Social, Ethical, and Legal Aspects

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Preventive approaches to congenital disorders always raise ethical problems, because traditionally the emphasis should be on treatment rather that on the avoidance of birth of children with congenital disorders, which is unfortunately unavailable for most of genetic disorders at the present time. On the other hand, the most ethically acceptable preventive approaches are indeed those that involve the primary preventive measures, which are better tolerated by society, than the secondary preventive measures involving pregnancy termination. As described in Chap. 1, one of the best examples of the most efficient primary preventive measure may be a population-based fortification of the major foodstuffs by folic acid containing multivitamins, which has been demonstrated to result in significant reduction of neural tube defects and congenital malformations overall. Still such programs have been introduced only in a few populations, so the lack of similar preventive measures in most of communities may be the reason that thousands of children with congenital disorders continue to be born, who otherwise might have been born healthy, which, therefore may represent an important legal, social and ethical issue. What is of special importance is that these primary preventive measures are ethically acceptable in any population, because they provide the actual gain in infants free of congenital malformations, rather that the avoidance of birth of affected children.

The same is true for preimplantation genetic diagnosis (PGD), which is also a primary preventive measure, although applied on a family level, allowing the genetically disadvantaged couples to produce unaffected children of their own, who might not otherwise be born at all because of fear of these couples to reproduce and face prenatal diagnosis and termination of pregnancy [1, 2]. So any legal restrictions of these patients' choices may only force them to achieve their goal by traveling to other countries where the regulations regarding PGD are more liberal. The available reviews on the status of PGD in different countries [3–8] show that the international legal practices range from explicit legalization (e.g., the Netherlands, United Kingdom, France, Spain) over more or less "lawless control" as in Belgium and the United States, to legal prohibition through restrictive laws, as in Italy, Germany, Austria or Switzerland. However, even in these countries, there is a tendency to ease such legal restrictions. For example, there is no interdiction of PGD in 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 would be prohibited [7]. In France, PGD is under the control of CNMBRDP, which is a governmental commission controlling also IVF [4, 5]. According to the regulation, an agreement is required to perform the embryo biopsy and genetic/FISH testing, the evolution of which and indications being the subject for a follow-up by the representatives on a regular basis. Only a few centers are allowed to perform PGD for the initial 5 years, the subject for the renewal afterwards; the regulations are

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under the "ethical" law, requiring a forthcoming re-examination. Similarly, PGD in the United Kingdom is regulated by HFEA, which is also a governmental organization, which provides the license for performing PGD and also has to approve any new condition to be performed. For example, PGD for chromosomal aneuploidies, practiced for more than 10 years in many other countries, has been allowed by HFEA much later. HFEA also initially refused to allow preimplantation HLA typing without PGD and then changed its position. Finally, PGD and many aspects of IVF were forbidden in Italy by the Act of Parliament almost for 7 years, according to which only three oocytes were allowed to be aspirated for fertilization in vitro, clearly following the opinions of the hierarchy of the Roman Catholic Church [9]. Of course, this made PGD impossible in Italy until only recently when this law was finally lifted, despite the fact that this country has been among the most active ones involved in the development and application of PGD for genetic and chromosomal disorders [2].

As described in Chap. 2, with the introduction of the methods of preconception diagnosis by polar body (PB) diagnosis, PGD has become ethically acceptable even in countries with restrictive laws, such as in Germany, where no manipulations are allowed after conception. According to the German Embryo Protection Act, the fertilized, viable ovum is already an embryo in the sense of the law [10], so no manipulation is allowed that could potentially damage it, despite the fact that approximately 120,000 abortions are performed annually in this country. Removing and examining blastomere in PGD, which is destroyed in this process, is punishable with a prison sentence, for up to 3 years or a fine. So PGD is an undisputable violation of this Act, as the life of a human being (namely the life of this biopsied cell) is destroyed. In these circumstances, PB testing is the only way to avoid violation of this law, as no embryo is formed by completing diagnosis prior to fusion of male and female pronuclei (see Chap. 2). In fact, this approach may also resolve the ethical issues of PGD in Austria, Switzerland, Malta, and other strictly Catholic countries [7] and may, in future, make PGD an acceptable procedure even in those countries, where no preventative measures have ever been allowed on religious grounds. No doubt that preconception diagnosis will also make PGD even more attractive in Muslim countries, where blastomere biopsy is currently acceptable and a more preferred option over prenatal diagnosis. Preconception diagnosis may no longer be restricted to the maternally derived genetic abnormalities, because the possible progress in sperm duplication may, in future, allow also sperm testing for the paternally derived abnormalities prior to fertilization (see Chap. 2).

On the other hand, the above law restriction on PGD, have stimulated the progress in the development of PGD technique, as could be observed in Italy, after introductions of restriction on IVF and PGD by the Roman Catholic Church. As the fertilization of no more than three oocytes was allowed, and PGD was prohibited, PB analysis was introduced to test the mature eggs prior to fertilization, so to avoid the use for fertilization of the oocytes with meiosis I errors (see Chap. 5).

The available experience show that PGD has become a routine procedure in an increasing number of countries, such the United States and Belgium, where no strict governmental regulations for PGD exist. It is, therefore, not surprising that the largest experiences in PGD for genetic and chromosomal disorders have been accumulated in these countries. The guidelines and standards for appropriate PGD practice have recently been developed by Preimplantation Genetic Diagnosis International Society (PGDIS) and ESHRE and may be followed to achieve the required standards of PGD [11, 12]. There are also regulations developed by the national scientific societies, such as in Japan, where no active PGD program is currently available, but there are regulations for PGD developed by the National Society of Obstetrics and Gynecology and by the Japan Society of Human Genetics, which provides the guidelines for genetic diagnosis [8].

The ethical issues of PGD have been recently evolving together with the development of the methods and with the expansion of the PGD indications. Initially, when PGD was applied only to pre-existing conditions, with the only goal of avoiding the risk of birth of children with genetic

disorders, PGD allowed avoiding traditional prenatal diagnosis and termination of pregnancy, so making prevention of genetic disorders more ethically acceptable. Some of the couples may have had the experience of the repeated pregnancy terminations before having a normal child, while the others could not accept prenatal diagnosis and termination of pregnancy at all. So PGD initially was an important alternative, so that the at-risk couples had the choice of either going through prenatal diagnosis and termination of pregnancy, or controlling their pregnancy outcome by testing the oocytes or embryos before implantation, to secure that the pregnancy is unaffected from the onset. Accordingly, not informing the genetically disadvantaged couples about PGD availability, which may have affected their possible choices, may present an important ethical and legal issue. It is especially important for those conditions, such as translocations, carriers of which have an absolutely miserable pregnancy outcome. As mentioned in Chap. 5, analysis of meiotic outcome in carriers of translocation leaves a little chance for prenatal diagnosis to be useful in identifying a balanced or normal fetus, as the carriers of translocations have more than 80% prospect of losing their pregnancy by spontaneous abortions. So, PGD for such couples is clearly the only hope, providing a realistic option of having unaffected children of their own.

As shown in Chap. 3, PGD will have the increasing practical implications with the current progress in the improvement of the quality of life, the life expectancy and the possibility to reproduce by the genetically affected patients. For example, the life expectancy in cystic fibrosis (CF) patients may presently be no different from the normal individuals, who may be able to procreate and have their own children. Similarly, with the success in stem cell transplantation, children with thalassemia may be radically cured, and these so-called ex-thalassemics require PGD to avoid 50% risk of producing their own thalassemic children. As seen from Chap. 3, PGD has already been applied for homozygous or double heterozygous affected individuals with CF, thalassemias and phenylketonuria (PKU), who were able to have their own unaffected children following PGD. On the other hand, this may still create the feeling that some extreme variations of the genotype are rejected by society, so the couples may face a complex decision of transferring back the embryos with different genotypes. For example, some couples may elect to transfer the embryos carrying the affected genes, such as for deafness or achondroplasia, so using PGD to conceive a disabled child, which sets a poor precedent for the patients facing complex familial decisions [13].

The important breakthrough from the ethical and social point of view was the introduction of PGD for the diseases with genetic predispositions, especially when it has become possible to avoid the transfer of the embryos carrying the genes predisposing to common disorders of adult life. Although there is no difference in the application of PGD for early or late onset disorders with genetic predisposition from the application of PGD to chromosomal disorders and autosomal recessive metabolic disorders with the onset at birth or early childhood, the discomfort of PGD for disorders with genetic predisposition can be explained by the fact that this has been controversial or even unacceptable in the practice of prenatal diagnosis. The same diagnosis is of course possible by chorionic villus sampling (CVS) or amniocentesis with the only difference that if the fetus would appear carrying the gene predisposing to late onset diseases with genetic predisposition, such as Alzheimer disease (AD) or other late onset diseases with genetic predispositions, described in Chap. 3, the couple would have to make an important decision of pregnancy termination. This could hardly be justified on the basis of genetic predisposition alone, taking into consideration that the clinical manifestation of the disease might not be realized at all in some proportion of cases. Alternatively, PGD technology allows genetic testing of human eggs and embryos before pregnancy, therefore, making it totally realistic to establish only potentially normal pregnancies without a disease with early or late onset disorder with genetic predisposition. Thus, the prospective at-risk parents have to be informed about the availability of the PGD technology, to

allow them to make the decision themselves about their reproductive options.

This is not similar for PGD for Hantington's disease (HD), which despite being also the late onset disease, always progressing and leading to death within approximately 15 years after start. Prenatal diagnosis is still controversial, as selective abortion will not be acceptable because the child might still expect many disease-free years. The well-known "nondisclosure PGD" is obviously the best option for these couples, as asymptomatic individuals with risk of carrying HD may be offered PGD to test embryos without ever being informed about the specific test results.

The situation is even more controversial for PGD of late onset common disorders, which may never be presented during the whole lifespan. On the other hand, with no current prospect for treatment of most late onset diseases with genetic predisposition, such as AD, which may arise despite presymptomatic diagnosis and follow-up, prevention of inherited predisposition to late onset disease may be the only possible option for the couples at risk, because the carriers of mutations causing the above group of diseases not only have up to 100% lifetime risk of developing a disease, but also pass this genetic predisposition to their children. The extremely difficult life experience of families affected by any catastrophic early or late onset inherited disorder, seeing suffering from the disease and being anxious that they themselves will be soon affected, make them responsible to ensure that future generation will not be faced by the same difficulties [14, 15].

As for helping couples with their fully responsible decision to use the option of PGD to avoid the inheritance of a causative gene to their progeny, such as a gene for AD, although one of the partners may not be around to see this child grow up, of course societal discussions on the issue will be of great use [16]. First of all, the situation when only one parent supports a child to grow up and takes the responsibility for his or her future is not rare. On the other hand, this is not much different from that in parents who may get cancer or killed in a car accident, which are the main killers in western countries. At least, using PGD is better than having children without testing, because these children will have 50% chance of having AD or other dominantly inherited predisposition to severe late onset disorders with genetic predisposition. The possibility that there may be some approaches to prevent the clinical manifestation of these disorders in carriers of the mutant gene should not be excluded either.

PGD for common late onset disorders provides a novel nontraditional option for patients, who may wish to avoid the transmission of the mutant gene predisposing to their potential children. This may appear for some patients the only reason for undertaking pregnancy, as the pregnancy may be established free from an inherited predisposition from the very onset. Because, as mentioned, such diseases never present at birth or early childhood and even later may not be expressed in 100% of the cases, the application of PGD is still controversial. However, with no current prospect for treatment of many of them, which may arise despite presymptomatic diagnosis and follow-up, PGD may be offered as the only relief for such at-risk couples.

Therefore, prospective parents should be informed about this emerging new technology, so they could make their choice between seizing their reproduction and forgoing pregnancy free from late onset disorders with genetic predisposition. This seems to be ethically more acceptable, than a denial of the information on the availability of PGD. Presented results of PGD for the early or late onset disorder in Chap. 3, demonstrate the extended practical implications of PGD, providing prospective couples at genetic risk with wider reproductive options for having unaffected children of their own.

One of emerging indications for PGD, presenting complex ethical issues is predisposition to different forms of cancer (see Chap. 3). For example, PGD for breast cancer, caused by BRCA1 and BRSA2 genes, is being performed for increasing number of cases, despite the high cost of the procedure. PGD for breast and ovarian cancer has recently been also allowed by HFEA, despite the lack of appropriate guidelines for its use. It is expected that PGD will be used selectively, depending on the gene mutation, factors around a particular condition, age of onset, treatability, the

average penetrance, and the medical history of the individual family.

Even more complicated decision for PGD may concern the inherited cardiac diseases, for which no preclinical diagnosis and preventive management may exist and which may lead to premature or sudden death. The cumulative experience of PGD for inherited cardiac diseases, presented in Chap. 3, showed first results of PGD for familial hypertrophic and dilated cardiomyopathy, which introduces the option for couples carrying cardiac disease predisposing genes to reproduce without much fear of having offsprings with these genes at risk for premature or sudden death. However, it is still not clear how complex the ethical concerns are in relation to PGD for these common disorders, which may not be realized even in the whole lifespan.

One of the important ethical issues of PGD is also preimplantation HLA typing, because PGD for this indication is done for the benefit of a potential recipient rather than for the embryo itself, particularly when there is no need for testing of causative gene [13, 17, 18]. This may lead to feelings of moral outrage in some, while others may justify the action as saving a child's life from a severe disease. It is of interest that the majority of Americans are supportive of using PGD to ensure that an infant will provide an HLA match to donate stem cells or even tissue to an older sibling [19].

However, attitudes may be different depending on whether the genetic testing in the embryo is done or not. If preimplantation HLA typing is performed in combination with PGD, with the primary purpose being testing for causative gene, such as in case of Fanconi anemia (FA) [20], it appeared morally more acceptable, than preimplantation HLA typing as a sole purpose. The example of the latter situation may be leukemia or sporadic Diamond-Blackfan anaemia (DBA) in older children that may be cured by HLA-matched stem cell transplantation [21], which, however, does not present any benefit to the embryos tested. For example, as mentioned, such parents have initially been denied permission for preimplantation HLA typing in the UK. The moral dilemma stands also on the need of parents to have another child. However, preimplantation HLA typing as the sole reason is currently allowed also in the UK.

Some issues associated with preimplantation HLA typing are related to the actual indications for preimplantation HLA testing, which seem to be similar to the indications for stem cell transplantation, because preimplantation HLA typing has the objective of improving the access to an HLA identical stem cell transplant, which is the key in achieving an acceptable engraftment and survival in stem cell therapy. No doubt that the indications will be modified with progress in treatment of bone marrow disorders. For example, with current success in cure rate by chemotherapy, acute lymphoid leukemia (ALL) and acute myeloid leukemia (AML) may no longer be an indication [22], but the option of the stem cell therapy should still be available for patients, taking into consideration a sizeable proportion of patients, for whom chemotherapy was not effective and who may still require compatible stem cell transplantation, especially if the parents plan to have another child anyway. So all the conditions, for which bone marrow or cord blood stem cell transplantation is required, are also indications for preimplantation HLA typing.

The other important issue is the applicability of preimplantation HLA typing for sporadic conditions, such as DBA, for which there are also inherited forms. Accordingly, the inherited forms might require PGD for the mutations involved, to exclude the risk of transplantation of compatible stem cells, which might contain exactly the same mutation as the sibling [23]. For example, there are already known mutations causing DBA, such as one in the gene encoding ribosomal protein S19 on chromosome 9, and another gene mapped to chromosome 8 (see Chap. 4). It cannot be excluded, that additional mutations will be found for some of the other sporadic forms, also requiring PGD [24]. Still without such information, the couples have to make the decision about the need for undertaking transplantation, because of serious iron overload in the patients requiring urgently the compatible stem cell transplantation from the family member. Therefore, all known mutations causing the disease should be excluded by detailed mutation testing in parents and affected children,

and this should also be confirmed by the ongoing follow-up studies of the HLA-matched children born after preimplantation HLA typing.

The other controversial issue involves the written consent form, which is signed by parents for the embryo, similar to the situation when parents sign the consent form for umbilical cord blood stem cell collection and storage. It may be also argued that parents do not actually need a baby, and have it merely as a means to save its older sibling, so it would then become a commodity in some peoples' eyes, although parents usually claim that another child is needed for their family anyway, the decision which is solely parents' right.

Although at the present time, only umbilical cord blood stem cells are being collected from the "designer babies" at birth, presenting no harm for the baby, it is argued that the same approach may be used for organ donation. While with the progress in differentiation of cord blood stem cells into the other types of cells [25], such possibilities cannot be entirely excluded. It should be mentioned that preimplantation HLA typing also allows avoiding many ethical issues of reproductive and therapeutic cloning, as it provides more ethically acceptable option of selecting an HLA-matched progeny, rather than obtaining custom-made embryonic stem cells following somatic nuclear transfer and cloning.

Of special ethical concern is a nonmedical use of PGD for sex selection, which has been considered acceptable for social reasons in the US, provided that it is applied for selection of sex of the second or subsequent children [26, 27]. On the other hand, in some countries, such as India or Jordan, PGD is legally used for sex balancing, which seems to be also well justified [28, 29], as it is a part of reproductive autonomy, privacy in reproductive decision making and the moral superiority of preimplantation selection over sex selection abortion [30, 31]. However, it may also be argued that PGD for gender determination reinforces existing sexism and the expectation of conformity to stereotypical gender norms, and inconsistent with the ideal of parents having unconditional love for their children [32, 33]. Despite this opposition and also the opinion of American Society of Reproductive Medicine [26], American College of Obstetricians and Gynecologists [34] and HFEA [35], that the creation of embryos to select sex or enhance gender variety in the family is an inappropriate way to allocate medical resources, the use of PGD for this purpose is steadily increasing, with approximately 3,000 PGD cycles conducted annually only in the USA [36]. While the majority of studied cases were performed for medical reasons or together with PGD for genetic conditions and aneuploidies [37–39], increasing number of cases is performed for non-medical reasons [40–42]. For example, the special study performed to investigate moral attitudes and beliefs of the couples pursuing PGD solely for the purpose related to sex selection showed that the motivations for requesting gender determination includes a desire to limit family size, concerns about parental age, and financial concerns [43]. Although one of the main desires is to achieve a gender-balanced family, it was also shown that the majority of couples (78%) were seeking sex selection in order to have a boy [41, 42].

Finally, PGD raises many ethical issues, which are not unique to its clinical practice and instead are the same as in assisted conception [13]. One of the major criticisms concerns the selection of the embryos according to certain genetic parameters and destruction of others. In fact, the selection of a few embryos for transfer from approximately a dozen available after hyperstimulation is a routine practice of IVF, the remaining embryos being either frozen or discarded. Such embryo selection is usually done routinely based on morphological criteria, which has the goal of identifying the embryos with highest developmental potential. PGD, on the other hand, allows the improvement of the embryo selection, by applying genetic tests, which has shown that perfectly morphologically normal embryos may be chromosomally abnormal and so destined to be lost during pre- and postimplantation development. As described in Chap. 5, approximately half of oocytes and embryos obtained from women of advanced reproductive age are chromosomally abnormal, suggesting that it might no longer be an acceptable practice to select embryos on morphological grounds. In other words, the advent of PGD is a natural evolution of assisted

reproduction, allowing replacement of an almost "blind" selection of embryos on morphological grounds by chromosomal testing, to ensure the transfer of chromosomally normal embryos, with the objective of improving the chances of IVF patients to become pregnant. It may be hoped that the genetic testing of the oocytes and embryos may be further extended also for cytoplasmic abnormalities, which together with testing of nuclear abnormalities will, in future, allow the identification of a single viable embryo for transfer, which will ensure the highest possible efficiency of IVF, allowing a singleton unaffected pregnancy and birth of a healthy baby.

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