

## Patient attitude to preimplantation genetic diagnosis and counseling issues

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### ABSTRACT

**Background:** During the last half of the twentieth century, there were a series of advancements in reproductive medicine and genetic testing. Preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS) are the two main methods of preconception genetic testing. The purpose of this article is to present the existing literature regarding the patients' attitudes towards PGD and to stress the important of genetic and infertility counseling.

**Methods:** The literature concerning the patients' attitudes towards PGD was reviewed. Relevant studies were identified by searching the following databases: the Cochrane Library, Medline, Embase and PubMed.

**Results:** The patients' attitudes towards PGD have been examined in a series of studies. In general the studies that have examined the acceptability of PGD have shown two main points. First, there is overall high general approval of PGD by couples at high risk and of PGS by infertile couples. Second, infertile patients have low concern about the extension of the technology to testing for non-health-related traits like social sexing. It has been also argued that Muslims might reject prenatal diagnosis and termination of pregnancy because of religious reasons. Preimplantation diagnosis may be preferable to prenatal diagnosis for Muslim parents.

**Conclusion:** This review shows that there is a general high approval of PGD by couples at high risk and low concern about the extension of the technology to testing for non-health-related traits. However, there is big debate on the advantages and disadvantages of PGS/PGS in IVF and the international use of PGD varies from explicit legislation with or without restriction to a 'professional guideline' approach to legal prohibition through restrictive laws. Therefore, all couples who consider PGD or PGS should first receive genetic and infertility counseling in order to have realistic expectations, understand the advantages and disadvantages, and consider the limitations and the risks of each technique. Countries which offer PGD should also provide training in genetic counseling and/or in reproductive genetic counseling.

**Key words:** Preimplantation genetic diagnosis, prenatal diagnosis, attitudes, counselling, legislation.

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### INTRODUCTION

**D**uring the last half of the twentieth century, there were a series of advancements in reproductive medicine and genetics. Some of these medical milestones include the birth of the first baby conceived via in vitro fertilization (IVF) in Great Britain in 1978 and the birth of the first baby following preimplantation genetic diagnosis (PGD) in 1989 in Great Britain. These achievements have enabled reproductive and genetic medicine to facilitate reproduction for infertile individuals or couples. However, this new field led would-be-parents to have unrealistic or misguided expectations of a 'perfect baby'- a baby with maximum health and minimum defects.<sup>1</sup> Furthermore, not unexpectedly, the potentials of reproductive medicine and medical genetics (facilitation of conception and/or birth of a healthy baby) can be fraught with moral dilemmas for individuals, communities and societies.<sup>1</sup> Today, approximately 3–5% of all live births worldwide will have a birth defect, chromosomal anomaly, or genetic disease. To date, more than 8,000 diseases are documented as having a genetic basis in McKusick's catalog, a reference text on single gene disorders that is updated regularly.<sup>2</sup> Moreover, all diseases are suspected of having some

genetic involvement, including common late-onset conditions such as cancer, heart disease, chemical addiction, and mental illnesses. Therefore, there are an increasing number of reasons for reproductive genetic testing to be suggested within the context of reproductive medicine.<sup>1</sup> Prenatal genetics was first reported in 1956 by Fuchs and Riis and it is the main method offered to avoid births with genetic defects. Preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS) are the two main methods of preconception genetic testing. Preimplantation genetic diagnosis was developed in 1989 by British physician Alan Handyside who used the technique to select female embryos in order to avoid X-linked diseases.<sup>3</sup> Preimplantation genetic screening is a genetic test that uses PGD technology and is used to screen for various chromosomal aneuploidies that commonly exist in embryos produced by IVF. As it has become obvious, both methods involve the integration of IVF, embryo biopsy and molecular genetic testing. However, these methods may produce a clear advantage over conventional prenatal diagnostic testing (amniocentesis, chorionic villus

sampling), which may lead to pregnancy termination in case of a positive result.

The purpose of this article is to present the existing literature regarding the patients' attitudes towards PGD. In addition this article will give a short description of the PGD technique, will summarize the most recent data on indications used and will stress the importance of genetic and infertility counseling.

### **Preimplantation genetic diagnosis and preimplantation genetic screening**

*Preimplantation genetic diagnosis* (PGD) involves the genetic analysis of cells from an oocyte or embryo for a specific molecular mutation or chromosomal abnormality<sup>4</sup> in an effort to avoid the transfer of IVF-created embryos with documented genetic abnormalities from couples who are carriers of a genetic disorder. In other words, the purpose of PGD is to determine which embryos generated by IVF are normal for the specific genetic abnormality for which they are assessed so that these can be selected for transfer.<sup>5</sup>

For PGD, biopsy has to be performed in the embryo or the polar body where one to a few cells are removed for the diagnosis. The most common biopsy method is the cleavage stage biopsy. In

that case, the embryos are grown in vitro after fertilization in an appropriate environment until they reach the 6- to 8-cell stage which occurs on the third day after insemination. In order to remove one or two cells from the embryo the zona pellucida is breached, using an acid solution or laser and a biopsy pipette is introduced through the hole into the embryo from where the cells are aspirated.<sup>6</sup> This biopsy technique is used most often compared to others and allows detection of the maternal, paternal and postzygotic errors. This technique was earlier evaluated on mouse embryos by various groups before it was applied in human embryos.<sup>7,8,9</sup>

Other biopsy methods that are not used so often include polar body biopsy and blastocyst biopsy. In polar body biopsy polar bodies are aspirated after a small cut is made in the zona pellucida by sharp needles or laser.<sup>10</sup> This technique is useful only for the genotype analysis of the oocyte and not the embryo. In blastocyst biopsy the embryos are left to grow until the blastocyst stage which gives the advantage that more cells can be obtained for analysis. The cells that are biopsied are the trophoctoderm cells and not the inner cell mass. Mosaicism of the trophoctoderm cells may increase the chances of misdiagnosis as later in pregnancy confined placental mosaicism

(CPM) is observed.<sup>11</sup> The main disadvantage of this biopsy method is that fewer embryos reach this stage in culture and the time left for diagnosis is limited. In a study performed by McArthur et al. (2005) 21% of the cases had no embryos suitable for biopsy.<sup>12</sup>

After the biopsy is performed, two types of tests that can be done for PGD; the first involves tests that target a specific single gene mutation that has been previously been identified in a family. For this type of test, polymerase chain reaction (PCR) technique is used where the site of mutation is detected at a molecular level and only the embryos that do not carry the mutated gene are transferred. The second type of test is used to detect chromosomal abnormalities. Usually in a family history with chromosomal abnormalities one of the parent carries the abnormality which it is a balanced structural aberration (roberstonian or reciprocal translocation) but is absolute healthy. The problem arises when meiosis takes place in the egg or the sperm and due to the structural abnormality an unbalanced chromosomal aberration is produced in the gametes. In that case where the abnormality is detected in the family, PGD can be applied with the use of fluorescent in situ hybridization

(FISH) analysis.<sup>13</sup> With this technique, specific areas of the desired chromosomes are painted with fluorescent colors so the healthy embryos can be detected and transferred to the mother's womb.

Initially PGD was developed for the evaluation of most common disorders, but over time its application has dramatically expanded to evaluate a wide array of genetic disorders including monogenic conditions and structural chromosomal defects.<sup>14</sup> Currently, PGD is recommended for monogenic disorders and chromosomal rearrangements that are lethal, seriously debilitating or life threatening later in life. Most common examples include autosomal recessive disorders, such as, cystic fibrosis, beta thalassaemia, myotonic dystrophy, Huntington's disease, X-linked recessive disorders (e.g., fragile X, Duchenne muscular dystrophy, and hemophilia), autosomal dominant disorders (e.g., myotonic dystrophy and Huntington's disease), chromosomal rearrangements (e.g., Robertsonian translocations), and mitochondrial disorders<sup>4,15</sup>. Regarding single gene diseases, more than two hundred different mutations have been tested in clinical PGD<sup>4</sup>. This number is growing fast in an equivalent way with families that request PGD for novel

mutations despite the difficulty to optimize a genetic test with very low amount of DNA obtained from the biopsy.<sup>15</sup> With PGD however, there is also an increasing number of diseases that can be diagnosed that are not offered in prenatal diagnosis; these include late-onset diseases (such as Alzheimer's and Huntington disease), and predisposition syndromes (such as cancer).<sup>16</sup> PGD is also being used to give birth to babies with compatible Human Leukocyte Antigen (HLA) tissue with that of an existing affected child. At birth, stem cells from the newborn umbilical cord blood are used to treat the affected child. In 2002, for the first time, it was reported that 10% of PGD cycles in 2001 were undertaken in three PGD centers for non-medical reasons, namely, social sexing for family balancing.<sup>17</sup> This approach is sharply criticized and refused by many scientists and ethicists.

***Preimplantation genetic screening (PGS)*** for aneuploidy is a genetic test that uses PGD technology, but with a different purpose.<sup>18</sup> PGS is used to screen for chromosomal aneuploidies in IVF embryos and consequently identify the most chromosomally normal embryo for transfer in an IVF cycle. The vast majority of PGS tests involve FISH

technique for five to 15 pairs of chromosomes. Therefore, PGS can lead to improved pregnancy rates after IVF and decreased miscarriage. PGS is used when no previous familiar risk of an affected offspring exists. The main indications for PGS include advanced maternal age repeated implantation failure, repeated early miscarriage and severe male infertility.<sup>16,19</sup> The most important difference with PGD is that PGS is not a diagnostic technique but a screening method for various chromosomal aneuploidies that commonly exist in embryos produced by IVF. As such, indications and applications are totally different. In PGD, the genetic defect is known and established in the parent(s) who carries the defect, whereas PGS is used to screen for aneuploidies when there is a possibility of an increased but unspecified risk.<sup>20</sup>

#### ***Advantages and disadvantages of PGD and PGS***

The couples should be aware of the advantages and disadvantages of PGD and PGS over prenatal diagnosis. In case of a recessive mutation there is 25% chance that the embryo will be affected whereas in case of a dominant disorder, the chance rises to 50%. Therefore, it could be concluded that prenatal

diagnosis may lead to pregnancy termination. In contrary, by PGD only the non-affected embryos will be transferred to the woman's womb and thus the chance of terminating a pregnancy is minimized. However, no treatment is perfect and the misdiagnosis rate with PGD is 2.2% globally, leading to the recommendation of prenatal testing as a safeguard against diagnostic error or a serious abnormality<sup>1</sup>. Nevertheless, even if prenatal testing should follow PGD the chance of terminating the pregnancy dramatically falls. Therefore, unlike prenatal diagnosis, PGD offers to couples an option that avoids the difficult decision of whether or not to terminate an affected pregnancy. In certain cases, PGD could also be offered in combination with preimplantation genetic screening. So, in advantage over prenatal diagnosis, with PGD the embryos selected for transfer can be free of the mutation and with PGS the embryos will be free of aneuploidies. In summary, PGD helps couples to avoid 'trial pregnancies', extensive prenatal genetic testing, and/or pregnancy termination of an affected pregnancy. By selecting embryos before they are transferred to the uterus, couples are better able to avoid moral dilemmas and

emotional distress<sup>21,22</sup>. In summary, criticisms of IVF/PGD are its limited accuracy (in comparison with other forms of prenatal testing), its current ability to detect limited number of genetic disorders, its invasiveness (IVF), financial costs and limited accessibility.<sup>1</sup> There is currently big debate on the advantages and disadvantages of PGS in IVF and if it is beneficial for the pregnancy rates. Although PGS is a complex, expensive and time consuming procedure, success rates are slightly lower (20-25%) or comparable to IVF/ICSI.<sup>23</sup> A conclusion is difficult to be drawn because every IVF centre that publishes its results may have used different techniques regarding the embryo manipulation and the PGS strategy or have different laboratory performance<sup>24</sup>. So, some IVF centers have concluded that PGS should not be applied to any IVF patient<sup>25</sup> whereas others recommended that PGS should be part to every IVF cycle.<sup>26</sup> The truth is that universal application of PGS in IVF patients should be mathematically flawed due to false negative diagnostic rates (1.2-4.7% as suggested from Munne et al.,<sup>27</sup> 2005) and due to existence of mosaicism and self-correction of preimplantation stage embryos. Most groups believe that PGS should be

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applied in IVF patients with certain criteria.

### **International Perspective**

International use of PGD varies from explicit legislation with or without a governmental regulatory agency and with or without restriction to a 'professional guideline' approach to legal prohibition through restrictive laws.<sup>1</sup>

Four general European approaches to the regulation of issues regarding human embryos were classified by Nielsen (1996) according to their restrictiveness.<sup>28</sup> The categories are as follows: prohibitive, cautious, liberal, and laissez-faire. Germany, Ireland, Switzerland, and, since 2003, Italy serve as examples for prohibitive management, France has taken a cautious approach, the UK and Spain a liberal one, and the Netherlands and Belgium have adopted a laissez-faire style in which the issue is left mostly to agreements within professional groups, although liberal legislation was recently implemented.<sup>29</sup>

Based on the findings of ESHRE/PGD Task Force, twenty-nine countries worldwide reported offering PGD at ninety-six medical centers ranging from the highest (19) in the United States to only one per country in Argentina, Chile, China, Columbia, Cyprus, Czech Republic, Iran, Korea, Portugal, Saudi

Arabia, Slovakia, and Thailand.<sup>30</sup>

According to the results generated from European registers by ESHRE PGD/PGS was recorded in nine countries (Belgium, Italy, Hungary, Netherlands, Greece, Portugal, Russia, Spain and United Kingdom).<sup>31</sup> The major contributors were Italy (534 cycles), Spain (430 cycles), Belgium (346 cycles) and the UK (123 cycles).

### **Patients' attitudes**

A number of studies have examined the acceptability of PGD by couples at high risk and by infertile couples. Pergament in 1991 examined potential patients' perspective of PGD in a sample of 58 American women who had previously experienced an affected pregnancy.<sup>32</sup> Fifty-five percent of them expressed a possible preference for PGD in the future rather than PND. Miedzybrodzka *et al.*, studied 474 women in Scotland, including some who were at risk of a single gene disorder, and found that 43% of women favoured PND and 38% of women favoured PGD.<sup>33</sup> In Snowdon and Green's study which was conducted in United Kingdom, 245 carriers of recessive disorders participated.<sup>34</sup> Only 11% of them thought that PGD was unacceptable, but of the reproductive technologies considered, PND was the first choice for 46% of the women and

50% of the men and PGD was the first choice for 28% of women and 23% of men. However, in a subsequent study of couples at risk of beta thalassaemia in Italy, Chamayou *et al.*,<sup>35</sup> found that 34 out of 50 (68%) couples who had previously terminated an affected pregnancy considered PGD to be more acceptable than PND. This preference was expressed by only a minority of couples without experiencing a pregnancy termination. A preference for PND (67%) over PGD (30%) was also seen in a study conducted in Hong Kong and included a sample of 141 women at risk of alpha or beta thalassaemia.<sup>36</sup> In the same year a study conducted by Lavery *et al.*, in UK and in Spain reported the experiences and attitudes of 36 couples who have undergone PGD.<sup>37</sup> A total of 25% of couples were carriers for cystic fibrosis, 56% were carriers of X-linked disorders and 17% of couples had chromosomal disorders. Of the 26 couples who contemplated a further pregnancy, 20 (76%) would choose PGD again; four (16%) would opt for PND and two (8%) would have no test at all. In an Australian study conducted by Katz *et al.*,<sup>38</sup> 89 couples undergone PGD. Forty one subjects presented for PGD of single gene disorders (PGD) and 48 subjects undertook PGD for aneuploidy screening

(PGD). In addition a control group consisted of 32 subjects that were about to commence their first IVF cycle. The majority of couples found PGD to be a highly acceptable treatment that was morally less problematic than abortion. They expressed little concern about its extension to testing non-disease states such as sex and they were strongly in favour of a shared decision-making model in which couples have considerable autonomy over decisions about the embryo(s) to transfer. Another study conducted in Saudi Arabia, examined potential patients' perspective of PGD.<sup>39</sup> In a sample of 32 families who had previously experienced an affected pregnancy with haemoglobinopathies 62% would accept PGD. Another study conducted in Saudi Arabia in 2006 examined the attitudes towards PND and PGD of 30 couples offered genetic counseling following the birth of a child with a single gene or chromosomal condition.<sup>40</sup> Eight of the 30 couples (27%) would only accept PGD; four (13%) only PND; three (10%) either technology; the remainder would accept neither test, or were unsure. The main concerns of those who would accept neither technology were related to personal religious views. Specific concerns about PGD related to the IVF



procedure, the risk of multiple pregnancies, the chance of mistakes and the chance of not getting pregnant. Few studies have looked at the attitudes of the general population, but Meister *et al.* (2005) report that over 60% of their German sample would accept PGD for certain serious conditions.<sup>41</sup> A subsequent survey was conducted with 265 German infertile couples.<sup>42</sup> Eighty-seven percent support a general legalization of PGD in Germany for severe, early-onset genetic diseases. Seventy-four percent consider PGD morally acceptable. Sixty percent supported legalizing PGD for HLA-matching. But only a minority approved PGD to test for non-health-related traits. The studies that have examined the acceptability of PGD have shown two main points. First, there is overall high general approval of PGD by couples at high risk<sup>32,33,34,40,42,43</sup> and of PGS by infertile couples.<sup>32,33,36,39,42,43</sup> Second, infertile patients have low concern about the extension of the technology to testing for non-health-related traits like social sexing<sup>38</sup>. It has been also argued that Muslims might reject prenatal diagnosis and termination of pregnancy because of religious reasons.<sup>39,44,45</sup> Preimplantation diagnosis may be preferable to prenatal diagnosis for Muslim parents, because it is done when

embryos are only at the eight-cell stage and 'breathing the soul' has not occurred at this stage.<sup>40</sup>

### **Counseling Issues**

A formal definition of counseling would be 'an interpersonal process, based on a theoretical framework, which is used to bring about change in a skilled and systematic way'.<sup>46</sup> However, counseling with infertile individuals is often also about support and the clarification of life goals.<sup>46</sup> According to Boivin several groups of infertile patients will need professional counseling.<sup>47</sup> These groups include: a) patients who experience great psychological distress, b) patients considered to be at risk because of their psychological history or presenting profile, c) patients who require some form of genetic counseling as part of their fertility treatment (e.g. PGD) and d) patients who use donated gametes, surrogacy and/or adoption. The aims of counseling are to explore, understand and resolve issues arising from infertility and infertility treatment and to clarify ways of dealing with the problem more effectively.<sup>46</sup> Counseling may have different functions and/or goals depending on the treatment desired (e.g. PGD). For example, the primary goals of reproductive genetic and infertility counseling are ensuring that patients

considering or undergoing any procedure (e.g., genetic testing, PGD, assisted reproductive) understand the scope and limitations of the testing and have realistic expectations of success rates, financial cost, and the timeframe of treatment.

The Consortium of European Society of Human Reproduction and Embryology (ESHRE) in 2005 issued practical guidelines on PGD that warrants both genetic and infertility counseling to address the complexity of medical treatment and genetic information that are required by couples. Genetic counselors and infertility counselors as mental health professionals working in reproductive medicine deal with basic issues of reproductive health and normality/abnormality.<sup>48,49</sup> Genetic and infertility counselors, as members of the reproductive medicine team, provide information and support to couples undergoing treatment for infertility and/or related genetic conditions. Genetic counseling is defined as a communication process meant to help an individual or family: (1) comprehend the medical facts, including diagnosis, probable cause, and available management of a disorder; (2) understand how heredity contributes to the disorder and risk of transmission to

offspring; (3) facilitate evaluation of risks and decision making regarding treatment; and (4) assist in the adjustment to a disorder in the individual or in an affected family member.<sup>49</sup> Genetic counseling uses many of the same principles and theoretical frameworks of psychology, but genetic counseling is mainly based on a definition of counseling as giving advice, expert opinion, or instruction in directing the judgment or conduct of an individual, couple, or family to make autonomous decisions.<sup>1</sup> Specifically, genetic counselors in reproductive medicine provide information about genetic conditions that could impact the individual's or couple's reproductive future and the risk of transmission of genetic disorders to offspring. Alternatively, infertility counselors must have knowledge about the impact of genetic diseases and disorders on reproduction and the psychosocial impact of these diagnoses on emotional and marital well-being. Infertility counselors are educated and trained to provide psychotherapy: the treatment of personality maladjustment or mental illness by psychological and/or psychopharmacological means as part of therapeutic relationship.<sup>1</sup> While both genetic counselors and infertility

counselors work together as integral members of the reproductive medicine team providing expert advice and support, only infertility counseling provides psychological treatment of patients.

There are international variations in qualifications, roles and expectations regarding the person who will act as a counselor in fertility clinics. However, genetic counselors are usually health care professionals with a master's level graduate degree<sup>1</sup>. In the past, nurses working with physicians and/or medical geneticists had traditionally provided genetic counseling in Australia and the United Kingdom<sup>1</sup>. Recently, with the introduction of master's level in genetics, a distinct genetic counseling profession has begun to develop. Master's level training is available in Mexico where genetic counselors are certified by the National Board of Medical Genetics and in Israel where master's level graduate training and clinical experience qualifies the genetic counselor for licensing by the Ministry of Health.<sup>1</sup> However, prenatal or reproductive genetic counseling may often be provided by obstetricians (e.g., Germany) or by midwives, with medical geneticists only involved in the diagnosis of rare disorders.<sup>50</sup> In other countries including Japan, Argentina, Chile, Italy, and China, physicians who may or may

not have additional training in genetics and/or reproductive genetics have been the ones to provide genetic counseling services.<sup>51</sup>

### **Conclusion**

Reproductive medicine has made great achievements over the last decades. With the use of PGD and PGS parents have more chances to give birth to babies that are free of serious/lethal genetic defects. As time passes by, PGD is becoming more known and it starts gaining ground over conventional prenatal diagnosis. On the other hand, due to the potential of these techniques, they can diverge from the reason for which they were created (detecting genetic defects) to detect non-disease related characteristics, such as sex (which is already performed), height and skin color. This could raise huge ethical dilemmas and it is left to the governments and the scientific community to direct the role of PGD. This review shows that there is a general high approval of PGD by couples at high risk and low concern about the extension of the technology to testing for non-health-related traits. However, there is a big debate on the advantages and disadvantages of PGS/PGS in IVF and the international use of PGD varies from explicit legislation with or without restriction to a 'professional guideline'

approach to legal prohibition through restrictive laws. Therefore, all couples who consider PGD or PGS should first receive genetic and infertility counseling in order to have realistic expectations, understand the advantages and disadvantages, and consider the limitations and the risks of each technique. Countries which offer PGD should also provide training in genetic counseling and/or in reproductive genetic counseling.

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