Bioethics Briefing

Number 3: Preimplantation Genetic Diagnosis

Chris Willmott, University of Leicester

Introduction

The term "**designer baby**" occurs liberally throughout the popular media whenever issues surrounding the selection of genetic features of a child are being considered. Despite the fact that this expression has entered the popular psyche, it is actually used in a slippery way that covers a broad range of technologies, which are variably real, potential, improbable and impossible. At an extreme end we have the near future as presented by a film such as GATTACA. A world is depicted in which genetic selection of individuals has become routine and genetically enhanced "Valids" lord it over the "Invalids" whose genomes have been assembled in the more time-honoured manner. Although an interesting reminder of the dangers of eugenics, the procedures required to deliberately introduce multiple characteristics into one individual, even in the unlikely event that each feature was the product of one gene, remains well beyond the bounds of current experience.

At the other end of the spectrum, however, science fiction has very definitely become science fact. In 1990, a research team headed by Robert Winston reported the first clinical application of preimplantation genetic diagnosis (PGD) when they used the polymerase chain reaction (PCR) to screen for Y-chromosome specific DNA sequence as a means of determining the gender of embryos (Handyside *et al*, 1990). Since that time, PGD has become an increasingly established method for checking for chromosome abnormalities in an embryo, and/or to look for the presence of a specified gene (see overleaf, the **Science of Preimplantation Genetic Diagnosis**, for more details). Although too labour intensive and thus expensive to be considered routine, PGD nevertheless represents an alternative to prenatal diagnosis techniques such as chorionic villus sampling and amniocentesis, which are means of screening *in utero*

embryos at 10-12 weeks and 14-22 weeks of gestation, respectively. For some people, this ability to check an embryo before rather than after implantation is a highly significant distinction (see p.5, **Ethical arguments regarding PGD**).

An ever-growing number of children worldwide are being born after PGD. The motivation for carrying out evaluation of the embryo can be varied, including the prevention of genetic illness, generation of stem cells for donation to an older sibling, and sex selection (see, for example, the real-life examples on p.9). PGD to check for predisposition to cancer and other late-onset disorders has also been reported (e.g. Rechitsky *et al*, 2002). It is worth pointing out, however, that despite discussion of genetic enhancement, current technology only facilitates selection for or against genes that are already present on the chromosomes of the parents. The deliberate introduction of other novel characteristics would involve combining PGD with other technologies, such as gene therapy, which are not yet routine.

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The Science of Preimplantation Genetic Diagnosis

It goes without saying that preimplantation genetic diagnosis is not a process that can be applied to natural conceptions; the potential to screen embryos before implantation is fundamentally reliant on the methodologies employed for *in vitro* fertilisation (IVF). In the most widely employed PGD protocols, embryos are screened on the third day after IVF, when they consist of approximately eight cells. One or two cells (blastomeres) are removed for genetic biopsy. There is a certain tension here; the availability of two cells to assay allows enhanced confidence in the outcome of the tests, particularly if there is suspicion of any form of mosaicism, i.e. "the presence of two or more cell lines which differ from each other in chromosome number or structure, in an individual that has developed from a single fertilized egg" (Robinson, 2003). Thus, allowing the embryo to develop to a stage where it has a larger number of cells and hence can cope with the removal of two blastomeres, rather than one, facilitates this additional testing. On the other hand, embryos are only viable *in vitro* for a finite period of time. Since the tests which must be undertaken prior to implantation can themselves take several hours to determine whether an embryo is suitable for continued development, it is important that it is not kept for so long that its existence is jeopardised.

In order to remove blastomeres, a hole must be made in the zona pellucida (ZP), the jelly coat surrounding the embryo. In early work in this field, the hole was formed using a jet of acidic solution. Greater accuracy and quicker processing has, however, been achieved through the use of laser technology and this has thus become the standard method for breaching the ZP (Sermon, 2002). A fine pipette is inserted into the embryo via the hole and one or two cells are drawn into the pipette, which is then retrieved.

The method of genetic testing carried out on isolated cell(s) depends upon the reason(s) for which the PGD has been undertaken. An individual blastomere only contains a few picograms of DNA, therefore early work in this field relied upon PCR to amplify the embryonic DNA to sufficient quantities for testing to be undertaken. In the intervening period, PCR-based techniques have become increasingly sophisticated and remain the preferred approach when screening for monogenetic (single gene) disorders. Other approaches are now being used to check the sex of the embryo and for gross chromosomal abnormalities (see below).

A number of problems associated with the use of PCR for PGD have been identified. As a result of hybridisation failure or other uncharacterised difficulties, a phenomenon known as **allele dropout (ADO)** in which only one allele of a gene becomes amplified is surprisingly common. This is most significant if the allele which does not amplify is a dominant mutation and an embryo which is in reality heterozygous appears to be homozygous for the normal allele.

Contamination of PCR samples is also a concern. If the embryo biopsy is contaminated with DNA from another source (e.g. maternal cells, other non-fertilising sperm still embedded in the zona pellucida, or DNA from previous PCR studies) then amplification reactions are going to generate unreliable results. Steps can be taken to minimise this problem. For example, the impact of DNA from other sperm can be negated by using **intracytoplasmic sperm injection (ICSI)** to achieve fertilisation by use of a micropipette to deliver one sperm directly into one egg in the absence of any other gametes.

Additionally, use of **multiplex PCR**, in which multiple pairs of primers are used to facilitate simultaneous amplification of several sequences, helps to identify both cases of contamination (by judicious selection of highly variable marker sequences) and of ADO (by using a linked polymorphism). Sensitivity of detection can be enhanced by using **fluorescent PCR**. With enhanced sensitivity you do not need the embryonic DNA in such high concentrations and therefore you can reduce the number of PCR cycles required and thus reduce the risk of contamination to or from other reactions.

There are increasing examples of PGD being undertaken to ensure a child is a suitable haematopoietic stem cell donor for an older sibling (see, for example, the Hashmi and Whitaker cases on p.9). Each individual has two different human leukocyte antigen (HLA) haplotypes, co-dominantly inherited from each parent. A suitable donor and the intended recipient must have the same profile of HLA proteins on the cell surface; **tissue match** is determined by a series of PCR reactions spanning the HLA region of Chromosome 6.

For **gender determination**, assessment of chromosome abnormalities (e.g. **translocations**) and screening for

aneuploidy (having an inappropriate number of chromosomes, e.g trisomy), **fluorescence *in situ* hybridisation (FISH)** and more recently **comparative genome hybridisation (CGH)** have become more widely used. In FISH, embryonic chromosomes are probed using cloned fragments of human DNA which have been labelled with fluorescent molecules. By exploiting a fluorescent signal there is no need to amplify the DNA. Unlike earlier cytogenetic processes, FISH is not limited to use with metaphase cells; it can equally well be used with cells in any phase of the cell cycle. For technical reasons, it is only possible to use a finite number of probes at any one time (typically five to nine) so it is necessary to give due consideration to which probes will be appropriate (Wells and Levy, 2003).

Although a number of variations of FISH have been developed, the biggest advances have come with CGH and now with the potential for **microarray-CGH**. In CGH, the entire genome can be tested simultaneously. The embryonic DNA and a reference genome are labelled with different fluorochromes, usually green for the sample and red for the normal DNA. Both are then hybridised to a metaphase spread of normal male DNA on a microscope slide. If the sample DNA is normal there should be an equal binding of red and green labelled DNA to the chromosomes, which should then look yellow. If, however, there are chromosomal abnormalities in the test DNA the ratio will shift either in favour of green (e.g. for trisomy) or red (for monosomy). With the assistance of computer-driven comparison, local deletions and duplications can also be visualised.

There are still difficulties associated with CGH. Unlike FISH, it does normally require some chromosomal amplification by PCR. This contributes to the major difficulty, namely the time taken to carry out the analysis (approx. 72 hours) is incompatible with the *in vitro* viability of the test embryo. In consequence, the embryo must either be frozen, a process that introduces additional risk, or CGH can be carried out on the second polar body (see below) which becomes available shortly after fertilisation. As you might imagine for such a complex procedure, CGH is technically demanding and also even more expensive than other already-costly IVF/PGD methods.

Combination of CGH with microarray (DNA chip) technology has proven useful in cancer studies and is now finding application in embryo biopsy. Microarrays of well-characterised cloned genomic DNA fragments rather than chromosome spreads are prepared. Embryonic and reference DNA is fluorescently-labelled as for conventional CGH. Information about hybridisation is now obtained by laser scanning rather than fluorescence microscopy. It is a fast and sensitive approach, which lends itself to automation and thus reduces both the cost and the required expertise to carry it out. It is likely to become the standard protocol for preimplantation diagnosis of chromosomal abnormality. Indeed, these are some suggestions that aneuploidy screening should become a routine feature of IVF treatment (see, for example, http://news.bbc.co.uk/1/hi/health/3123633.htm).

It is technically possible to carry out pre-conception analysis of the developing egg (oocyte) by **polar body biopsy (PBB)**. Unlike the development of sperm where all four products of meiosis become mature cells, in oogenesis only one becomes an egg, the others being rejected as smaller polar bodies. At the start of meiosis, the immature egg cell copies its entire genome, so that it has 4 copies of each chromosome. If the mother was, for example, heterozygous for a monogenetic disorder there would now be 2 copies of the normal gene and 2 of the mutant form. At the end of meiosis I, the developing oocyte extrudes half of the chromosomes in the form of the first polar body. If the latter can be shown by PCR to have both mutant copies of the gene, it means that the egg must have the normal copies and is suitable for fertilisation. Conversely, if the polar body contains both normal copies of the gene, then the egg will be rejected. Biopsy of the first polar body has the ethical advantage that it occurs before conception, and is thus an acceptable alternative for many who are opposed to PGD on the grounds that fertilised embryos are *de facto* human and should not be discarded for having the 'wrong' genes (see **Ethical arguments regarding PGD**, p.5). The situation is more problematic if the polar body contains one normal and one mutant form. Under these circumstances it is necessary to also examine the second polar body. In human development, however, the second polar body is not released until after fertilisation, negating the ethical advantage of dealing with an unfertilised cell. Assessment of chromosomal abnormality by FISH also involves examination of both polar bodies.

The fact that PBB can be carried out on cells before fertilisation is also one of the principal disadvantages of the technique because fertilisation of a suitable egg must follow screening. Since this process is by no means guaranteed, a significantly larger number of oocytes must be screened to prepare facilitate several attempts to produce an embryo, thus incurring increased expense. Furthermore, because PBB is limited to evaluation of the maternal contribution, it is clearly of no value if the potential genetic problems originate from the father. Likewise, since the gender of an embryo is determined by DNA in the fertilising sperm, PBB is also inappropriate for sexing.

Ethical arguments regarding PGD

A broad range of opinions are held concerning the appropriate use of preimplantation genetic diagnosis, not least as a consequence of the diversity of ways in which people are seeking to apply the technology (see, for example, the cases considered on p. 6). Arguments are made either from first principles, or based on expected consequences; these are described, respectively, as deontological and teleological viewpoints (see *Bioethics Briefing 1* for more background on moral philosophy).

Before reflecting on arguments relating to the different uses of PGD, it is necessary to consider the more fundamental question; whether PGD is ever an appropriate technique. The diagnostic process pre-supposes that some embryos will not be deemed suitable for implantation into the mother and will thus be allowed to die. The moral **status of the embryo** is therefore a central issue at the start of the debate. Several different views are held regarding the point at which human life begins. The obvious view that life begins when an egg is fertilised by a sperm does not find universal approval. Opponents to the 'life begins at conception' school point out that more than 50% of eggs fertilised by sperm spontaneously abort. A number of other key events in development have therefore been offered as alternative landmarks for the start of life, these include: implantation in the uterus (approx 8 days after conception), start of neural development (14 days). Cameron and Williamson (2003) point out that prior to the advent of ultrasound scanning, a woman would not be confident she was pregnant until the first detection of foetal movement (at 15 to 18 weeks).

What, then, is the moral status of the early embryo? Three positions are held – the preembryo is merely a collection of undifferentiated cells and has no moral status; the preembryo has its own completed genome and thus has the full status of a human being; the preembryo is a potential human being (Schenker, 2003). For some, the lack of consensus on this pivotal issue requires the '**precautionary principle**' to be adopted. Thus, "while it may be unclear what status the early embryo has, to be willing to kill what for all one knows is a person is to be willing to kill a person." (Song, 2002, p.35). From this standpoint embryos should be given the benefit of the doubt and any use of PGD is therefore problematic.

It is not only advocates of pro-life positions who wish to maintain an outright ban on PGD. The whole notion of **selection** of children raises objections from several quarters. Firstly, there are those who object to selection on the grounds that it fundamentally alters the relationship between parent and child; a 'gift' becomes a '**commodity**'. Secondly, a willingness to deselect embryos facing genetic **disabilities** (such as achondroplasia) is taken as a huge slur on individuals living with those conditions. Many disabled rights activists argue that it is society's attitude to disability rather than the life of a 'handicapped' individual which needs to be rejected. Proponents of PGD counter that embryo selection makes no value statement regarding people already alive.

Thirdly, objections to PGD are raised over the spectre of **eugenics**, i.e. the attempt to influence the genetic make-up of the population by exerting control over reproduction which has been manifest in less technologically-able times by rules regarding who was allowed to procreate and the forced sterilisation of individuals deemed unsuitable breeding stock. The worry is that benign and well-meaning selections undertaken now will be Trojan horses letting in all manner of other more questionable pressures, in particular the deliberate selection of characteristics such as intelligence, sporting ability or sexuality. It is important at this point to repeat the oft-overlooked caveat that PGD itself can only select for or against genes that are already present in the genetic make-up of the parents. Therefore, whilst such '**slippery slope**' arguments may present a possible picture of the future, the technology that would give rise to such developments is more akin to gene therapy than PGD *per se*.

The strongest advocates of PGD in all its forms are the libertarians (e.g. McCarthy, 2001; Harris, 2002). Freedom to make one's own **reproductive choices**, they argue, is as much a mark of democratic society as freedom of thought or freedom of speech. For them, a choice to use PGD to ensure a child has a desired characteristic is, in essence, no different from a decision to use contraception or, indeed, about how many children to have. Harris presents an evolving series of scenarios to support a view that allowing PGD under some circumstances but not under others is nonsensical. Imagine, he asks, that a woman has six embryos available for PGD, with the intention to implant three. If three embryos prove to be normal and three have genetic disease, there is a clear expectation that the three healthy embryos will be transferred.

Now, however, assume that three are normal, but the other three will have longer, healthier lives – which three should you choose to implant? Finally, assume that three are normal, but three are diagnosed as having superior intelligence – which now should you implant? Thus, Harris argues, if knowledge is available to make decisions on these grounds then we ought to do so; "if it is not wrong to wish for a bonny, bouncing, brown-eyed, intelligent baby girl, with athletic potential and musical ability, in virtue of what might it be wrong to use technology to play fairy godmother to oneself and grant the wish?" (p. 50-51).

Advocates of PGD often focus on the distinctions between PGD and **prenatal testing** followed by abortion in situations of known genetic risk. In their thorough evaluation of these two methods for trying to achieve a healthy child, Cameron and Williamson (2003) conclude that PGD is preferable because it involves positive as well as negative outcomes, i.e. although affected embryos are 'allowed to die', suitable embryos are implanted and thus there is a 'let live' aspect to the procedure. In contrast, prenatal diagnosis with unfavourable findings only leads to a negative event, the killing of a foetus. This argument does not wash with those that consider life begins at conception and thus view the destruction of multiple 'unsuitable' embryos in PGD as equally or perhaps more objectionable than prenatal testing followed by termination (though they are, of course, generally opposed to both). Interestingly, it has been argued that the same objections can be raised from a utilitarian standpoint; if a greater number of embryos are destroyed during PGD than during prenatal screening then this implies the latter is the preferable procedure (Munthe, 1999). Clearly, however, there are additional differences between the two procedures; the establishment of a pregnancy, the greater advancement of the development of the foetus, the greater bonding of the mother with the foetus and the psychological stress of, perhaps, a repeat pattern of screening and abortion mean that mathematics alone is not adequate grounds for distinguishing the relative merit of these techniques.

Different applications of PGD raise their own specific debates, which are well illustrated by the specific cases considered on page 9. For example, there are questions over whether HLA **tissue matching** is appropriate, particularly if the new child will gain no personal benefit from the procedure. The

advantage is clear, not only can it offer a perfect match, but the fact that umbilical stem cells can be used circumvents the donor having to undergo bone marrow extraction – a painful invasive procedure. Opponents raise questions concerning the **psychological impact** on the "saviour siblings", particularly if the treatment of the recipient proves unsuccessful.

Cultural bias in favour of male children, particularly in India and in China is a source of concern regarding **sex selection** for non-medical reasons. It might be argued that in the absence of PGD, parents responding to these pressures will elect instead for prenatal testing and termination of daughters. Birth ratios skewed in favour of male children in some parts of the world certainly suggest that this practice is already occurring. The Human Fertilisation and Embryology Authority in the UK does not allow gender selection (except for bona fide X-linked conditions), but the practice is not regulated in some other countries. An interesting compromise position has been proposed in which PGD would not be permitted for a first child, but would be allowed for subsequent children, e.g. to allow a couple to ensure that they had a daughter if they already had one or more sons, or vice versa (Robertson, 2003).

Genetic tests exist for a variety of conditions which are either of no threat at all to the child (e.g. being a **carrier** for a recessive genetic disorder) or are **late-onset** illnesses (such as Huntington's disease) or which bestow upon the recipient an increased risk of disease (e.g. the BRCA1 gene as an indicator of the potential to develop cancer). A question asked here is whether such burdens are sufficient grounds for selecting against an embryo. Even more problematic is the scenario thrown up by the "deaf lesbian" case in which two deaf women sought out a sperm donor with a long familial history of deafness to produce a non-hearing child. They did not themselves use PGD to reach this end, but the potential is definitely there for selection of monogenetic forms of deafness. Under such circumstances, an embryo would be selected against because the resultant child would be able to hear.

This leads into an additional area of contention, namely **harm**. It would seem that someone selecting for a deaf baby might be open to accusations of deliberate harm against that child. Not so, say the defenders of such action. If a different embryo had been selected, then <u>this</u> child would not have existed at all, therefore "the child is harmed by being selected to exist

only if his or her life is so bad it is not worth living" (Savulescu, 2002). Other arguments based on harm are sometimes made, e.g. if being a multiple birth (as is often the case in IVF pregnancies) leads to prematurity and associated health problems then there is a case for saying that the resultant children have been harmed by the process. Harm to the mother is sometimes cited. In keeping with any woman undergoing IVF, she will have to receive fertility treatments, which can result in ovarian hyperstimulation syndrome, ectopic pregnancy or multiple pregnancy, which is of course a potential problem to her wellbeing in addition to any difficulties for the babies themselves.

Finally, the expense of IVF and PGD (several thousand pounds per cycle) means that **financial arguments** are frequently raised, albeit employed to support different viewpoints. As it stands, the cost of treatment is generally carried by the prospective parents. There is, therefore, an issue of **justice** – are poorer individuals disenfranchised from PGD because of the expense? Advocates of the procedure suggest that state assistance should be available. Such a move is opposed by others on the grounds that the NHS (or equivalent) has **limited resources** available to it and the money could be better spent on more worthy treatments. The cost of IVF/PGD is also used to counter the fear of a 'slippery slope' to widespread selection of trivial characteristics since few people would be in a financial position to follow this route to pregnancy.

Case Study

Four year old Nikos Zagorakis is not well. When he was a baby he was pale, prone to infections and generally 'failed to thrive'. Investigations showed that he is suffering from the blood disorder beta-thalassaemia major, because he does not have sufficient quantities of normal haemoglobin to carry oxygen around his body. Haemoglobin should be composed of four subunits, two alpha chains and two beta chains. Nikos has unfortunately inherited a faulty copy of the HBB gene (which codes for beta chains) from each of his parents and this is why he cannot make active haemoglobin. His parents are carriers for the condition, but because they each had a copy of the normal gene as well as the mutant copy, they were sufficiently well not to realise that they had the trait.

Unable to make normal haemoglobin, Nikos relies on the small amounts of foetal haemoglobin his body continues to make using a different gene. His body tries hard to cope, but Nikos is anaemic and has to have blood transfusions every six weeks. This therapy is not, however, a long-term solution; repeated transfusions cause a build-up of iron and will inevitably lead to serious side-effects such as diabetes, heart failure or liver disease by the time Nikos reaches adolescence.

The only cure for Nikos would be a bone marrow transplant. His parents, Dimitri and Maria, have sought in vain to find a suitable donor. They are now discussing with doctors the radical solution that they use preimplantation genetic diagnosis (PGD) to choose a baby brother or sister for Nikos. They hope to carry out two tests on an *in vitro* fertilised embryo before it is implanted into Maria's uterus. Firstly, they would check that the new embryo does not have the thalassaemia mutations. Left to nature, there would be 25% chance of the second child also suffering from thalassaemia, and a 50% change that they would be a carrier; only 1-in-4 children would not have either faulty gene. Secondly, they want to do a 'tissue match' to make sure that the new baby will be a suitable donor for Nikos. There is also likely to be about a 1-in-4 chance of a perfect tissue match, giving an overall 1-in-16 chance of an embryo being ideal. Maria is therefore going to require significant fertility treatment to stimulate her ovaries to overproduce eggs, and the couple must reconcile themselves with the 'waste' of a large number of embryos that are not suitable. If successful, however, it will be possible to take stem cells for donation to Nikos from the placenta, sparing the new child (or any other potential donor) from undergoing a painful marrow operation.

You are in the medical team advising the Zagorakis family. Do you recommend that they proceed with this programme? You must be prepared to justify your decision.

Additional questions that could be used to extend the discussion:

- ◼ It turns out that none of the embryos matches both criteria – if one is a perfect tissue match but is a carrier (with one faulty beta-globin gene) should this be implanted?

- ◼ Would it make a difference if the new baby was unlikely themselves to benefit from the screening; e.g. if it only involved tissue-matching to ensure that the child was an appropriate donor for an older sibling?

- ◼ Would it make a difference if the screening was for a condition that was merely inconvenient rather than life-threatening in any way?

Points to consider

This case study is fictional, but is deliberately positioned part-way along the spectrum of potential uses of PGD. Once groups have considered how they might respond to this particular proposal, a discussion of UK news reports on genuine uses of PGD can be a very effective way to illustrate the legal position in this country. One of the earliest UK uses of PGD resulted in the successful birth of **Ethan Paget Dunthorne** (see, for example, http://news.bbc.co.uk/1 /hi/health/1027076.stm). Both of Ethan's parents are carriers for cystic fibrosis (CF). A recessive condition, requiring the faulty gene to be inherited from both parents, there is a 1-in-4 chance that a child will have CF. Sadly, this proved to be the case for Ethan's older brother Joshua who had died from the condition at the age of 4 months. Not wanting to take the chance of having another CF child, Ethan's parents undertook PGD at Hammersmith Hospital. The important point to note in this case is that the PGD was entirely for the benefit of the new child.

Compare this with a second case, involving the **Hashmi family**. Zain Hashmi, four years old at the time of the controversy in 2003, was suffering from an inherited thalassaemia (see http://news.bbc.co.uk/1/hi/health/ 2928655.stm and links from that page to previous aspects of the case). Zain was being treated with blood transfusions, but this was not a suitable long-term strategy and he therefore needed a bone marrow transplant to improve his health. Unfortunately no living relative appeared to be a suitable donor and his parents therefore turned to PGD. In this case they had two aims from the screening; to ensure that the new child did not have beta-thalassaemia but also to undertake tissue matching so that they would be a suitable donor for Zain. The Human Fertilisation and Embryology Authority (HFEA) approved this twin use of PGD, but after a High Court ruling that it had overstepped its authority, the procedure was banned for three months until the Appeal Court overturned the previous verdict.

The third interesting case involves the **Whitaker family** (see http://news.bbc.co.uk/1/hi/health/3083239.stm). Like Zain Hashmi, Charlie Whitaker has a blood disorder, but in his case it is Diamond Blackfan Anaemia (DBA). Although some chromosomal loci have been association with DBA, no links have been confirmed, and occurrence of the condition is thought to be sporadic. There is therefore no genetic screening for DBA, and thus it would not be possible to see whether or not the new child has the disease. In the eyes of the HFEA in the UK (and similar authorities in Australia) this represents an important line in the sand. With no material benefit to the new baby, only to the older sibling, they have determined that this is not a suitable use of PGD and ruled that it is not permissible in this country. Such legislation is not, however, universal and such a procedure is allowed elsewhere. The Whitaker family therefore sought the help of a reproductive genetics institute in Chicago. As a result of their assistance, a second son was born in June 2003. The new boy, Jamie, was shown to be a perfect genetic match for Charlie.

This kind of overseas travel to exploit differences in reproductive legislation has become known as "**fertility tourism**". It has also become an established route for parents wishing, for whatever reason, to specify the gender of their next child. Once again, this is helpfully illustrated by reference to recent news stories. One such case involves **Alan and Louise Masterton** (see http://news.bbc.co.uk/1/ hi/health/3260827.stm and links from that page). The Mastertons have four boys and were delighted in 1995 by the birth of a daughter, Nicole. Tragically, Nicole died as the result of a bonfire accident in 1999. Determined to have a new daughter, the Mastertons sought permission to use PGD to select the gender of their child, but were refused permission by the HFEA, which only allows sex-selection for medical reasons, i.e. to avoid sex-linked genetic diseases. The Mastertons subsequently travelled to Italy for treatment, but the only resulting embryo was male, so they donated it to an infertile couple. They remain campaigners for a change in the law.

Mike and Nicola Chenery from Devon also have four boys. Adamant that their next child should be a girl, but similarly unable to undergo gender-selection procedures in the UK, Mrs Chenery went to Spain for treatment and in November 2003 gave birth to twin girls (http://news.bbc.co.uk/1/ hi/england/devon/3236385.stm). The HFEA has subsequently reiterated that sex selection is only allowed for medical reasons and is not to be permitted for "family balancing" (e.g., see http://news.bbc.co.uk/1/hi/health/ 3257893.stm).

Annotated references

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Delhanty J.D.A. and Harper J.C. (2000) Pre-implantation genetic diagnosis *Baillière's Clinical Obstetrics and Gynaecology* **14**:691-708

Handyside A., Kontogianni E., Hardy K. and Winston R. (1990) Pregnancies from biopsied human preimplantation embryos sexed by Y-specific DNA amplification *Nature* **344**:768-770

- The first report of clinical application of PGD, in which two couples known to be at risk of transmitting X-linked conditions had embryos screened to ensure than only female embryos were implanted. Much of the pioneering work in PGD was performed by this team from Hammersmith Hospital/ University College London and their colleagues

Harris J. (2002) Liberation in reproduction, in *Designer babies: where should we draw the line?* (ed. E. Lee), Hodder and Stoughton ISBN 0340848359

McCarthy D. (2001) Why sex selection should be legal *Journal of Medical Ethics* **27**:302-307

Munthe C. (1999) Pure selection: the ethics of pre-implantation genetic diagnosis and choosing children without abortion, Acta Universitatis Gothoburgensis, reviewed by **Gillam L. (2001)**, in *Journal of Medical Ethics* **27**:415-416

Retchitsky S., Verlinsky O., Chistokhina A., Sharapova T., Ozen S., Mascaiangelo C., Kuliev A. and Verlinsky Y. (2002) Preimplantation genetic diagnosis for cancer predisposition *Reproductive Biomedicine Online* **5**:148-155

- A paper from the Reproductive Genetics Institute in Chicago which has been responsible for many of the landmark reports in the PGD field (including the birth of Jamie Whitaker)

Robertson J.A. (2003) Extending preimplantation genetic diagnosis: the ethical debate *Human Reproduction* **18**:465-471

- This is not the first paper in which Robertson has proposed PGD for second and subsequent children, but it contains helpful additional discussion

Robinson W.P. (2003) Chromosomal mosaicism http://www.medgen.ubc.ca/wrobinson/mosaic/glossary.htm (Last accessed, June 30th 2004)

Savulescu J. (2002) Deaf lesbians, "designer disability", and the future of medicine *British Medical Journal* **325**:771-773

Schenker J.G. (2003) Ethical aspects of advanced reproductive technologies *Annals of the New York Academy of Science* **997**:11-21

Sermon K. (2002) Current concepts in preimplantation genetic diagnosis (PGD): a molecular biologist's view *Human Reproduction Update* **8**:11-20

- As the title of this article implies, it is a good starting point for those interested in the molecular biology undergirding PGD. The review can be freely accessed http://humupd.oupjournals.org/cgi/reprint/8/1/11.pdf

Song R. (2002) Human genetics: fabricating the future (Darton, Longman and Todd, London ISBN 02232523932, now listed as Pilgrim Press, ISBN 0829814825)

- Written from a Christian ethics standpoint, this highly readable book contains well-reasoned positions, of interest to religious and secular readers alike

Wells D. and Delhanty J.D.A. (2001) Preimplantation genetic diagnosis: applications for molecular medicine *Trends in Molecular Medicine* **7**:23-30

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Video and drama

In recent years, a number of television science programmes have picked up on PGD. These include the following, which may be available to you locally as off-air recordings:

Bitter Inheritance – The Needell Family (video, 40 minutes) Shown on BBC TV in 2002, this programme tells the true story of Juliet Wheeler who has suffered multiple miscarriages

as the result of a chromosome translocation inherited from her father. The programme describes her situation and shows her undergoing fertility treatment and PGD by FISH to find a suitable embryo. If 40 minutes is too long, a 10 minute section towards the end conveys the science well, though the whole programme is thoroughly recommended.

Designer Babies (video, 50 minutes) This programme was transmitted a number of times, as part of different series on the BBC. In 1999, it was branded "Babies of the millennium – designer babies" and in 2000 it reappeared as the Horizon episode "Life and death in the 21st century – designer babies". The programme as a whole is somewhat sensationalist and covers a lot of ground including the human genome project, cloning and gene therapy. The section on PGD (about seven minutes in length, starting 18 minutes into the programme) is quite balanced and looks at the birth of Brittany Abshire, the first PGD baby in the USA, born after an older sister died of Tay-Sach's disease.

News footage (various) The Hashmi case received widespread coverage on April 8th 2003 and the birth of Jamie Whitaker on June 19th 2003. In particular, the 6 o'clock news on the BBC that day led with the story, and includes an excellent comparison of the Whitaker situation with the Hashmis. Similarly, the HFEA decision to rule out sex selection for non-medical reasons (e.g. family balancing) had blanket coverage in news programmes on November 12th 2003.

A Present for Anna an interactive drama focused around the fictional story of Anna who is suffering from Fanconi Anaemia and desperately needs a bone marrow transplant. In the absence of a suitable donor, her parents consider whether to employ PGD to generate a suitable donor. The audience takes on the role of the public consultation panel considering whether to grant approval for this use. This drama, performed by the Exstream theatre group, has toured successfully to schools and universities around the UK, but is dependent on intermittent funding. To find out if a performance is viable for you contact the group at exstream@exeter.ac.uk

The Gift is a drama from Y Touring theatre, a company with a growing collection of plays on bioethical themes. The gift has been available as a video for a number of years and has been quite widely used in schools. It tells the story of parents who select for sporting ability in their son. To purchase the video and/or find details of possible performances contact Y touring via their website www.ytouring.org.uk

Websites

Embryo biopsy Several websites allow you to download QuickTime movies showing the removal of a cell from the 8 cell embryo. Recommended are http://www.layyous.com/Videoclips/pgd.htm which allows you to download a video for your own use, and http://www.infertile.com/media_pages/video_pages/emb_biopsy.htm which has the advantage of an online commentary, though the image itself is rather small.

News websites The BBC News website continues to be a reliable source of reports on bioethics related stories and, unlike some newspaper sites, seems likely to keep its archive live for the foreseeable future. Links to several pertinent PGD stories are listed in the case studies section, above. The Guardian newspaper website (www.guardian.co.uk) also has a substantial archive and is a useful alternative source.

Acknowledgements

Stop Press

On July 21st 2004, as this Briefing was going to press, the HFEA amended the rules on "saviour sibling" selection. This was in response to another request to use PGD to find a tissue match for a child with Diamond Blackfan Anaemia (see, for example, http://news.bbc.co.uk/1/hi/health/3913053.stm). Under the new rules, the Whitaker family (p.9) would, therefore, have been permitted to receive the treatment they requested without the need to travel to the USA.

List of available Bioethics Briefings

The following Bioethics Briefings are freely available at
http://bio.ltsn.ac.uk/resources/ethicsbrief.htm

Briefing 1: Ethics and Bioethics

Briefing 2: Genetically Modified Crops

Briefing 3: Pre-implantation Genetic Diagnosis

Briefing 4: Xenotransplantation

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