OPINION

PGD gender selection for non-Mendelian disorders with unequal sex incidence

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Preimplantation genetic diagnosis (PGD) was originally developed for couples whose potential offspring were at risk of severe Mendelian disorders, but has since been extended to other indications. One possible use of PGD is to perform gender selection for couples whose offspring are at increased risk of disorders that do not follow Mendelian inheritance, but which are substantially more common in one sex than another (unequal sex incidence). Here, we examine the clinical and ethical issues to be considered prior to offering PGD gender selection to reduce the risk of a child being affected by a non-Mendelian condition with unequal sex incidence. Factors to be considered include: the risk that a child of either sex will be affected by the condition; the overall reduction in risk provided by gender selection and the potential harms of the procedure. Consideration should also be given to the interests of the family and the child to be born, the seriousness of the condition and the couple’s procreative autonomy. To illustrate these issues we use the example of autism, a non-Mendelian disorder that is considerably more common in males than in females.

Keywords: preimplantation genetic diagnosis; gender selection; IVF; autism

Introduction

Preimplantation genetic diagnosis (PGD) is, in a sense, a very early form of prenatal diagnosis (PND), in which embryos created in vitro are analysed for specific genetic defects so that only those that are free of these defects are transferred into the womb. PGD was originally developed as an alternative to PND and selective abortion for couples at high risk of having a child with a severe Mendelian genetic disorder. However, over the last 10 years, the indications for PGD have broadened to include inherited and sporadic chromosomal abnormalities, genetic abnormalities associated with adult onset disorders, blood group incompatibilities and HLA tissue typing (Kuliev and Verlinsky, 2005).

PGD can also be utilized for gender selection, in favour of either female or male embryos. Although medically assisted gender selection for non-medical reasons is illegal in many countries (Knoppers et al., 2006), gender selection is permitted in most Western countries when performed for a medical indication. Most commonly, PGD gender selection involves selection of female embryos, requested by couples whose male embryos would be at risk of an X-linked disorder, but in cases where specific testing of the causative gene is not readily available.

Another potential use of PGD gender selection is by couples whose embryos are at risk of non-Mendelian disorders that have unequal sex incidence (Pennings, 2002). We use here the expression ‘non-Mendelian’ as synonymous with ‘polygenic’, which is to say, disorders that are caused by multiple additive genetic influences rather than the single gene effects that produce Mendelian inheritance patterns. For most non-Mendelian disorders, the contributing genes are either unknown or poorly understood, and specific gene testing is not available. Environmental influences may also be important. Non-Mendelian disorders include many common birth defects (e.g. neural tube defects, congenital heart disease) and chronic disorders of later life (e.g. ischaemic heart disease, diabetes, common cancers). For some non-Mendelian disorders, males and females are affected approximately equally, but others affect one sex more than the other. For couples whose embryos are at increased risk of a non-Mendelian disorder with unequal sex incidence, the risk of the child being affected by the disorder differs according to whether the child is male or female. Examples of non-Mendelian disorders with unequal sex incidence are set out in Table I.

This paper examines whether it is clinically or ethically appropriate to offer PGD gender selection for non-Mendelian disorders.
disorders with unequal sex incidence, using autism as an example. Autism is a lifelong neurodevelopmental disorder with onset in childhood, characterized by impairments in social interaction and communication, and restricted and repetitive patterns of interest or behaviour (Folstein and Rosen-Sheidley, 2001). Autism fulfils the criteria of non-Mendelian inheritance and unequal sex incidence, being considerably more common in males than females. Autism is common, with recent estimates suggesting the combined prevalence of classical autism and other autism spectrum disorders (such as Asperger syndrome) to be between 5 and 10 per 1000 (Chakrabarti and Fombonne, 2005; Baird et al., 2006).

Demonstration of increased risk

The first criterion to be fulfilled prior to offering PGD selection is demonstration that the couple is at increased risk of having a child with the disorder in question. Usually for non-Mendelian disorders, such risk will have been determined by empiric studies of recurrence risk in other families with the disorder.

For autism, the rate of recurrence in siblings of affected individuals is significantly higher than the incidence of autism in the general population (Jorde et al., 1991; Simonoff, 1998). For parents with one autistic child, the risk of autism in a subsequent child is ~5%, provided that rare Mendelian or chromosomal causes of autism have been excluded (Jorde et al., 1991; Simonoff, 1998) (see discussion below). A substantially higher risk, possibly around 25%, applies when more than one child is affected (Folstein and Rosen-Sheidley, 2001). In addition to the 5% risk of recurrence for autism, immediate relatives of individuals with autism are more likely to exhibit milder autistic traits that fall below the threshold for a diagnosis of autism (Bolton et al., 1994; Murphy et al., 2000; Pickles et al., 2000; Constantino et al., 2006). The risk of a sibling exhibiting one or more features of the ‘broader autism phenotype’ may be as high as 30% (Folstein and Rosen-Sheidley, 2001).

Demonstration of unequal sex incidence

Unequal sex incidence is the second criterion that should be established before PGD gender selection can be offered. Unequal sex incidence is also recognized from a review of empiric data. Preferably this data should exist for familial as well as sporadic cases, because the sex ratio of randomly ascertained probands may be more extreme than that of their affected relatives (James, 1991).

For autism, the recurrence risk is highly dependent on the sex of the offspring. Among the sibships of randomly ascertained probands, subsequently born males are 3–4 times more likely than females to develop autism (Yeargin-Allsopp et al., 2003; Chakrabarti and Fombonne, 2005). This male preponderance persists for familial cases of autism: an analysis of 512 sibships containing more than one affected child from the AGRE database (www.agre.org) also shows a male:female ratio of 3:1 to 4:1. When the recurrence risk for autism is stratified according to sex, the figure is therefore closer to 2% for a female sibling, and 8% for a male.

Exclusion of disorders for which specific gene testing is available

For some disorders that are usually non-Mendelian, rare subsets exist with chromosomal or Mendelian inheritance. For example, in autism in less than 10% of patients, a specific genetic cause can be identified, such as Fragile X syndrome, Rett syndrome, chromosome disorders, neurofibromatosis, tuberous sclerosis and various inborn errors of metabolism (Folstein and Rosen-Sheidley, 2001; Muhle et al., 2004). It is important that these causes be identified, because for these disorders, the risk of recurrence in a subsequent pregnancy may

### Table I. Examples of non-Mendelian disorders with unequal sex incidence.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Ratio of male to female (approx)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disorders more prevalent in males</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autism spectrum disorder</td>
<td>4:1</td>
<td>Chakrabarti and Fombonne (2005)</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>2.5:1</td>
<td>Kennedy et al. (1993)</td>
</tr>
<tr>
<td>pyloric stenosis</td>
<td>4.1</td>
<td>Myrianthopoulos and Chung (1974)</td>
</tr>
<tr>
<td>Hirschsprung disease</td>
<td>4:1</td>
<td>Badner et al. (1990)</td>
</tr>
<tr>
<td>Otosclerosis</td>
<td>3:1</td>
<td>Larsson (1960)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Male limited</td>
<td></td>
</tr>
<tr>
<td>Cryptorchidism</td>
<td>Male limited</td>
<td></td>
</tr>
<tr>
<td>Hypospadius</td>
<td>Male limited</td>
<td></td>
</tr>
<tr>
<td><strong>Disorders more prevalent in females</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1:90</td>
<td>Jemal et al. (2007)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>1:2.5</td>
<td>Lockshin (2006)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1:2.5</td>
<td>Lockshin (2006)</td>
</tr>
<tr>
<td>Graves Disease</td>
<td>1:9</td>
<td>Lockshin (2006)</td>
</tr>
<tr>
<td>Congenital dislocation of the hip</td>
<td>1:4.5</td>
<td>Myrianthopoulos and Chung (1974)</td>
</tr>
<tr>
<td>Idiopathic Scoliosis</td>
<td>1:4</td>
<td>Riseborough and Wynne-Davies (1973)</td>
</tr>
<tr>
<td>Gynaecological cancer</td>
<td>Female limited</td>
<td></td>
</tr>
</tbody>
</table>
vary from <1% to 50%, and PGD for gender selection would be entirely inappropriate.

The absolute reduction of risk through gender selection: the benefit of the procedure

For disorders with unequal sex incidence, the difference in incidence between the sexes is frequently expressed as a ratio of relative risk, as set out in Table I. However, when assessing the benefits of PGD gender selection, the relative risk is of limited utility. If PGD gender selection is being considered, it is more important to calculate the ‘absolute risk’ of recurrence for a child of each sex. It is then possible to calculate the ‘difference’ between the risk of having an affected child when PGD sex-selection is used, compared with the risk of having an affected child with natural conception (no gender selection) (‘the overall reduction in risk’).

To illustrate this point, Table II shows the risk of having a child with autism faced by three different couples: the first with no family history of autism, the second with one child affected by autism and the third with two children affected by autism. For the purpose of this calculation, we have used a male:female ratio for autism of 4:1, and a prevalence of classical autism in the general population of 1:1000.

For all three couples, the risk of autism in a male child is approximately four times greater than the risk in a female child. However, for the couple with no family history of autism, the a priori risk of having a child with autism is low (0.1%). For them, gender selection in favour of female embryos would reduce the risk of having an affected child from 0.1% to ~0.04%, an overall reduction in risk of only 0.06%. In contrast, for the couple with one autistic child, gender selection in favour of female embryos would reduce their risk of having an affected child from 5% to 2%, an overall reduction of 3%. For the couple with two autistic children, the equivalent risk reduction is from 25% to 10%, an overall reduction of 15%. This example demonstrates clearly that it is the ‘overall reduction in risk’ figure that best demonstrates the potential benefit of gender selection.

In counselling, attention should also be given to the ‘residual risk’ after PGD gender selection. It is critical that the couple understand that even following ‘successful’ PGD gender selection, their daughter could still be affected by autism. The magnitude of the residual risk should also be considered in assessing the overall utility of the procedure. A high residual risk after PGD gender selection could potentially be a reason for a physician to decline a request for PGD gender selection, in the interests of the welfare of child to be born (see below), although we are not aware of any practical examples that fit this category.

Table II. Recurrence risk for autism according to the sex of the child and reduction in risk provided by gender selection.

<table>
<thead>
<tr>
<th>Population risk</th>
<th>Risk without gender selection (%)</th>
<th>Relative risk (Male:Female)</th>
<th>Risk for male child (%)</th>
<th>Risk for female child (%)</th>
<th>Reduction in risk by gender selection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>4:1</td>
<td>0.16</td>
<td>0.04</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>One affected</td>
<td>5</td>
<td>4:1</td>
<td>8</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Two affected</td>
<td>25</td>
<td>4:1</td>
<td>40</td>
<td>10</td>
<td>15</td>
</tr>
</tbody>
</table>

\[\text{Ratio of Male:Female} = \frac{m}{f}, \text{ male-specific risk} = \text{population risk} \times \frac{2m}{m+f}.

\[\text{If ratio of Male:Female} = \frac{m}{f}, \text{ female-specific risk} = \text{population risk} \times \frac{2f}{m+f}.

Risks associated with gender selection by PGD: harms of the procedure

The potential harms of the IVF/PGD procedure must also be considered when deciding the appropriateness of PGD gender selection. Many unanswered questions still exist about the safety and health consequences of IVF and PGD, and further research is required. To date, the best available evidence indicates that children conceived through assisted reproductive technologies (ART) are at an increased risk of birth defects compared with spontaneous conceptions. This increase in risk is estimated to be 30–40% above the baseline prevalence of birth defects within that population (Hansen et al., 2005), although the extent to which this increase is attributable to the IVF procedure versus the underlying cause of infertility remains to be determined. Assuming a baseline prevalence of birth defects of around 3% (Harper, 2004), this equates to an additional risk of 1% associated with ART. Limited information is available about the safety of PGD, but available data suggests that the frequency of birth defects in babies conceived through PGD is similar to that for babies conceived through standard IVF treatment without PGD (Sermon et al., 2007).

In addition to an increased risk of birth defects, other adverse pregnancy outcomes that increase significantly with IVF include multiple pregnancy (even with a single embryo transfer, monozygous twinning may ensue), pre-eclampsia, gestational hypertension, placental abruption, placenta praevia and preterm delivery (Mukhopadhaya and Arulkumaran, 2007).

In this context, it would be inappropriate to offer PGD gender selection in a situation when the overall reduction in risk from gender selection was 1% or less, because any potential benefit would be lost due to IVF-associated risks (acknowledging that the consequences of a disorder occurring as a result of the IVF procedure may not be identical to those of autism, or other disorders with unequal sex incidence). In the example of a family with one autistic child, it may be appropriate to offer PGD gender selection, because the overall reduction in risk by selection of a female embryo (3%) outweighs the risks to the embryo associated with ART (1%).

Perception of risk and seriousness of the condition

Using a calculation similar to that illustrated in Table II, it should be possible in most clinical situations to estimate the
overall reduction in risk offered by PGD gender selection. What magnitude of risk reduction is then sufficient for gender selection to be offered? Provided that the potential benefits of the PGD gender selection clearly outweigh the risks associated with the procedure, the appropriateness of PGD gender selection will be influenced by the perception of risk by the people seeking treatment, and critically, how seriously they view the condition (Nelson, 2006).

Where PGD is permitted for medical reasons, the test most commonly used is ‘to avoid the risk of transmission of a “serious” genetic condition’ or some form of this test (Knoppers et al., 2006). In countries that allow PGD, the law does not define what constitutes a ‘serious’ condition for which PGD is allowed, but rather leaves it up to the specialist clinicians or the responsible organizations (Hudson, 2006; Knoppers et al., 2006). This viewpoint may leave a degree of uncertainty in respect of the conditions for which PGD may be offered, but it does allow flexibility in a complex and progressing field. In the UK, the HFEA Code of Practice provides that the seriousness of the condition is not to be determined solely on the basis of the clinician’s opinion, but is to be a ‘matter for discussion between the people seeking treatment and the clinical team’ (Nelson, 2006).

In the example of autism, the clinical range is broad, ranging from relatively minor difficulties with communication and socialization, to individuals with severe intellectual impairment who are unable to communicate. This clinical range can be quantified in an objective fashion by using a standardized autism assessment tool such as the Childhood Autism Rating Scale (CARS) (Schopler et al., 1988). Nonetheless families with children affected by autism of similar severity may have very different subjective experiences of the effect of the affected child on themselves and their families. Thus, even though the clinical range of autism is broad, it is difficult to draw a line and say only those parents with a child with particular symptoms should be entitled to PGD gender selection. It is true to say that some parents find the experience of having had a child with autism extremely difficult and stressful, and would be reluctant to take the risk of having a further child without some means of diminishing that risk.

Consideration need also be given to whether a treatment is available, whether the treatment is effective and whether there is potential morbidity associated with treatment. Any treatment should also be currently available and accessible to the family. If a condition is diagnosed early and there is an effective and accessible treatment, e.g. as with pyloric stenosis, then gender selection would not usually be offered. With a condition such as autism, there is no known prevention or cure and there has been limited success with treatments, although early detection and intervention may improve a child’s long-term outcome (Muhle et al., 2004).

**Interests of the child to be born**

When deciding whether a condition is ‘serious’ enough to offer PGD gender selection, it is necessary to consider what is in the best interests of the child to be born. In most countries where IVF is performed, the welfare and interests of the child to be born are considered in relation to reproductive technology (Knoppers et al., 2006; Nelson, 2006), and it has been suggested that the physician has an obligation to ensure that any risk for the future child is minimized (Pennings et al., 2007). However, PGD differs from standard IVF in that it involves the selection between different potential persons, where one is not maximizing the chances of a particular person, but choosing to give birth to a different person (Knoppers et al., 2006). Thus PGD gender selection requires a value judgment as to the ‘life worth living’ of a child of one sex versus a child of the opposite sex, where a child of one sex has a higher risk of developing a certain condition than another. For a family where one child is affected by autism, it is the choice between selecting a female child who has a 2% chance of being affected by autism, rather than a male child who has an 8% chance of being affected by autism.

**Interests of other siblings and the family**

Consideration may also be given to other children who might be affected by the birth of a child born as a result of IVF treatment (Nelson, 2006). The effect on each sibling and their family will vary greatly, with some families and siblings adjusting more successfully than others. Siblings of a child with autism may be presented with challenging behaviour from the affected child, including aggressive and self-injurious behaviours, impulsivity, hyperactivity, rituals, severe communication deficits, as well as the need to face the response of others (Kaminsky and Dewey, 2002). The siblings may have to cope with changes in family roles, structure and activities, feelings of guilt and shame, loss of parental attention and increases in parental stress (Pilowsky et al., 2004). Parents of siblings of children with autism may feel that their children are burdened with the duty of looking after the child with autism, after they are deceased. This may be a psychological burden not only borne by the parents but also by the siblings, throughout their lives. It can be argued that parents have a duty to give their children the best possible life and, in doing so, should give their children every possible advantage (Savulescu, 1999; Hudson, 2006). This may include reducing the risk of giving birth to a sibling (and second child) with autism.

**Procreative autonomy**

The principle of procreative autonomy gives parents the choice as to when and how to have children. It invokes the concept that parents know best their own circumstances, and ultimately it is parents who must live with and make sacrifices for their children (Savulescu, 1999). Parents have a right to be involved in decisions that affect such a personal matter as reproduction. Their autonomy should be respected, as they will be the most directly affected parties by the birth of a child (Knoppers et al., 2006), and they will ultimately be responsible for the raising and support of their children, both financially and emotionally. If they are unable adequately to support their children, the lives of the children will be affected. Each family requesting PGD gender selection brings their own individual
perspective on the seriousness of the condition, and this perspective should be respected.

IVF and PGD is by no means a trivial undertaking, and the process is usually associated with a number of difficulties for the couple, including financial cost, emotional stress, disruption to usual routines and, for the mother, the side effects of hormonal stimulation and invasive procedures. There are risks associated with the procedure, and there is no guarantee of a successful pregnancy. We argue that once a couple has been fully informed about the process and risks associated with PGD (which gives due respect to parental autonomy and which is required by law in most countries that offer PGD), if they still wish to proceed, this is indicative of the seriousness of the condition according to their perceptions.

There may be concerns that PGD gender selection for non-Mendelian disorders with unequal sex incidence will be requested by couples whose real desire is for social gender selection, but who cannot access gender selection without medical justification. Many couples in this situation will be able to find a medical justification for sex selection somewhere within their family history, thereby blurring the distinction between medical and non-medical gender selection (Penning, 2002). The role of the physician in this circumstance is not to question the motivations of the couple requesting PGD gender selection, but rather to ensure that sufficient evidence exists to justify gender selection on medical grounds. In the absence of sufficient medical justification, the physician can reasonably decline a request for PGD gender selection. Beyond this point, the autonomy of the couple, and mutual trust between them and the physician, should be preserved.

**Consistency/compatibility with PND and termination of pregnancy**

PND followed by termination of pregnancy is another reproductive technology that enables parents to terminate a pregnancy where the embryo is diagnosed as having a genetic condition. PND can be used to determine the sex of an embryo, and in countries such as China and India, it has been used as a means of gender selection for non-medical reasons (Savulescu, 1999). PND to determine the sex of the fetus, followed by termination of pregnancy, could be used as a form of gender selection to reduce the risk of having a child with a non-Mendelian disorder with unequal sex incidence. Such reproductive procedures may have already been used in some countries.

There are two issues relevant to this process: is it legally possible, and would it be ethically acceptable? Legally, in many of the countries that allow PGD as a reproductive technique, the laws would also allow PND and termination of a pregnancy; for example, if there were a high risk the child would be born with autism. Regulation of PND and termination of pregnancy differs from the regulation of PGD. For example, in the United Kingdom a termination of pregnancy may be performed where, if the child were to be born, there is a substantial risk of it having a physical or mental disability. Autism may be considered to be a mental disability, and an 8% risk for a male embryo may be a ‘substantial risk’. In some States in Australia, termination of pregnancy is permitted in circumstances where to carry on the pregnancy would cause serious danger to the life or physical or mental health of the mother (Skene, 2004). Where PND reveals the child is a male, and thus there is a relatively higher risk that the child may be born with autism, such risk may cause such danger to the mental health of the mother, depending on the mother’s perception of risk and view of the condition. This may enable the mother to terminate the pregnancy of the male embryo/fetus.

Even though the procedure may be available legally, whether or not a couple would terminate the pregnancy is not clear. From an ethical viewpoint, the couple may for religious, moral or other reasons be reluctant to terminate the pregnancy of a male embryo/fetus. Studies have shown that for ethical reasons, some women prefer PGD to PND followed by termination of a pregnancy (Knoppers et al., 2006). Each individual case would differ depending on many factors.

It is important that the inconsistencies between the laws on termination of pregnancy and PGD be resolved (Braude, 2006). If PND followed by termination of pregnancy is permitted for a condition such as autism, from an ethical viewpoint, it would be unacceptable if PGD were not allowed for the same condition, as many of the ethical issues in respect of both procedures are comparable, and indeed the very early stage at which gender selection is undertaken in PGD could be seen as less controversial than midtrimester PND-related termination.

**Concluding comments**

The decision as to whether or not people seeking treatment should be offered PGD gender selection for conditions with unequal sex incidence is complex, and consideration should be given to the factors detailed above. A doctor who specializes in the area of medical genetics has the expertise required to determine whether the couple is at increased risk of having a child affected by the relevant condition, the recurrence risk for each sex and the overall reduction in risk provided by gender selection. It is the people seeking treatment, however, who are best placed to decide whether the condition is serious enough to warrant PGD gender selection.

The argument above has been largely focused around the question of autism, and to our knowledge, this is the only non-Mendelian disorder for which PGD gender selection has been undertaken. Many physicians will have reservations about offering PGD gender selection for some of the disorders listed in Table I, and autism is likely to remain the most frequent non-Mendelian disorder for which gender selection will be sought. Nonetheless, the approach we have outlined can be applied to new requests for PGD gender selection for other non-Mendelian disorders as they arise. Our approach could also be used when considering other new technologies for gender selection, such as sperm sorting by flow cytometry (Fugger et al., 1998), provided that differences in the accuracy and risks associated with other technologies are taken into account.
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References


