostic methods required and cooperate with IVF centers, a good solution that has to be proposed and favored at this stage.

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