Regulating Preimplantation Genetic Diagnosis (PGD)

Preimplantation Genetic Diagnosis (PGD) in France

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In vitro fertilization is strongly regulated in France. An agreement is needed for the clinicians and the embryologists; and the activity is under the control of CNMBRDP, a governmental commission. PGD is even more controlled; an agreement is needed for embryo biopsy and for genetic/FISH testing. Only three centers are allowed to perform PGD. All the agreements are given for five years and submitted to renewal. Regulations are under the "Ethical" law which should have been re-examined in 1999, but still not redone. This leads to problems, especially in relation with the research on embryos. Evolution of the techniques and indications necessitates a follow-up by the representatives on a regular basis.

KEY WORDS: PGD; FISH; IVF; regulations.

INTRODUCTION

Preimplantation genetic diagnosis in the early 1990s has been a matter of debate and controversy. The risk is naturally the shift towards eugenic manipulations, but also sex selection. In order to avoid these possible drifts, a law was voted in 1994 to regulate these activities (L 94-654, July 29th, 1994).

BIOLOGISTS AND GENETICIANS: WHO CAN PERFORM PGD?

First of all, it has to be said that IVF per se is strongly regulated. It is important to mention this, as PGD is performed by IVF units in relation with molecular biologists, cytogeneticians, and geneticists. To perform IVF, both clinicians and biologists need to have an agreement, given by the ministry of health after the advice of a specialized commission CNMBRDP (Commission Nationale de Médecine et de Biologie de la Reproduction et du Diagnostic Préimplantaire). This commission is supposed to control the

diploma and the expertise. The agreement is given to the candidates in a clinic (clinician) and in a laboratory (biologist). There is a mandatory link between the two. France has a worldwide originality: The biologist has to be a pharmacist or physician, with few exceptions (PhD), whereas for other countries having regulations, the biologist has to have a PhD in reproductive biology (see Alpha, *Scientists in Reproductive Medicine*). The agreement is given for a period of 5 years and the renewal is given after control, by the commission, of the results and the level of activity: A minimum threshold of activity is obviously required in order to maintain a satisfying expertise.

PGD is naturally also strongly regulated. PGD agreement is given to teams having the IVF/ICSI agreement. The team needs to have a special agreement for the biologist, allowing him to do biopsies. This agreement is also given by the CNMBRDP commission after control of the expertise, i.e. biopsies performed on animal embryos and/or on human blocked embryos. Then two other agreements are needed for the analysis of the blastomeres: Molecular biology for the genetic diseases and one for the cytogenetic analysis, basically translocations as PGD is not allowed for aneuploidy in elderly patients or female patients, with repeated miscarriages. These agreements are also given by the CNMBRDP commission; qualification is given after control of the expertise in genetic or

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cytogenetic testing on single cells (PCR and or FISH). The PGD center must be located in a multidisciplinary unit already agreed for prenatal diagnosis. PCR is used for the determination of the mutations for dominant and recessive mutations. The mutation has to be perfectly determined before testing.

FISH is used for the determination of the chromosomal content, but also for sex determination, especially for the X-linked recessive diseases. One of the major problems is that research on human embryos is obviously prohibited in France. A part of the problem is solved by the interrelations and the cooperation between the European teams (ESHRE consortium). PGD is classically performed by biopsy of two blastomeres on Day 3 post retrieval.

Two major centers practice PGD, even though agreement has been given for three centers. Those already fully working are the Center of Hopital Necker/Clamart in Paris and the Center of Strasbourg. These centers presented their data after 5 years of agreement in 2002.

WHAT LABORATORY FACILITIES ARE NEEDED?

For the biologist and the genetician, the main problem arises from the tiny quantity of material to be analyzed. The risk of loss of material and the risk of contamination originating from the biopsy and/or the manipulator are of major importance, especially for PCR. In order to avoid these problems, a room specifically designed for PGD is needed, with a laminar hood. A positive pressure in the biopsy room is requested.

WHICH PATIENTS?

The French law stipulates that "PGD realized by biopsy on human embryos in vitro is authorized exceptionally in the following conditions: A physician working in a multidisciplinary unit center of counseling for prenatal diagnosis must attest that the couple has high probability to give birth to a child with a heavy genetic disease, without any chance of successful treatment at the time of the diagnosis."

The diagnostic can only be done when the genetic defect(s) has been precisely identified in one member

of the couple. The two members of the couple have to give their consent for PGD. The only aim has to be the detection of the specific defect detected without any drift. Assisted reproductive technology is here fully designed to avoid transmission of a genetic defect (art. 152-2 of the code of public health). The request is then evaluated by the full PGD team.

WHAT IS CURRENTLY TESTED?

Even if France has started with a certain delay, the activity is now fully working. For cytogenetic, structural anomalies (translocation) as well as anomalies of numbers (risks of trisomy in case of mosaic) have been already tested. Genic testing has been performed on monogenic autosomic dominant and recessive and X-linked pathologies. Several hundreds of files of couples have been studied by the teams.

DISCUSSION AND CONCLUSION

The Current Problems

Again, as for all of the ART-related technologies; a reexamination of the law was scheduled after 5 years, i.e. July 1999. This has not been the case yet, after a delay of already 4 years. The ongoing law does not allow any research on human embryos. The only modification has been the possibility to import stem cells. In fact, it is obvious that no country can avoid an improvement of the ART techniques through research. It is unbearable to see that some techniques arise without any animal experimentation, followed by a validation on the human embryo; it is even more obvious for PGD. Some indications show that the current PGD could switch to biopsies at the blastocysts stage; again, if confirmed, a training with human embryos will point out the difficulty linked to the impossibility of doing research. Earlier, we (1) noticed that human trophoblast has a very special behavior. The other point to be highlighted is the delay for the patients: The waiting list is usually 1 year. How to decrease the delay? By increasing the number of centers allowed to perform PGD? By increasing the volume of activity of the centers in order to multiply the cases? This is not really possible at least for one of the centers. So there is a medical tourism at the moment.

There are still questions concerning the basic organization of the centers: Should they be specialized

is certain pathologies (i.e. a kind of sharing the of indications), or should all the centers deal with all the indications? At the level of a country like France, this is an important question. However, another possibility can be found in a European organization. There is already a European consortium on PGD: Information is shared and data are published on a yearly basis in *Human Reproduction*. It would be interesting that

PGD boost a common European Health policy on ART and related bioethics.

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