

Prenatal Diagnosis for "Minor" Genetic Abnormalities is Ethical

Robert J. Boyle, Murdoch Children's Research Institute, Australia

Julian Savulescu, University of Oxford, United Kingdom

Abstract

Is it justified to detect minor genetic aberrations before birth and terminate pregnancies based upon such information? We present the case of a woman who wanted Prenatal Diagnosis (PND) to detect whether her female fetus was a Haemophilia mutation carrier. Such carriers are usually healthy. She wished to eradicate the Haemophilia mutation from her family to avoid future generations being affected and to protect her children from having to go through PND themselves.

We explore existing practice guidelines, public attitudes and possible objections to providing PND for minor abnormalities. We argue that in a society where couples have considerable autonomy relating to decisions about the fetus at least until viability, the routine restriction of PND for minor genetic abnormalities would be an unjust infringement of individual liberty.

Introduction

Over 22,000 mutations have been identified in human genes and the number of recognized genetic disorders increases each year (Human genome mutation database; Online Mendelian Inheritance in Man). Even the commonest genetic disorders are rare, but together they affect around 2% of births (McKusick 1994). Minor genetic variations with health implications are even more common - for example Factor V Leiden which predisposes to venous thrombosis is present in up to 12% of people in some countries - and every one of us carry mutations which have the potential to cause genetic disorders in our children (Lucotte and Mercier 2001).

Genetic testing is available for over 800 conditions and such testing may be used prenatally to detect severe or less severe disorders (Online Mendelian Inheritance in Man; GeneTests TM). There is uncertainty surrounding the ethics of PND for more minor genetic disorders, or its use for fetal sexing (Savulescu 1999; Simpson and Carson 1999; Benagiano and Bianchi 1999; Statham et al. 1993; Sureau 1999). Moreover the distinction between genetic disease, risk factor and normal variant is sometimes subjective - an example being the C282Y polymorphism seen in 85% of those in Northern Europe with Haemochromatosis. This polymorphism is viewed by some as a genetic condition worthy of population screening and others as a risk factor rather than a genetic disease (Jeffrey and Adams 2000; Burke, Franks and Bradly 1999; Allen and Williamson 1999). An important question in

PND is whether women should be allowed complete autonomy over which prenatal tests they request regarding the health of their fetus.

We have recently received a number of requests for PND of carrier status for an X linked genetic disease - the diseases in question were Haemophilia A and Fragile X syndrome. These requests came from couples interested in eradicating a particular genetic abnormality from their family. We present one of these cases, and use it to explore the ethical status of PND for minor genetic abnormalities.

PND for Haemophilia carrier status

A woman presented to the Genetics Clinic whose father was affected by severe Haemophilia A and died in his 40s from complications of treatment. She made a promise to her father not to continue the Haemophilia gene in the family. She is a carrier of Haemophilia and has had no bleeding problems. She expresses a desire for PND when she becomes pregnant, wishes to know the carrier status of a female fetus and would terminate both an affected male and a carrier female. Her possible reproductive outcomes are shown in Table 1.

Pregnancy outcome	Clinical problems	Probability	Implications for next generation
A Healthy Male	Nil	25%	Nil
B Male with Haemophilia	Bleeding tendency Lifelong therapy	25%	Daughters have 50% risk of being carriers
C Healthy Female	Nil	25%	Nil
D Carrier Female	90% healthy 10% mild bleeding	25%	Daughters 50% risk carriers Sons 50% risk Haemophilia

Table 1: Reproductive outcome for a female carrier of a Haemophilia mutation

PND of Haemophilia

The usual procedure for PND of Haemophilia is to determine the sex of the fetus first and only proceed to mutation analysis if the fetus is male. The woman in this case would like to terminate both an affected male (B in Table 1) and a carrier female (D in Table 1) and therefore requests that a female fetus undergo mutation analysis also. She has strong personal reasons for not wishing to pass the mutation to her children, and wants to avoid having a daughter who is a Haemophilia mutation carrier and who must therefore make the same difficult antenatal decisions that she has made.

Prognosis in Haemophilia A

In the past patients with severe Haemophilia A suffered recurrent bleeding into joints and muscles and debilitating arthritis, and in the 1980s around two thirds of those with Haemophilia A in Western Europe and the United States were infected with Human Immunodeficiency Virus due to contamination of factor VIII treatment. The condition now has a much improved prognosis, the use of recombinant factor VIII has reduced concerns related to infection risk, and there is hope that gene therapy may become available (Mannucci and Tuddenham 2001). Nevertheless a proportion of women at risk of having a son with Haemophilia A choose PND and termination of affected males (Miller, Hilgartner, and Aledort 1987).

Discussion

This and similar cases have posed a difficult ethical question for the medical teams looking after them - could they justify providing PND for genetic abnormalities of little consequence to the fetus' health and facilitating termination of pregnancy based on this information?

We shall examine this question and its wider implications by first reviewing professional statements and public opinion regarding the restriction of PND. Then we shall explore possible objections to the process of PND and termination for minor genetic abnormalities, and briefly extend our discussion to Preimplantation Genetic Diagnosis (PGD).

Professional and Public views on restricting PND

1. The law

Abortion is illegal in most of Europe, Australasia and North America except under specific circumstances - often that the fetus should not be independently viable (taken as up to 24 weeks gestation in many countries) and that continuation of the pregnancy represents a risk to the mother's life or health. In practice, the continuation of an unwanted pregnancy is usually considered a sufficient risk to a woman's mental health to justify termination if she requests it. Thus until 24 weeks gestation in many Western countries there are no legal barriers to the provision of PND for minor genetic abnormalities and subsequent termination of pregnancy. Indeed it is possible that a refusal to offer PND for a genetic abnormality may be viewed by the law as breach of the doctor's duty of care and so be negligent practice, especially if failing to do the test had significant psychological consequences for the woman. Doctors may be considered also to have a legal duty not to withhold any information they have derived from a patient if that information is important for the patient's health care, or for the care of a fetus. Women with a family history of Haemophilia may be regarded as having a right to have male fetuses tested since they are at risk of inheriting a serious genetic condition (Rogers v Witaker 1992). However it is not clear that doctors have a legal duty to provide genetic testing for carrier status or minor genetic abnormalities even if they are feared by the pregnant

woman.

2. The views of professionals

A 19-nation survey of medical geneticists in the 1980s addressed the question of which genetic tests should be made available prenatally (Wertz and Fletcher 1988; Wertz and Fletcher 1989). Some geneticists were in favor of limiting PND for minor genetic conditions in some way (for example by refusing sex selection) but there was no clear consensus as to which genetic traits warrant PND. A Canadian survey in 1997 of physicians offering PND services found that over half of them would oppose termination of pregnancy if the fetal anomaly was considered minor - again, which anomalies they considered minor is unclear (Bouchard and Renaud 1997).

The current policy statements of professional medical and genetic bodies imply that prenatal testing should concern the health of the fetus (rather than that of the offspring of the fetus) and some statements use the terms 'high risk' or 'serious' disorder as prerequisites for PND (World Health Organization 1997; Department of Health Advisory committee on Genetic Testing 2000; Reilly 1992; Human Genetics Society of Australasia 1997). For example the American Society of Human Genetics states that termination of pregnancy is justified for fetuses 'likely to have a serious genetic disorder', and the United Kingdom's Human Genetics Commission comments that testing should be to confirm the presence of a genetic disorder *in the fetus*.

3. Political bodies

At a political level there is also a will to restrict the indications for PND. A recent recommendation from the Council of Europe Committee of Ministers suggests that PND 'should be aimed only at detecting a serious risk to health of the child' and a report for the Canadian government likewise recommended that indications for PND be restricted (Council of Europe Committee of Ministers 1990; Royal Commission of New Reproductive Technologies 1993).

4. The views of the public

The public in many countries clearly sanction PND and termination of pregnancy for severe genetic disorders - a consistent majority (around 75%) of individuals surveyed between 1972 and 1987 by the United States National Opinion Research Centre supported abortion for a serious genetic disease, and more recent studies in the UK and France have similar findings (National Opinion Research Center 1987; Julian-Reynier et al. 2001; Human Genetics Commission 2001).

The views of the public regarding PND for more minor genetic abnormalities however are unclear. While it is likely that a significant proportion of them object at some level - in the same recent UK survey 87% felt that genetic information should not be used by parents to choose the mental and physical characteristics of their children - there is a clear demand from some for PND and termination on the

basis of non disease traits. For example a recent survey in Finland suggested that around 1 in 10 adult Finns would be willing to terminate a pregnancy if their fetus was found to be homosexual (Hietala et al. 1995).

5. The views of people with genetic disorders

Some disability rights advocates consider PND to be a form of discrimination against those with disabilities (Holtug 1997). However the Genetic Interest Group (GIG) in the UK, which provides a voice for those affected by a variety of genetic conditions, oppose restricting PND. They state 'if conditions were drawn up for which antenatal testing and termination on the grounds of fetal abnormality were or were not allowed, people would be denied the opportunity to make the choices appropriate for their family. Such a denial of choice would be discriminatory (Genetic Interest Group 1999).

6. How important are the views of society regarding these very private decisions?

There is clearly support at a policy and professional level for restricting the availability of some prenatal tests particularly those for non-medical sex selection. The public in North America and Europe while supporting PND for severe disabling conditions may object to PND for minor genetic abnormalities (although there is clearly a demand for such testing), and the voices of those with genetic conditions give a mixed message.

Evidently the views of society in this area are not well established, in part as a result of the paucity of public debate on the issue. It is possible at least in the short term that there would be significant public objection to PND for minor genetic abnormalities. If there were such public objection, the question arises as to whether such an objection should overrule the desire of individual couples to make what are very personal and intimate decisions. It is important to explore the reasons why society might object to PND for minor abnormalities, but any objection should not automatically be used to restrict the freedom of couples - in liberal societies individuals may be assumed to have freedom of action unless their actions risk causing harm to others in that society. This principle was important in establishing the legalization of homosexuality in the last century, and we have argued elsewhere that the same principle should apply to our private reproductive decision-making (Hart 1963; Boyle and Savulescu 2001). In the next section we explore reasons why society might object to these decisions.

Ethical objections to PND for minor genetic abnormalities

1. Irrationality

All of us carry a number of recessive genetic mutations, and minor genetic abnormalities are common - the desire to eradicate such minor variations may appear irrational. However the woman in the case above, and potentially

those requesting PND for other minor abnormalities has strong personal reasons for her request. She was so adversely affected by witnessing her father's Haemophilia as to wish not to be part of the continuation of such suffering in any generation. Even in an era of much improved prognosis for Haemophilia, she values the possibility of future generations being affected by this condition very negatively. There is a 50:50 risk that each son of a future carrier female will be affected by Haemophilia, and the avoidance of this potential burden of disease is a reason to offer PND for carrier status. Even if PND will be available to these carrier females, some may not know of their carrier status or choose not to avail themselves of it. It is better, other things being equal, that children in the future be born without haemophilia rather than different children are born with haemophilia.

For her and her family it may be rational to eradicate any chance of their children's children being affected by Haemophilia.

2. Discrimination

There is controversy over the degree to which PND is discriminatory - discriminatory against the unborn child with a genetic abnormality and against those alive with the same genetic condition (Holtug 1997; Gillam 1999). One of us (JS) has recently argued that allowing access to termination of pregnancy on the basis of perceived severity of fetal abnormality constitutes a form of discrimination and unacceptable eugenics (Savulescu 2001). Since we all carry recessive mutations, the stigmatising effect of allowing selection against carrier state or minor genetic abnormalities is likely to be less than the stigmatising effect of the current choice to select against clinically apparent genetic disorders.

3. Rationing of Resources - 'Injustice'

PND may need to be rationed within publicly funded healthcare systems, and examples exist of such rationing. In Hungary in the 1980s PND was limited to those pregnancies with a greater than 2% risk of a severe and untreatable disorder in the fetus (Harper 1998). However the number of couples requesting PND for *minor* genetic abnormalities is likely to be low and to have limited economic implications. The extra testing requested by the woman in the case above costs AU\$700 (US\$370), but this cost may be outweighed by savings in terms of reduced requirement for PND or Haemophilia treatment in future generations. Carriers of Haemophilia have a 25% risk of having a fetus with Haemophilia each time that they conceive, and such children have considerable lifelong treatment costs (Bohn 2000). PND for carrier status of rare recessive conditions (where the risk of a carrier's children being affected is extremely low) may be more difficult to justify economically, although in the context of private healthcare such considerations are less important.

4. Reduced Genetic Diversity

There is a theoretical risk that by the widespread selection

of fetuses based on their genetic make up we may risk affecting the genetic mix of our species and exposing the human race to unforeseen risks. However Haemophilia carriers are not known to have a survival advantage and indeed may occasionally suffer minor bleeding problems. The probability of Haemophilia mutations or other minor genetic abnormalities conferring a significant survival advantage is low in a world where technology and lifestyle modification play a major role in influencing lifespan and susceptibility to disease. The number of such requests is likely to be limited, and with this in mind reduced genetic diversity is not of great enough concern to warrant interference in this area of private decision-making (Human Genetics Commission 2001; Hietala et al. 1995).

5. Harm to the Fetus

In practice in much of Europe, Australasia and the United States until 'viability' (usually 24 weeks gestation) any rights the fetus may be said to have are secondary to those of the pregnant woman. The fetus may however have some limited rights, as reflected by the restrictions regarding experimentation on human embryos (Department of Health 2000). It is conceivable that where PND and termination is requested for genetic abnormalities of little significance to the fetus (albeit of concern to the pregnant woman) then these fetal rights may become relevant and provide a basis to refuse the woman's request. However terminations of pregnancy for social indications are not subject to the same rigor - in practice if a woman is sufficiently concerned by the prospect of continuing a pregnancy then her concern is accepted and the reasons underlying it not explored in detail. To restrict the detection of even minor genetic variations in fetuses by PND while allowing indiscriminate termination of other healthy fetuses for poorly specified reasons would be unjust, unless a distinction can be made between these two forms of pregnancy selection. We shall see in the next section that such a distinction cannot be clearly made.

6. Distinguishing between social terminations and terminations following PND

The ethical status of social terminations, where the pregnancy is not wanted under any circumstances may be viewed differently from that of terminations subsequent to PND, where prior to PND the pregnancy is 'wanted'. But such a distinction is not clear - social terminations may in fact be for pregnancies that are initially *wanted*, but conditionally wanted and the conditions may change during the pregnancy. Or a woman having a termination for social reasons may wish to have a baby, but by a different man - her desire for a baby is conditional on who is the baby's father, that is on its genetic make up. Conversely pregnancies undergoing PND may be *unwanted* in the absence of PND - there is evidence that the availability of PND has increased pregnancy rates in families with Haemophilia A, and it is possible that refusal to provide genetic information about a pregnancy via PND may occasionally result in the termination of that pregnancy due to concerns about

the possible genetic make up of the fetus (Tedgard, Ljung, and McNeil 1999; Francis and Kasper 1983). To draw a line between wanted and unwanted pregnancies is overly simplistic - many pregnancies are conditionally wanted, and that includes those terminated for personal reasons and those terminated following PND. It is difficult to draw a distinction between the ethics surrounding these two forms of pregnancy termination.

7. Harm to Society

If individual couples' requests for PND for minor abnormalities are to be restricted then such testing should first be shown to be harmful to society. Such testing may risk a conceptual shift in our attitude towards reproduction, children and the fetus. The practice of seeking 'designer babies' may be seen as eugenic practice at an individual family level, and as running the risk at a societal level of overemphasizing the genetic make up of our individuals. However information of minor consequence to a fetus' health is already routinely provided at antenatal ultrasound scanning (for example the sex of the fetus, or the presence of minor variations in physical parameters), and indeed selection of fetuses based upon their genetic make up is commonplace. PND for the detection of chromosomal abnormalities (some of which may have only minor health implications) is chosen by many thousands of women each year. For society to dictate which genetic abnormalities are important enough to justify prenatal testing, to make some professional or societal value judgment that some genetic abnormalities are worth selecting against but others are not, has far more in common with the State run eugenic practices of the last century than giving families the option of selecting against the genetic abnormalities of their choice and the freedom to construct their families as they choose. The onus is upon those who oppose PND for minor genetic abnormalities to show that there is a clear harm to society caused by allowing these women access to such information about their fetus.

Preimplantation Genetic Diagnosis

PGD is a relatively new technique that involves the genetic analysis of artificially fertilised embryos (at around the 8 cell stage) so as to select a desired genotype prior to embryo implantation (Handyside et al. 1990). The potential demand for minor genetic information at PGD may be greater than that for similar information by PND since in vitro fertilization (IVF) frequently produces excess embryos and selection among these embryos is necessary. Moreover, the costs of selection in the case of IVF are much less - the psychological burden of termination of established pregnancy is not present. This means that the implications of using PGD to prevent minor genetic abnormalities would be greater for society in terms of both resources and the effect on genetic diversity. However this technique is still likely to be used in only a small minority of pregnancies given its economic, physical and emotional implications for the couple. Any impact on genetic diversity is unlikely to be significant. To date little over

2500 cycles of PGD have been completed worldwide, whereas over 18,000 amniocenteses are performed each year in the UK alone, mostly for PND of a chromosomal abnormality (Human Genetics Commission 2001). The objections to testing for carrier status are also weaker in PGD, where there are already several embryos only some of which are to be implanted. Resource implications are likely to limit the use of PGD solely to detect minor genetic abnormalities, at least within a public health service. However if it is being employed anyway for the selection of an embryo without a specific genetic disease, there seems little reason not to select an embryo who isn't a carrier either if that is what the couple wishes.

Aside from considerations of the fair allocation of scarce resources, there is no good reason to routinely restrict either PND or PGD for the detection of minor genetic abnormalities in a society where the termination of healthy fetuses early in pregnancy is largely unrestricted.

Conclusions

PND is aimed at preventing (and where possible treating) the social and individual burden of genetic disease. Providing PND for more minor traits such as Haemophilia carrier status is controversial. This controversy arises from the limited burden that such genetic features have for society, although as we have shown couples may have good and rational personal reasons for requesting such tests. There may be a will at a public, professional and governmental level to place limitations on the level of genetic information provided by PND. We have suggested that this will alone is not sufficient grounds for restricting what are very personal and intimate decisions. We have explored some of the reasons why society might object to PND for minor genetic abnormalities such as Haemophilia carrier status and have found little justification for such objection. A clear distinction cannot be drawn between the ethics surrounding termination of pregnancy for social reasons and that following PND, and in the context of unrestricted access to early terminations for social reasons there is no good reason to prohibit PND and termination of pregnancy for Haemophilia carrier status.

PND and PGD for carrier status of other X linked conditions with a significant risk of affecting future generations (e.g., Duchenne muscular dystrophy) might similarly be justified. Requests for PND or PGD to detect more minor or non-disease characteristics may prove unacceptable to a majority of society on rationing grounds, due to concerns about the perceived rights of the fetus or concerns about 'reproductive eugenics'. Before such views are used as a basis for preventing access to genetic testing they need to be backed up by evidence that such testing is harmful to society or that healthcare resources might be better used elsewhere. For the moment, we should be offering prenatal tests for minor genetic conditions or else fall into the trap of interfering in individual liberty for no good reason.

Table 2: Conclusions

1. It is possible to test for minor genetic abnormalities prenatally
2. People may have strong personal reasons for requesting such testing
3. There is some evidence that society wishes to restrict prenatal testing to genetic information of greater significance
4. There may be economic grounds for limiting prenatal testing within a public health system
5. In the absence of economic pressures the onus is upon those who wish to restrict such testing to demonstrate that it may be harmful to society

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