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Taskforce 5: preimplantation genetic diagnosis

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The European Society of Human Reproduction and Embryology (ESHRE) Ethics Task Force sets out a recommended multidisciplinary approach to the application of preimplantation genetic diagnosis (PGD). The statement includes consideration of fundamental ethical principles, specific problems in cases of high genetic risk, and PGD for aneuploidy screening, HLA typing and sex selection for non-medical reasons.

Key words: affected embryos/carriers/ESHRE/ethics/PGD

Introduction

Preimplantation genetic diagnosis (PGD) is a technique which was originally developed as an alternative to prenatal diagnosis for couples at high risk of transmitting a genetic defect. It allows scientists to check specific genetic defects of the embryo obtained through IVF so that only embryos not affected by the tested disease or balanced for the tested chromosomes can be replaced. It is also used for sex determination in case of X-linked diseases and for enumeration of chromosomes for couples, at low risk of transmitting a genetic disease, but with high risk of poor prognosis in ART treatment, for instance because of repeated abortions or advanced age.

Given the difficulty of defining 'disease' and 'abnormality' and of determining what constitutes an 'acceptable' risk, and keeping in mind the dangers of eugenics, we recommend a multidisciplinary approach to this new technology. In view of the complexity and sensitivity of decisions in the field of genetics in general, genetic counselling should be part of it.

Scientific background

There are two major approaches to obtain nuclear material for genetic analysis: the aspiration of the two polar bodies and the removal of one or two blastomeres from early embryos. The former is informative only for disorders of maternal origin, the second is also able to detect defects originating in the father and in the embryo and to determine the sex of the embryo. There are several techniques currently used to identify genetic defects. PCR is used for the detection of single gene defects (e.g. cystic fibrosis), and amplifies short sequences of DNA in such a quantity that the subsequent detection of a single base mutation through different techniques is possible. Fluorescence in-situ hybridization (FISH) permits sexing of the embryos (in cases of X-linked diseases such as haemophilia and Duchenne muscular dystrophy), simultaneous enumeration of up to nine chromosomes for aneuploidy screening (for the detection of abnormal numbers of chromosomes as in Down's syndrome) and structural chromosome abnormalities (such as unbalanced translocations). New methods, such as comparative genomic hybridization (CGH), may enable enumeration of every chromosome in a single cell.

In principle, diagnosis implies looking for a specific disease mutation or chromosomal aberration. In the case of sex-linked diseases, looking for specific mutations might be impossible, technically difficult or not accessible to all potential patients. Hence, sexing of the embryo for sex-linked diseases can be included in the category of PGD.

Generally, the term 'screening' implies looking for a genetic defect in all members of a population at risk. Preimplantation genetic screening implies screening embryos at risk. The estimation of the risk depends on the incidence and seriousness of the defect. This explains why some experts prefer the term preimplantation genetic *diagnosis* for aneuploidy screening (PGD-AS). However, this is screening as it applies to a population which is at increased risk because of a common feature, for instance female age, and without a family history to indicate that there is an increased genetic risk.

The analysis of the PGD cycles until now demonstrates the clinical value of preimplantation testing for (i) preventing genetic disorders in couples at risk of having offspring with a genetic disease; (ii) reducing the risk of spontaneous abortions in couples carrying translocations, and (iii) improving the effectiveness of assisted reproduction in poor prognosis patients, such as women of advanced age.

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Ethical considerations in PGD

Fundamental ethical principles

At stake are two main principles. Firstly, the technology is justified by referring to the welfare of the child by avoiding harm to the future offspring. Secondly, the application of PGD increases the autonomy of the parents, both by allowing them to choose a technique that better fits their moral principles and reduces the psychological burden (by avoiding repeated terminations of pregnancy) and by giving them the possibility to protect their interest in favouring the health of their offspring.

Before embarking on the IVF cycle and PGD, there should be a deliberation between the team and the patients. Each party has the right to withdraw in case of disagreement. The clinic has the right to refuse participation in the reproductive project if they consider the risk of the future child being affected as too high despite PGD. The final decision should be a joint decision between the centre and the patient, which should be reached according to the shared partnership model. Nevertheless, the onus of flexibility is on the side of the carer.

Safety considerations: there is no evidence for the time being that the removal of one cell for the biopsy affects the embryo. At present, not enough data are available to determine whether taking two cells leads to a greater loss of embryos or endangers the health of the offspring. The aim of taking two cells is to reduce the number of misdiagnoses. At present, PGD babies do not seem to be exposed to greater risk of neonatal problems or malformations.

Information giving is essential, with the adjunct of genetic and implication counselling related to all the different steps of the procedure. This involves the need for IVF, including ovarian stimulation, the possible unavailability of unaffected embryos, the limitations of the PGD method including the rate of misdiagnosis, inconclusive diagnosis and possible long term negative effects which are at present unknown.

Specific problems

Carrier detection and replacement

The crucial argument for not replacing carrier embryos lies not in eugenic considerations (i.e. the wish to clean the gene pool and to eradicate the illness from humanity) but in the wish to spare the offspring the burden of having to make similar decisions for their own reproduction. The risks for the child are largely determined by the type of disease. If the child is a carrier of an autosomal recessive disease (such as cystic fibrosis), the risk that his or her children will be affected is 1%. For X-linked diseases such as Duchenne's muscular dystrophy, the risk for a female carrier of transmitting the disease is 50% for each son. If—among the embryos available after PGD—there are both non-carriers and carriers, the healthy embryos should be replaced first while the carrier embryos should be cryopreserved. If there are only carrier embryos, the couple should be counselled regarding the risk involved for the offspring. It is important that the transfer of carrier embryos is discussed with the patients before the PGD cycle, especially in the case of X-linked diseases. Ultimately, the couple decides whether or not carrier embryos will be replaced.

Late onset and multifactorial diseases

PGD for late onset diseases is acceptable, in spite of the still existing uncertainties concerning therapy in the time gap between the birth of the child and the onset of the disease. PGD can also be accepted in the case of multifactorial diseases (like BRCA) notwithstanding the uncertainties about the genetic predisposition and the epigenetic influence.

It is essential to take into account the severity of the illness and the effects on the quality of life of the future offspring. Still, it is almost impossible to objectively assess the suffering and quality of life of a person. Furthermore, the imperfection in predicting the development of the disease forces us to accept that a number of embryos will be discarded that will not develop the disease. This is similar to the selection of embryos on the basis of sex in case of sex-linked diseases.

In order not to impose unethical behaviour on the practitioners and to respect their autonomy, it is advisable to test only the embryos of couples who agree to know the results and who accept all the implications of the test. Non-disclosure testing, as for Huntington's disease, is not favoured but PGD exclusion testing is considered morally acceptable. PGD exclusion testing has the same implications in terms of the loss of embryos for replacement as exclusion testing by means of sexing. It is not subject to the practical and ethical objections raised against non-disclosure testing. Exclusion testing recognises the right of the parent not to know whether or not they are themselves affected while enabling them to have children not affected by the disease. Genetic implication counselling is a necessary part of the procedure.

PGD–AS

The principle is to increase the reproductive efficiency of patients with reproductive problems. At present, the existing data support the notion that the application of PGD-AS has some advantages, e.g. in women >37 years and in couples with repeated abortions or multiple failed IVF cycles. This improvement is achieved by reducing the miscarriage rate and consequently by improving live birth rate per transfer. However, at present the advantages of applying this technique on a larger scale have not been demonstrated. There are few controlled trials for the efficacy of aneuploidy screening. Before wider application is considered, hard data on the possible benefits for the couple have to be available.

The same principles of the welfare of the child and the autonomy of the couple apply. The safety issues are similar to those in PGD.

PGD for human leukocyte antigens (HLA) typing

For a number of diseases, transplantation of haematopoietic stem cells is the only known cure. Parents with a child affected with such a disease may want to generate a future child who may serve as a donor of haematopoietic stem cells or other tissues for the sick sibling. In order to ensure a matching donor, they request HLA typing of the embryo by PGD. This use of PGD is usually combined with a test to ensure that the future child is not affected by the same disease.

The benefits for the receiving sibling whose life can be saved outweigh the disadvantages (if any) for the future child. This

solution is morally acceptable if the use as a donor is not the only motive for the parents to have the child (i.e. they intend to love and care for this child to the same extent as they love and care for the affected child) and if the operation would be acceptable if the donor child already exists. If parents have the authority to 'volunteer' an existing child as a bone marrow donor for a sibling, it is also acceptable that they create a child as a bone marrow donor for a sibling. The creation of a child for the purpose of harvesting non-regenerating organs seems extremely difficult to justify in view of the risks involved for the donor child.

Affected embryos

The request of disabled parents to replace embryos with a disability (e.g. deafness) can only be defended if the welfare of the child is strictly considered within the familial boundaries or subculture. However, the functioning of this child within society at large would be severely impaired due to the imposed disability. Therefore, such deliberate restriction of the autonomy of the child is not considered justifiable. Consequently, no PGD cycle should be started for such requests.

A similar reasoning applies to cases where it is not known whether the embryos are affected but where the risk is considered as high. This would be the case when, after sexing for a sex-linked disease such as Duchenne's muscular dystrophy, only male embryos are available and the couple requests their replacement. Considering the high risk for a serious disease, we find the replacement of such embryos should be avoided. Discussion of this issue should take place before the start of the PGD cycle.

PGD for sex-selection for non-medical reasons

Regarding the issue of sex selection for non-medical reasons by means of PGD, the Task Force has not been able to reach a unanimous decision. Two positions can be distinguished: those opposed to every application of sexing for non-medical reasons and those who accept sex selection for family balancing.

Position 1: sex selection and human rights

For some, sex selection for non-medical reasons is intrinsically sexist. Sex selection for social reasons is seen as an issue of human rights which entails non-discrimination on grounds of sex (as well as religion or phenotype), enshrined in both the Universal Declaration of Human Rights of 1948 and the European Convention of Human Rights of 1950.

It may also be asked whether making it acceptable to select one sex in preference to another at the moment of conception or by PGD will make it easier or harder to promote anti-discriminatory measures in other areas of life, at a time when world-wide discrimination, usually against women, is still very widespread. Moreover, PGD is a method used to prevent disease or suffering and to be of the 'wrong' gender in the eyes of one's family, whether male or female, cannot be defined as a disease. The possible compromise of family balancing is still regarded as inherently sexist.

Finally, it is felt that children would benefit to be born in a society in which acceptance rather than rejection of any difference (phenotype, gender or disabilities) is the norm to the extent that the protection offered by the human rights has become redundant. However, there is no evidence as yet that this ideal is within reach.

Position 2: sex selection for family balancing

The wish to increase autonomy while avoiding conflicts with other ethical principles leads to the position that sex selection for non-medical reasons is only allowed to balance the family. No selection is allowed for the first child or where there is an equal number of both sexes. The application of the technology for family balancing is not considered as good but as morally acceptable. Consequently, sex selection for this reason should be permitted.

The restriction of sex selection to applications for family balancing gives parents more control of the composition of their family and simultaneously avoids the potential disasters (like a skewed sex ratio in society) caused by the unrestricted application of sex selection.

However, the application should not jeopardize other generally accepted moral principles, like the principle of justice (as expressed in the equality of the sexes) and the principle of respect for the autonomy of the future person. The application for family balancing differs from the unrestricted application because the parents do not and cannot choose a child of a certain sex but choose a child of the *other* sex. This choice does not express a hierarchy or inequality between the sexes and thus cannot be considered as intrinsically sexist. Parents who wish to have children of both sexes believe that the upbringing of boys can be different from the upbringing of girls and that the parent-child relationships may differ according to the sex of the child.

The parental choice does not endanger the autonomy of the future child. If the autonomy of the child is not threatened by being born as a girl (or a boy), then this principle is not infringed either when the girl (or boy) is born as a result of parental choice. Moreover, the parents do not choose the sex of a future child but a future child of the other sex.

Similar to the decision-making concerning other matters in reproduction, the decision about the technique to be used should be discussed between fertility specialist and patient. The preference for a specific method will be influenced by the reproductive history of the patient. Depending on a number of characteristics such as age of the mother, desired family size and strength of the desire for the other sex, patients may opt for a more reliable method rather than for a less reliable but cheaper and less invasive method. The technique should be safe and performed according to the rules of good clinical practice. The application should be supported by psychological counselling to inform the parents of the different aspects of the treatment. This implies, for PGD, a thorough discussion of all possible scenarios including the possibility of not having embryos of the desired sex, not getting pregnant and misdiagnosis. The need to rely on PGD for non-medical sexing will decrease if other methods reach a comparable level of reliability without the costs and efforts connected to this method.