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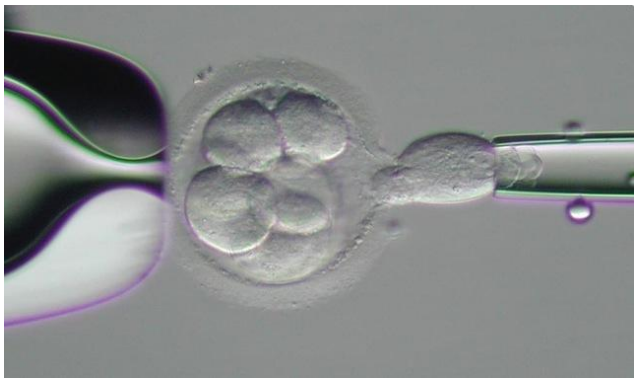
Pre-implantation Genetic Diagnosis



Pre-implantation genetic diagnosis (PGD), used in combination with IVF, allows families with a history of a serious genetic disorder to have a child unaffected by the condition. This POSTnote covers the applications of PGD in the UK and how the technology is regulated.

Overview

- PGD is used by families with a history of a serious genetic disorder to select embryos for IVF that are unaffected by the condition.
- As knowledge about the genetic basis of disease grows, more conditions are being authorised for PGD.
- PGD can now be used for diagnosis of later onset diseases such as breast cancer, as well as disorders with symptoms that reduce the quality of life rather than life expectancy.
- Concerns have been expressed over the increasing number of conditions authorised for PGD and over the broadening range of licensed conditions.

Background

Since 2009 the Human Fertilisation and Embryology Authority (HFEA) has authorised PGD on a condition-by-condition basis; once a condition is on the approved list, any clinic licensed to carry out embryo testing can provide it to suitable patients. The past 10 years have seen an increase in the overall number of conditions authorised and in the different types of disorders approved for PGD. As genetic sequencing technologies become cheaper and more accurate, these trends are expected to continue.

Undergoing PGD

Families with a history of a genetic disorder can be referred to a PGD centre by their GP or a genetic counsellor. Staff at the genetics centre will discuss the family planning options open to the couple. These can include:

- Conceiving naturally and accepting the risk of passing on the genetic condition or of having a miscarriage.
- Conceiving naturally and undergoing prenatal diagnosis. This involves the use of invasive techniques to sample the amniotic fluid or placental tissue. The accuracy of the test varies depending on the condition being tested. If the test shows the foetus is affected, the parents have to choose whether to terminate the pregnancy.
- Remaining childless or not having further children.
- Adopting a child.
- Pursuing gamete (egg or sperm) donation. This involves assisted conception techniques in which one or both parents would not be the biological parent of the child.
- Undergoing PGD.

How PGD Works

The main steps in performing the most common type of PGD are:

- patients undergo IVF and embryos are grown for two to three days until they consist of around eight cells
- one or two cells are removed from each embryo and are tested for the genetic condition of interest
- if available, one or two unaffected embryo(s) are transferred to the womb to develop
- remaining unaffected embryos can be stored for later use
- embryos affected by the condition are allowed to perish, or may be donated for research.

All couples must undergo IVF treatment in order to use PGD for the selection of an unaffected embryo even though they are mostly not infertile. The overall process has a relatively low success rate as there is no guarantee that an unaffected embryo suitable for implantation will result from a round of PGD.

Success rates and safety

Between 25 and 50% of couples referred to fertility clinics proceed to treatment after they have discussed the process, the chances of success and the risks involved. The success rate of PGD is similar to that of IVF without PGD. In 2010 a total of ten UK clinics performed 383 cycles of PGD, resulting in 135 live births of unaffected babies, a success rate of 31.6% per cycle started.[1]

Studies on the safety of PGD and IVF show that:

- The process of embryo biopsy necessary for PGD does not adversely affect the health of new-born children. This was the conclusion of a study of 995 babies born through PGD between 1993 and 2008.[2]
- There is a small risk of mis-diagnosis with PGD. International data collected between 1997 and 2008 reported 17 cases of PGD mis-diagnosis, representing 2 false negatives per 1,000 embryo transfers (0.23%).[3]
- Multiple births carry a high risk of complications. The HFEA code of practice recommends a maximum of two embryos be transferred at once. If a woman is under 40 preferably only one embryo is transferred. Any remaining healthy embryos can be frozen for subsequent implantation if necessary.

Authorising Conditions

PGD was first used in the UK in 1990 to prevent the inheritance of sex-linked disorders affecting boys such as haemophilia and muscular dystrophy by selecting female embryos for implantation. Shortly after this the Human Fertilisation and Embryology Act 1990 (as amended in 2008) laid down the regulatory framework for assisted reproduction in the UK. The Act was implemented by the newly formed HFEA. PGD was initially regulated on a case-by-case basis, whereby clinics applied to have a particular condition added to their licence. In 2009, the regulation of PGD changed to a condition-by-condition system. Once a condition is authorised by the HFEA for PGD it is placed on an approved list. Licensed PGD clinics can then offer tests for any condition on the list. An exception to this is the use of pre-implantation tissue typing (PTT) for the purposes of having a tissue-matched sibling, which is still regulated on a case-by-case basis (see page 3).

A clinic can submit an application to the HFEA to add a particular condition (or group of conditions) to the PGD list. This is then considered by the HFEA's Statutory Approvals Committee which decides whether the condition meets the criteria for approval, taking into account recommendations from expert reviewers and patient support groups. Some have argued that it should be left to parents, with guidance from clinical geneticists and genetic counsellors, to decide whether a condition is sufficiently serious to warrant PGD. [4]

Assessing seriousness

Current legislation only allows the use of PGD to test for serious inherited disorders. When assessing what constitutes a serious genetic condition, the HFEA's Statutory Approvals Committee takes the following into consideration:

- **Age of onset**: disorders such as cystic fibrosis affect a child from birth. Other conditions such as Huntington's disease are late onset, affecting people in middle age.
- **Symptoms of the disease**: symptoms of genetic disorders vary in severity. Diseases such as cystic fibrosis can result in death during early childhood or limit life expectancy whereas disorders like CFEM (see later) do not affect life expectancy but limit the quality of life.

Box 1. Treatments and cures for genetic disorders

Very few genetic disorders have effective treatments available; most health care for genetic disorders is palliative. Gaucher disease, which is a condition licensed for PGD, can be treated with enzyme replacement therapy, greatly improving the quality of life. However, enzyme replacement treatments are expensive and require regular intravenous transfusions. Some sufferers of cystic fibrosis can be treated with a lung transplant, and thalassaemia can be cured with a bone marrow transplant; however these treatments are dependent on the availability of a suitable donor (see POSTnote 441).

- **Variability of symptoms**: the seriousness of the symptoms associated with a genetic disorder can vary between individuals. In such cases HFEA makes a decision based on the worst possible symptoms. [5]
- **Penetrance**: if a genetic mutation inevitably results in a disorder it is said to show complete penetrance. A mutation that does not always result in the development of a condition has incomplete penetrance. Where a condition has incomplete penetrance, HFEA makes a decision based on the worst case scenario.
- **Availability and efficacy of treatments**: very few genetic disorders can be cured, although some have treatments available that can extend life expectancy and manage the symptoms (See Box 1).

Broadening the range of conditions authorised

At the time of writing there were 263 conditions authorised for PGD in the UK. The number of diseases caused by single gene mutations is currently estimated at around 10,000.[6] Many newly licensed conditions are sub-types of previously licensed conditions, with some being very rare disorders. There has also been a broadening in the range of conditions authorised. For instance, PGD is now licensed for genetic mutations that:

- pose an increased risk of developing a disease, or
- are disabling rather than fatal.

PGD for disease risk

In 2007 a test for mutations associated with the development of breast cancer was approved. This was the first test used to identify genetic markers (the BRCA1 and BRCA2 genes) that represent an increased risk of developing a disease; previous tests had been used to identify genes that would definitely result in the development of a disorder. Use of PGD for conditions caused by mutations with incomplete penetrance such as breast, ovarian and bowel cancer was initially licensed on a case-by-case basis, but this was changed to condition-by-condition in 2010. [7]

PGD for disabling conditions

PGD has also been used to identify genetic defects leading to disabling, rather than life threatening, disorders. For instance, it is licensed for the diagnosis of CFEM, a disorder that affects the muscles around the eye and results in visual problems of varying severity. Groups such as the watchdog organisation Human Genetics Alert, opposed the licensing of PGD for CFEM, claiming that it is primarily a cosmetic concern that does not limit life expectancy. However HFEA

approved the use of PGD for this condition in 2006 as it was found to be a serious condition that met the statutory requirements for PGD authorisation.

Saviour siblings

Families with a child in need of a stem cell transfusion to treat a serious medical condition can use pre-implantation tissue typing (PTT) to ensure they have a child that can act as a donor. PTT is permitted in such cases only when there are no family members that can act as donors, and the use of an unrelated donation has been deemed unsuitable. In many cases the existing child suffers from a heritable condition, so PGD benefits both the embryo being tested (by ensuring it does not carry the same genetic defect) and the existing child (by ensuring the embryo selected is a tissue match). However, in some cases the condition to be treated is not inherited. Such cases raise ethical concerns because only the existing sibling benefits from embryo testing; it is of no benefit to the embryo being tested. Such concerns mean that tissue typing is licensed by the HFEA on a case-by-case basis.[8] The committee that considers PTT applications meets more regularly than the committee that licenses new conditions because quick decisions are vital where there is an existing child suffering with a potentially fatal disease.

Review of the list of approved conditions

In 2009, HFEA agreed that the list of genetic conditions authorised for PGD should be periodically reviewed. The review was set up to assess whether effective treatments (see Box 1) have been developed that affect the prognosis or illness associated with licensed conditions. Of 109 conditions approved for PGD before October 2009, seven were identified as warranting further scrutiny, one of which was Marfan syndrome (see Box 2). Having reviewed all the evidence, HFEA concluded in July 2013 that none of the conditions on the approved list had been subject to significant treatment advances that would warrant their removal from the PGD list.[9] At the same time, a formal PGD reconsideration procedure was agreed by HFEA which sets out the various steps that are to be carried out for all future PGD reviews.

In April 2013, HFEA began the process of streamlining peer review of new PGD applications. A bank of peer reviewers has been assembled in order to speed up applications and decision making guidance provided to assist reviewers considering a new condition for authorisation.[10]

Other Possible Uses of PGD

PGD technology can be used for purposes other than preventing serious genetic disease. Some of these raise ethical concerns and are not currently permitted in the UK.

Sex selection

The use of PGD to select an embryo's sex is permissible in the UK, but only to avoid the inheritance of a sex-linked disorder. Under the HFE Act 1990 (as amended) it is illegal to use PGD to select an embryo based on sex for social reasons. This is in line with a public consultation which found that 82% of participants disagreed with the use of PGD to select the sex of offspring for non-medical purposes, with most citing ethical concerns as the reason.[11]

Box 2. Reconsideration of Marfan Syndrome

Marfan Syndrome is a genetic disorder affecting around 1 in 5,000 people. It affects the eyes, skeleton and heart. Sufferers have a life expectancy of around 44 years. Around 75 % of cases are inherited with the remainder resulting from a spontaneous mutation. A couple where one person has the syndrome has a 50% chance of having an affected child through natural conception. Women with Marfan Syndrome are at high risk of complications during pregnancy due to heart problems, so repeated pregnancy is not recommended; PGD can be used to ensure one pregnancy produces a healthy baby.

Treatment for Marfan Syndrome has been improving as surgical techniques to correct dislocated lenses and heart faults have developed. These advances mean the life expectancy of Marfan sufferers has increased with many more reaching reproductive age. While some see this as an argument in favour of PGD to ensure there is no increase in Marfan cases, others see improved treatment as a reason to review whether PGD is necessary. Marfan Syndrome was initially included in the list of conditions under reconsideration for PGD authorisation. However, the HFEA received expert opinions strongly opposing the restriction of access to PGD for Marfan sufferers and has since stated that Marfan Syndrome will continue to be authorised for PGD.

Pre-implantation genetic screening (PGS)

Fertility clinics may offer pre-implantation genetic screening to couples undergoing IVF who are over 35, have a history of recurrent miscarriages or have undergone multiple unsuccessful rounds of IVF, with the intention of improving success of their fertility treatment. Embryos are screened for any abnormalities that may reduce the chance of successful implantation before being transferred to the woman. However, there is a lack of evidence that PGS improves the chances of a successful pregnancy. Randomised controlled trials have shown no benefit of using PGS in conjunction with IVF, and older women were found to have decreased live birth rate following PGS (13-23%) compared to those using IVF without PGS (26%).[12] The British Fertility Society recommends PGS only be used in the context of a randomised controlled trial, and that couples should be made aware that there is no evidence to suggest PGS improves live birth rate.

Selecting for disability

In 2002 a deaf lesbian couple in the US chose to use a sperm donor with a heritable form of deafness to increase their chances of having a deaf child. This sparked a debate about the ethical implications of using PGD to choose to have a child with a disability. Some members of the deaf community do not identify themselves as disabled; instead they see the signing deaf community as a distinct culture. However, in 2008 the HFE Act was amended to include a clause stating that an embryo with a genetic defect that could result in a serious disability must not be used in preference to an unaffected embryo. Similarly, an egg or sperm donor who is a carrier of a genetic condition cannot be preferred over one that is not. There is very little evidence of demand from the deaf community, or any other

disability group, for the right to choose disability. However, some have said they would not have a preference for either a deaf or hearing child and would rather leave it to chance; by being obliged to choose a hearing child some argue that their reproductive autonomy is compromised.

Ethical concerns

Some pro-life groups oppose all uses of PGD as it involves discarding embryos not suitable for implantation. Those who believe life begins at conception argue this is not morally acceptable. Other groups are more concerned about the increase in the number and types of conditions licensed for PGD, which they see as a 'slippery slope' toward the use of PGD to create 'designer babies'. However, current technology is not suitable for the selection of complex traits under the control of multiple genes. Among other technical challenges, very few embryos suitable for implantation are created in a PGD cycle and the likelihood of producing one with the desired combination of genes that would result in a complex trait is very low.

Funding PGD

Each UK country has set eligibility criteria for access to NHS-funded PGD. All are similar to the main criteria set for England and Wales that:

- a couple are at risk of passing on a serious genetic disorder to a child conceived naturally
- the condition is licensed for PGD by the HFEA
- the couple do not have an unaffected child
- the female partner is under 40 when referred
- the female partner is not underweight or obese
- both partners should be non-smokers.

PGD services in the UK are now centrally commissioned. In England, the abolition of primary care trusts in April 2013 is widely seen as providing more equitable access to PGD as the previous commissioning policies led to "inconsistent policies on access to PGD".[13] In England and Wales couples are eligible for three cycles of PGD. In Scotland, couples receive two cycles of PGD [14] whereas the Northern Ireland Health and Social Care Board decides on a case-by-case basis. At the time of writing there were no licensed PGD clinics in Wales or Northern Ireland, so PGD must be commissioned from clinics in England or Scotland. Patients who do not meet the criteria above can privately fund PGD. This costs around £8,000 per cycle plus £1,000 for the necessary drugs.[15]

Some disagree with the condition that NHS funding can only be used to produce one healthy child. They argue that access to PGD should be increased on the grounds that the financial cost of caring for a baby conceived naturally that is affected by a genetic disorder is far greater than the cost of funding PGD to ensure a second healthy child.

Box 3. Autism

Autism is a complex spectrum of behavioural disorders with varying severity. The genetic basis of the disorder is unclear, but in some families there is a strong correlation between being male and having autism. IVF Hammersmith submitted an application to HFEA to use PGD to select a female embryo in order to avoid the inheritance of autism. The application cited a four-fold increase in the incidence of autistic diagnosis in males. However, the peer reviewer and the Genetic Alliance patient group objected to the application. Gender selection was deemed inappropriate as gender segregation of autism tends to occur at the less severe end of the spectrum. HFEA refused the application; however further applications are currently being compiled.

It is likely that the licensing of PGD to select for embryos unaffected by autism would receive widespread public attention and would lead to protests from disability rights groups. It would represent a further change in the types of conditions licensed, as no behavioural disorders have previously been authorised for PGD.

The Future of PGD

It is now possible to sequence an embryo's entire genome as sequencing technologies have become quicker, cheaper and more accurate. It is possible that, along with single gene defects that lead to a specific disorder, clinicians will be able to identify genetic elements that increase the risk of more complex but less serious disorders such as asthma or autism (see Box 3).

Gene sequencing technology has already been used in PGS to check embryos for chromosome disorders that would make the embryo unsuitable for implantation. This involves the sequencing of about 2% of the embryo's DNA, but in the future sequencing could be used to reveal the status of individual genes associated with inherited disorders, both for use in PGD, but also for pre-implantation genetic screening of embryos during IVF treatment.

Sequencing technology could reveal information about additional diseases and predispositions that were not the initial target of PGD. It has been suggested that 'masking' of genetic information could be used so only results pertaining to the genetic disorder of interest are seen, and unrelated genes remain unknown. Such technologies raise ethical considerations concerning both the patient's right to know the genetic make-up of the embryo, and their right not to know.

Endnotes

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4 Handyside A, Nature 464, 978-979, 2010
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7 Case by case decision making in embryo testing. HFEA http://goo.gl/pMyMgI
8 A qualitative study of public attitudes to embryo selection for tissue donation. HFEA 2004
9 HFEA Authority Meeting Agenda, July 2013 http://goo.gl/NW1zSj
10 HFEA: Progress Report and Decision Trees. HFEA, May 2013
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15 Guy's & St Thomas' Hospital, PGD Centre http://goo.gl/xbUhmV

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