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Preimplantation Genetic Diagnosis: Rationale and Ethics, an Islamic Perspective

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Abstract

Preimplantation genetic diagnosis (PGD) is a relatively new procedure meant to diagnose genetic or chromosomal defects in fertilized eggs produced by in vitro fertilization (IVF) so as to avoid implanting an affected embryo. It has also been used to diagnose mutations associated with several types of cancer. One or two blastomeres are removed from the preembryo (8-16 cell morula stage). A polymerase chain reaction (PCR) procedure tests for genetic mutations, and fluoresence in situ hybridization (FISH) tests for chromosomal abnormalities.

The various clinical applications of PGD are presented and classified into acceptable, questionable, and unacceptable. The main advantage of PGD is that it will eliminate or significantly reduce the risk couples with genetic diseases face of having a baby with those diseases, thus avoiding some terminations of pregnancy.

However, PGD raises significant ethical issues, the most important of which is the sanctity of human life. While PGD does not result in loss of biopsied "healthy" preembryos, it involves discarding of "affected" human embryos. The arguments for and against this are discussed in detail. Further, the implications of PGD on a societal level and the danger of using it for eugenics are also discussed. While the use of PGD for sex selection for medical reasons is acceptable, its use for nonmedical reasons is controversial.

Islam encourages scientific developments as long as they benefit humankind and do not contradict basic Islamic rulings. Most Muslim scholars approve of PGD use as it involves a preembryo before it is implanted and allows for benefits to the couple involved, i.e. the prevention of having a baby with genetic diseases. They do not approve of its use for sex selection for nonmedical reasons.

Key words: Preimplantation genetic diagnosis, medical ethics, Islam, shariah, sex selection, in vitro fertilization, eugenics.

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Introduction

Preimplantation genetic diagnosis (PGD) is a relatively new procedure meant to diagnose genetic or chromosomal defects in fertilized eggs produced by in vitro fertilization (IVF) so as to avoid implanting an affected embryo. The first

report of PGD of cystic fibrosis (CF) was published in 1992.[1] Later, it was successfully used in the diagnosis of hemoglobinopathies.[2-5] Since then, it has been successfully used in the diagnosis of many other autosomal recessive, autosomal dominant, and X-linked inherited syndromes. Now there are reports of PGD of 38 such conditions.[6]

More recently, it has been used in the diagnosis of mutations that are associated with hereditary breast, ovarian, colon, and many other cancers.[7-8] It also can be used to diagnose chromosomal abnormalities in fertilized eggs in women at high risk of having fetuses with aneuploidy based on age,[9-10] recurrent miscarriages,[11] or in women with repeat IVF failure.[12]

Procedure

Preimplantation genetic diagnosis requires the performance of IVF. After fertilization, the eggs start to divide in vitro. When the developing fertilized eggs reach the 8-16 cell morula stage on day three, one to two blastomeres are removed from each of them. The morula is held stationary on a glass micropipette by gentle suction. A sampling pipette is introduced in the preembryo (morula), and a nucleated blastomere is removed by suction. The cells that are removed are subjected to testing for genetic mutations and chromosomal abnormalities. The testing should be rapid. For single gene studies, polymerase chain reaction (PCR) is used to amplify specific DNA fragments that can then be analyzed for mutations. For the study of chromosomes, fluorescence in situ hybridization (FISH) is used to identify chromosomal abnormalities. Fluorochromome-labeled probes that are complementary to DNA sequences specific to regions or individual chromosomes are used to identify different chromosomes, detect abnormalities in these chromosones, and identify the sex.

The affected preembryos are discarded, while one or two unaffected preembryos are transferred into the uterus.[6] Removal of one cell for this analysis may delay embryonic development for a short time, but implantation and subsequent development continues.[6] Only 0.9% of the preembryos were damaged during the biopsy when only one cell was obtained for biopsy.[13] To improve the accuracy of the testing, removal and analysis of two cells has been suggested but thought to increase the loss ratio. However, this was not shown to be the case.[14]

Because of the risk of damage to the biopsied preembryo, the use of polar bodies in PGD has been suggested. In this procedure, sequential analysis of first and second polar bodies is performed. The oocytes predicted to contain the abnormal genes were not further cultured to avoid formation and discarding of an affected embryo; thus, it is more ethically acceptable. Polar body biopsy has been shown to be accurate in PGD of several single gene disorders e.g. thalassemia, cystic fibrosis, and sickle cell disease. However, polar bodies do not include the paternal contribution and, therefore, polar body biopsy cannot rule out paternally derived genetic disorders or aneuploidy.[6]

Diagnostic Accuracy of PGD

The technology of single cell analysis is complex and demanding; thus, there is potential for diagnostic errors in PGD. Misdiagnosis can be attributed to technical difficulties in the PCR analysis resulting from either paternal contamination i.e. sperm remaining on the surface of the zygote or maternal contamination from stuck cumulus cells. Paternal contamination may be overcome with the use of intracytoplasmic sperm injection (ICSI).[15] Further, the phenomenon of allele dropout or amplification failure of an allele during PCR may lead to a misdiagnosis.[6,16]

The possibility of misdiagnoses can be decreased by the use of multiplex fluorescent PCR techniques in which simultaneous amplification of two or more loci containing the mutation and one or more containing informative polymorphic markers in close proximity to the mutation confirms the embryonic origin of the DNA.[16]

As far as the diagnosis of chromosomal abnormalities is concerned, it should be noted that full karyotype cannot be performed in the short time (one to two days) that is required to be able to maintain the preembryo before it can be safely transferred to the uterus. Therefore, analysis has to be done using FISH. With this technique, one is able to analyze up to only 10 chromosomes at a time. FISH analysis may, therefore, miss chromosomal abnormalities that are important for implantation, and that may explain the inability of PGD to improve the reproductive efficiency of women with recurrent miscarriages or repeated IVF failures. Also, chromo-

somal mosaicism in cleavage-stage embryos is high. Therefore. ideally two blastomeres should be analyzed and only preembryos with two normal cells transferred. Further, technical difficulties with FISH due to signal failure or overlap may result in misdiagnoses.[17]

The European PGD Consortium reported 8 misdiagnoses out of 451 pregnancies (1.8%), based on May 2001 data.[18] A more recent study published in 2004 based on 3 of the largest series reported 5 misdiagnoses out of 754 live births over the previous 10 years.[19]

Applications of PGD

1. Inherited genetic disorders with a recurrence risk of 25-50% i.e. autosomal recessive and autosomal dominant conditions.
2. Sex-linked disease. If the mutation cannot be diagnosed, only female preembryos are transferred to the uterus. This will not eliminate the disease from the family in the future as half of these female embryos maybe carriers.
3. Increased risk of aneuploidy in cases of advanced maternal age (AMA) and balanced chromosomal rearrangement in one of the partners i.e. translocation or inversion. Chromosomally abnormal preembryos are discarded.
4. To improve the reproductive efficiency in women with recurrent miscarriages and repeated IVF failures. The rationale is that the inefficiency is due to chromosomally abnormal preembryos. In these populations, PGD did confirm a high incidence of embryo aneuploidy. However PGD has not been shown to increase successful pregnancy outcomes.[12]
5. Preimplantation genetic diagnosis allows testing for traits that are not associated with disease in the tested embryo itself but could be of benefit to a sibling or another relative who has leukemia or another disease that can benefit from stem cell transplant. Preimplantation genetic diagnosis is used to determine an embryo's human leukocyte antigen (HLA) type and then to select the embryo(s) with HLA type that matches the diseased sibling for implantation. At birth, umbilical cord blood could be harvested for stem cells that can be transplanted in the affected older sibling or relative.[20] In the case of leukemia (an acquired disease) the PGD test is of no benefit to the potential child; the HLA type of the child has no bearing on that child, but only on the sibling who needs the HLA-matched stem cells. However, in case of Fanconi's anemia or β-thalassemia major or other inherited diseases, PGD is used to both ensure that the transplanted embryo is free of the disease and is also an HLA match.[21] Until now, the parents' only option was to conceive another child and take the 25% chance that the baby will be an HLA match. They could then have chorionic villus sampling (CVS) or amniocentesis to determine the HLA type of the fetus. This is what happened in the well-publicized case of the Ayala family in 1989.[22] Fortunately, the fetus in this case was a match and the older sister was cured of leukemia.[21] In other cases, however, if the fetus is not of the desired HLA type, the parents would have to decide if they wanted to abort this healthy fetus and try another pregnancy while possibly running out of time with a dying child.
6. It is now possible to diagnose mutations that are associated with hereditary breast, ovarian, colon, and many other cancers.[7,8]
7. It is now possible to diagnose mutations that are associated with increased risk for certain multifactorial diseases e.g. diabetes, heart disease, etc.[21]
8. It is possible that PGD can be used for the selection of any trait whose genetic composition is known e.g. height, intelligence, beauty or even personality traits such as cheerful disposition. If this happens, a society of "engineered" individuals will result. If a relative consensus of ideal traits develop, biodiversity will be limited. There could be less creativity as distinction between individuals is diminished.[21]

Moral Arguments about PGD

The major advantage of PGD is that it allows couples who are carriers of traits of genetic disease to eliminate or significantly reduce their risk of having a baby with that genetic disease. It allows the diagnosis of an unaffected embryo before implantation, thus avoiding an affected pregnancy. Before the advent of PGD, the options that were available to couples at risk of transmitting genetic disease to their offspring were limited. These included accepting the risks of having an affected fetus and baby and hoping for favorable odds, accepting chorionic villus sampling (CVS) or amniocentesis and then terminat-

ing an affected pregnancy, use of donor gametes, adoption, or remaining childless. In the case of X-linked disorders, the couple would rely on the technique of fluorescent-activated cell sorting to separate X and Y chromosomes.[23,24] While not completely accurate, this technique can increase the odds of having a female child that will not have the disease. Otherwise, they will have the option to terminate a pregnancy with a male fetus if CVS or amniocentesis cannot rule out the disease.

Preimplantation genetic diagnosis eliminates the need for these couples to go through invasive prenatal diagnostic tests i.e. CVS or amniocentesis and secondarily to avoid the need for therapeutic termination of pregnancy. Instead, it gives them the chance of having their own unaffected child.

However they achieve this, the couple has to undergo IVF every time they want to conceive, even if they are fertile, exposing the woman to the inconveniences and risks of the procedure. Further, there are ethical concerns. The most serious is the ethicality of discarding a defective or diseased embryo. This depends on what one believes the moral status of a preembryo is. There is great controversy among ethicists about this question. Their opinions can be roughly classified into one of three positions: 1. The fertilized egg (zygote) has a full moral status. 2. While the fertilized egg has a moral status, it becomes deserving of protection only at a later stage. The status increases in degree as the fertilized egg becomes more human-like. 3. The embryo has no moral status at all. It is an organic material with a status no different from any other body part. Hug[25] and a previous publication[26] discuss these positions in detail. The most reasonable view is to use the appearance of the primitive streak at the 14th day postfertilization as the beginning of "human" life that needs full protection. The primitive streak defines the head-tail and right-left orientation, around which major tissues and organs begin to develop. Also, after the 14th day, there is no possibility of twinning. The stage before the appearance of the primitive streak has been named the preembryo. If this position is accepted, then discarding diseased preembryos before implantation, which is the case in PGD, would be acceptable. This has to be balanced against the alternative, which would be the probability that the couple will terminate the pregnancy if the diseased preembryo is implanted and the disorder is later diagnosed via CVS or amniocentesis. It is also to be noted that in regular IVF procedures, there are six to eight preembryos produced and only one or two "healthy-appearing" preembryos are selected for implantation. Only the other healthy-appearing embryos are cryopreserved, while the others are discarded.

A second ethical concern is that of unequal access. Preimplantation genetic diagnosis requires IVF. It can be added to IVF done for the infertile or subfertile couples with little or no additional inconvenience and at a relatively small additional cost. However, fertile couples who want to avail themselves to PGD would be required to undergo IVF with its inherent risks, inconveniences, and costs. In that sense, PGD is more readily available to the infertile and subfertile population, and they will unequally reap the benefits inherent in PGD. On another level, there is the potential of unequal access based on the ability to pay. Is it ethically acceptable to have differential access to medical technology simply based on the ability to pay? Unfortunately, this is the case in all spheres of life including medical care. It applies to regular care, so it is not surprising that it will be the case in high-tech procedures or therapies. It is probable that PGD will be available not to couples who need it the most but to those who are most capable of paying for it. The less financially advantaged are going to be left only with the options of terminating an affected pregnancy or not even knowing if their child is affected before birth. The rich will reproduce babies not affected by the disease. This will further accentuate socioeconomic disparities.[21]

There are additional ethical concerns specific to PGD. Selecting an embryo with a specific HLA type to provide bone marrow or cord blood stem cells transplant to a sibling is probably not ethically acceptable. While it is lifesaving for this child, it uses the fetus as a commodity. It violates the Kantian imperative that a person should never be used as a means.

Moreover, how would this child feel? Is he or she being loved intrinsically or only because of the benefit he or she gave to the sibling? What if the transplant did not work and the diseased sibling died? How would this child be looked upon?

Gender selection for nonmedical reasons is another major ethical concern. It has been practiced for decades. Because the techniques used were widely perceived to be ineffective, they never rose to a

level of relevance that would raise concern or attract scrutiny.[23,24] With the advent of PGD, gender selection became almost 100% reliable and, therefore, ethical concerns were raised, and nonmedical gender selection is now open to debate.

On one hand, one can argue that gender selection is part of the rights of parents to reproductive choice, that gender balance in a family is an acceptable aim, and that it is acceptable for a couple to prefer a certain gender order among their children. Proponents of this view suggest that it is a better alternative than having a couple intent on having a child of a specific gender continue to reproduce until they achieve the desired goal with the attendant risks of grandmultiparity or, worse still, termination of pregnancies if the fetus is the "wrong" sex.[27]

On the other hand, opponents cite several objections to gender selection for nonmedical reasons (Table 1).

Different professional organizations have issued their positions regarding this issue. The Ethics Committee of the American Society of Reproductive Medicine statement described several situations and stated that PGD for sex selection for nonmedical indications should not be encouraged in certain cases and should be discouraged in others.[28,29] The Ethics Committee of the American College of Obstetricians and Gynecologists (ACOG)[30] stated in part "gender selection should not be performed except in instances in which a clear medical indication exists i.e. known genetic X-linked diseases." The Human Fertilization and Embryology Authority of the United Kingdom "recommend against the use of sex-selection techniques in assisted reproduction except in X-linked disease."[31]

While sex selection for nonmedical conditions is banned in most industrialized nations, it is allowed in the United States, making it a destination for couples with means to select the gender of their babies.[32]

Preimplantation genetic diagnosis can be used to test for diseases with multifactorial inheritance that are not expressed until later in life e.g. diabetes and coronary artery disease. Would these individuals be more likely to gain weight, smoke, and lead a sedentary life if they knew that their risk of acquiring such disease is very low? Would individuals who were born with a known lack of known cancer mutation genes have a false sense of security and not seek early detection?

Over time many more diseases could be selected out of the gene pool. Is it acceptable to select out diseases that currently have no cure but may be curable within the lifespan of the potential child? Possibly by overselecting out certain traits and diseases we will decrease genetic diversity, thus creating a population susceptible to as yet unknown diseases? What will be the effect on individuals alive with a disease that is now being selected out by PGD? Will a child with CF be impacted by the knowledge that his parents chose to use PGD to prevent the birth of another child with the disease? Will society be biased against individuals with inherited diseases as their parents did not choose to use PGD to prevent their birth?

It is probable that more and more gene mutations are going to be discovered and become amendable to PGD. If the few fertilized eggs produced in an IVF cycle are tested for enough diseases, each will possess some potentially lethal recessive gene as well as a host of factors predisposing to chronic disease. Would couples then face the impossible task of choosing between embryos that have genes predisposing their children to breast cancer in their 40s or Huntington's chorea in their 50s and embryos affected by cystic fibrosis or sickle cell anemia.[21]

As PGD involves discarding defective human preembryos, the prevailing ethical view classifies its use in the following categories:

A. Acceptable uses:
   1. Families with genetic disorders that carry a significant risk of transmitting these to their offspring, diseases that cause life-threatening, incurable disease in infants or children.
   2. Avoidance of sex-linked diseases e.g. hemophilia A and B, Lesch-Nyhan syndrome, Duchene-Becker Muscular dystrophy, Hunter syndrome, etc.
   3. Women of advanced age who prefer that only chromosomally normal preembryos be implanted instead of terminating the pregnancy if CVS or amniocentesis diagnosis a chromosomal abnormality.

B. Questionable uses:
   1. To avoid late-onset disease e.g. Huntington's chorea, adult polycystic kidney disease, or early onset Alzheimer's disease.
   2. To avoid predisposition to future disease e.g.

breast or colon cancer.
3. To avoid life-compatible genetic disease e.g. deafness.
4. To create a transplant match for a sibling.
5. To screen couples without any specific increased risk for disease, just to "ensure" a healthy baby.

C. Unacceptable uses:
1. Sex selection for nonmedical reasons.
2. Enhancement of certain traits (eugenics) e.g. height, intelligence.
3. Selection against nonpathologic behavioral characteristics.

It is important to conclude this section by noting that despite PGD being mentioned as a harbinger of a reproductive future with genetic selection and alteration, its impact is likely to be quite limited in that regard due to its cost and limited accessibility.[33] Nevertheless, because of these concerns, professional organizations, or even government agencies, should tightly regulate and supervise the use of PGD, especially when its practice is questionable or unacceptable.[34-36]

Islamic Perspective

Islam means submission to the will of God ﷻ. Islam is a complete way of life addressing the spiritual as well as the material aspects of Muslims' lives. Before performing any action, Muslims have to find out if it is *ḥalal* (permissible) or *ḥarām* (not permissible) according to the shariah (Islamic moral law). When Muslim jurists (*fuqahā'*) are asked to decide on the permissibility of an action, they consult the primary sources of shariah, namely the Glorious Qur'an, the Sunnah (the actions and sayings of Prophet Muhammad ﷺ), and the consensus of the previous scholars. If they do not find the answer, they have to exert *ijtihād* (independent reasoning). This will take into account *maqāṣid al-sharī`a* (the objectives of Islamic moral law). These are the preservation of religion, life, intellect, wealth, and progeny. They will then use methods that are well known but worth summarizing here. These include *qiyās* (analogy), *maṣlaḥa mursala* (public interest), *istiḥsān* (juristic preference), *`ādāt* and *`urf* (customary practice), *istiṣḥāb* (presumption of continuity), and *sadd al-dharā'i`* (blocking of means). In Islamic jurisprudence, all actions are in principle permissible as long as they are not categorically prohibited. Another rule is that, in matters when other invocations are silent, "where the welfare of the people resides, there resides the statute of God." Other applicable principles include choosing the lesser of two harms, if harm cannot be avoided, and the permissibility of forbidden things in case of necessity.[37]

Preimplantation genetic diagnosis is a new technology, and the question of its permissibility merits the *ijtihād* cited above. On one hand, Islam has always encouraged men to contemplate, explore new horizons, and make use of all things Allah ﷻ has created for them.[38-41] Also the Prophet ﷺ ordered the believers to seek cure for their diseases.

إن الله تعالى أنزل الداء والدواء وجعل لكلِّ داءٍ
دواءً فتداووا ولا تداووا بحرامٍ

> Allah ﷻ created disease and treatment, and He made for each disease a treatment. So seek treatment but do not use *ḥarām* (forbidden things).[42]

Based on the significant potential benefit of PGD in many situations, it would seem that PGD would be permissible. On the other hand, the question arises whether it is permissible to discard a diseased or defective human fertilized egg. The central question then becomes when human life starts. Is it at the time of conception or later when ensoulment occurs at either 40 or 120 days postfertilization? This has been discussed in detail in a previous publication.[26] Most Muslim jurists will accept that the preembryo before implantation is not a human being as it can not have independent life. Muslim jurists permit discarding unused supernumerary preembryos in IVF cycles if the couple is not going to use them in future cycles. They cannot be donated to other couples.[26]

While there is no specific *fatwā* (religious decree) issued — to my knowledge — about PGD, based on the discussion above, PGD for the enumerated acceptable indications appears to be permissible, while PGD for the questionable and the unacceptable indications, including sex selection other than in the context of X-linked disease, is not.

Allah ﷻ knows best. After all, we are given only

"little" knowledge and we have always to ask Allah ﷻ to increase our knowledge.

وَمَا أُوتِيتُم مِّن الْعِلْمِ إِلاَّ قَلِيلاً

.... of knowledge it is only a little that is communicated to you (O Man!).[43]

وَقُل رَّبِّ زِدْنِي عِلْماً

... but say O my Lord advance me in knowledge.[44]

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