

PRENATAL TESTING

Proceedings of a symposium organised by the Science and Ethics Advisory
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Netherlands on June 18, 2003

Royal Netherlands Academy of Arts and Sciences

Prenatal testing

NEW DEVELOPMENTS AND ETHICAL DILEMMAS

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Cover photo: Removal of a cell from an eight-cell embryo. The embryo is secured at the tip of the pipette on the left. The pipette on the right is used to draw off one or two cells from the embryo. These cells are already partially in the pipette.

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Preface

The Science and Ethics Advisory Committee of the Royal Netherlands Academy of Arts and Sciences (KNAW) provides both solicited and unsolicited advice to the KNAW Board concerning ethical issues in scientific research.

One of the members of the Committee, Professor Hans Galjaard, drew the attention of the Committee to possible ethical implications of new developments in the field of molecular genetics and its spin-off in prenatal testing. These developments are beneficial in many respects and may lead to improved intervention procedures either to prevent disease or to cure disease at an early stage of its development. However, considerable ethical problems may arise as well. For instance, is it acceptable to test for late-onset diseases when the person can live a normal, healthy life for many years? Is prenatal testing acceptable for diseases when the test results reflect a risk rather than a certainty of developing the disease? And why not prevent disease from the start by selecting embryos on their genetic constitution using the new technique of pre-implantation genetic diagnosis? This technique also creates the possibility of selecting an embryo with the aim of curing a sibling suffering from a life-threatening disease. Should we extend the use of prenatal diagnostic techniques to selection of embryos based on sex or other normal characteristics? How should medical doctors and prospective parents handle genetic information about their offspring as revealed by prenatal testing? These issues show the need for careful consideration of the different applications of prenatal testing and their ethical aspects.

The Committee organised a symposium dealing with new scientific aspects of prenatal diagnosis and a number of the ethical issues it raises. The morning programme was devoted to the introduction of the subject, with an outline of the history, present-day techniques and possible future developments; this was followed by case studies focusing on prenatal testing for hereditary breast cancer and embryo selection using pre-implantation genetic diagnoses. The afternoon programme consisted of two case studies, one on sex selection and family balancing and one on prenatal testing for normal characteristics. The presentations of the four case studies were followed by a discussion with an international panel, which has been invited to respond to the presentations, placing special emphasis on the ethical and societal dimensions of the outlined developments. The programme ended with a lecture on possible legislative consequences, both national and international.

This publication summarises the lectures, case study presentations and discussions at the symposium. We hope it will help stimulate and guide further discussions among scientists, policymakers, politicians and the public at large.

Jan H. Koeman,
Chairman Science and Ethics Advisory Committee

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Summary

New technological developments in prenatal genetic diagnosis, and the ethical dilemmas they create, require timely discussion. This report reflects the content of a series of lectures, case reports and discussions at a symposium organized on 18 June 2003 by the Royal Netherlands Academy of Arts and Sciences (KNAW). The symposium focused on four main themes:

- 1 Prenatal testing for genetic risk of late-onset diseases such as breast cancer.
- 2 Pre-implantation HLA testing for suitability as a later donor for a sick brother or sister.
- 3 Prenatal sex selection.
- 4 Prenatal testing for normal physical, mental or behavioural characteristics.

Prenatal diagnosis of severe disabilities and disorders which express immediately after birth or during infancy is a technique that has developed since the early 1970s. The most frequently used methods were and still are amniocenteses at about 16 weeks of pregnancy, cultivation of foetal cells and cytogenetic or biochemical analysis. In the mid-1980s, earlier and more rapid prenatal diagnosis became possible using chorionic villus analysis at about 12 weeks of pregnancy. During the same period DNA technology enabled the direct testing of gene mutations for an increasing number of Mendelian disorders. At present it is possible to test for some 1,500 such disorders using biochemical or DNA analyses.

Prenatal diagnosis and non-invasive ultrasonography are now widely used techniques, and each year hundreds of thousands of higher-risk pregnant women are tested. In most Western countries termination of pregnancy is considered as a morally acceptable means of preventing the birth of a severely disabled child. A minority reject this approach because they give priority to the protection of the foetus. In this context it is worth mentioning that follow-up studies have revealed that about 50% of couples at high risk of having affected offspring refrain from pregnancy if no prenatal test is available, and that 87% are willing to take the risk if prenatal diagnosis is possible.

In a few European countries such as Ireland, Poland and Portugal, as well as in most Latin American countries, the Roman Catholic dogma of the sanctity of life from the moment of fertilization is translated into laws which prevent individual couples from taking an autonomous decision on the termination of their pregnancy, at least legally. Here public morality prevails over private morality.

With the impressive advances in (human) gene mapping, more and more DNA sequences and gene mutations are being found to be associated with a higher risk of

developing a disease later in life. Examples are breast cancer, colorectal cancer, diabetes and various neurodegenerative diseases, including Alzheimer's disease.

One of the case studies presented concerned breast cancer. Five to ten percent of women with this disease carry what is known as a BRCA1 or 2 mutation, and their close relatives have a high risk of also carrying such mutation. If this is the case, their lifetime chance of developing cancer of the breast or ovary increases to 60-90% compared with 10% for the general population. Would such a risk justify prenatal diagnosis and selective abortion? An argument against this is the fact that contrary to 'conventional prenatal diagnosis', there is no certainty but only a risk, so that a carrier might in fact never develop cancer. Moreover, carriers will live several decades of healthy life, and in the long run nearly everybody might be identified as being at higher risk of some disease manifesting in (late) adulthood.

Arguments in favour are the very high risk of BRCA carriers developing cancer, the severity of the disease, the limited means of prevention and cure and the personal experience most carriers have with suffering and mortality in their family. The balance between parental autonomy and the responsibility of the professionals involved was discussed at the symposium and some participants expressed the opinion that the government has a responsibility in deciding which indications are acceptable for prenatal testing. Such decisions should be taken only after a public debate.

In practice, there have to date been hardly any requests for prenatal diagnosis by BRCA-carriers, despite the fact that in the Netherlands alone thousands of them have been identified in recent years. Several clinical geneticists and obstetricians involved, including one of the speakers at this symposium, have expressed the opinion that the option of prenatal testing for BRCA carriership should not be categorically denied but that requests should be judged on individual merit.

During the discussion it was also mentioned that around 25,000 pregnancies are terminated each year in the Netherlands for psychosocial reasons, where the foetus may in principle have no abnormality. Only 2-3% of abortions are performed because of a negative outcome of prenatal testing. Practical experience to date has shown that prospective parents have their own norms. Where they perceive a disease as very severe and where it becomes manifest during early childhood – disorders such as Down syndrome, Duchenne's muscular dystrophy or X-linked mental retardation, for example – the proportion of couples requesting prenatal diagnosis is high. In the case of a late-onset diseases such as Huntington's Chorea, the percentage of requests from carriers is much lower. It may be that in the latter case couples do not want to take decisions about events that will not occur until the adulthood of their offspring; they may also be hoping for new therapeutic developments. More generally, some doubts are raised as to whether a disease during adulthood fulfils the criterion applied by several countries in their abortion laws, namely that 'the actual or future physical or physiological health of the woman requesting the abortion is endangered'.

Since the beginning of the 1990s an alternative to 'conventional' prenatal diagnosis has been developed, namely pre-implantation genetic diagnosis (PGD). After the usual in vitro fertilization procedure one or two cells are biopsied from an eight-cell embryo and analysed for chromosomal aberrations or gene mutations associated

with Mendelian disorders which can be detected using DNA assays on a single cell. Embryos that are found to be affected are discarded and one or two of those found to be unaffected are replaced in the womb. This approach has the advantage of avoiding the decision to terminate a pregnancy, but the disadvantages of technical complexity and high costs, a low (20-25%) chance of pregnancy and a high (approx. 30%) risk of multiple pregnancy and premature birth, with all the associated complications.

In the USA and UK this PGD procedure has recently been extended by taking an extra embryonic cell to perform immunological (HLA) testing for the fitness of the embryo to serve as a donor of bone marrow stem cells after birth. The requests for these tests have come from parents of children with a fatal blood disease whose life could be saved by transplanting immunologically matched bone marrow.

The majority view of the discussants has been that this approach should be condemned as an 'instrumental use' of human embryos which does not serve the interests of the 'donor child' itself. The procedure is legally forbidden in the Netherlands, though it has been criticized that this decision was taken without prior public debate.

During the discussions at the symposium, questions were raised concerning the expectations of parents of a future child that has been conceived (solely?) to save a sick brother or sister. How much pressure will there be on the 'donor child', and will parent-child relations be negatively influenced in the event of a therapeutic failure?

Arguments in favour of the procedure were also put forward, however. Kant's proscription is 'against using people *solely* as a means' and in most instances parents of a sick child would have wanted another child anyway. PGD would enable them to ensure that this subsequent child would not suffer from the same disease, while in addition the child might save the life of a brother or sister. The argument was also put forward that no-one in a democratic society controls the motives for pregnancy and that it is questionable whether having a second child 'as a playmate' is morally more acceptable than 'as a life-saver'.

With regard to the latter aspect it was unanimously agreed that the life-saving procedure should carry no health risk for the donor. This is true in the case of the use of some umbilical cord blood after birth, but not true if the child were to be used as a donor of an organ such as a kidney.

A concern of a more general nature, separate from the 'right to life of an early embryo', is the issue of the 'medical model'. This implies that a medical procedure will only be carried out if it carries a potential (health) benefit for the recipient. This is not the case with HLA testing, and some discussants express the fear that it could mark the beginning of a 'slippery slope' where embryo selection for any normal genetic characteristic will be allowed. Others do not share this view and argue that the moral acceptability of each new technology /application can be reappraised.

In practice, the necessity of selecting human embryos for two independent genetic criteria reduces the chance of finding a suitable embryo to 3 out of 16. Taking into account the relatively low chance of pregnancy and childbirth after replacing the embryos, most experts do not foresee large-scale application of combined PGD-HLA testing.

Many of the arguments described above also apply to sex selection. In this instance an additional objection is that the procedure has no counterbalance in the sense of saving someone else's life; here, the only selection criterion is the desired sex of the future child. The discussion during this symposium was limited to non-medical reasons for such selection. Firstly, it was established that in large parts of the world a preference for male offspring has a deeply rooted socio-cultural and economic background. In India alone it has been estimated that more than 50,000 pregnancies are terminated annually following prenatal detection (usually by ultrasound) of a female foetus.

In Western countries there are relatively few requests for prenatal sex determination, although the presence of certain immigrant groups may cause complications. Professionals are virtually unanimous in refusing requests for prenatal sex determination for non-medical reasons, and most participants at this symposium agree with this position. The main arguments against the procedure are the equal value of males and females, objections to discrimination and the use of costly medical procedures which are intended to diagnose and prevent severe disabilities or diseases.

Although some authors have claimed absolute procreative freedom, including the right of parents to all information about their future offspring, there is a consensus that professionals and governments have their own responsibility to set limits. A recent inquiry by the European Society of Human Reproduction involving the majority of centres involved in PGD revealed that most centres are against sex selection for non-medical reasons and that only a few use this practice for family balancing. This implies that only requests during a second pregnancy are granted, based on the idea that couples want a child of each gender. During the symposium it was pointed out that the public would consider dietary measures or selection of sperm as acceptable means of achieving the aim of family balancing.

In developing countries with a socio-cultural preference for (male) gender, medical technology should not be used to maintain a heavily disadvantageous position of females.

In countries with sufficient infrastructure for PGD the increasing use of chromosomal testing to select against abnormal embryos, known as aneuploidy testing, will increase the opportunity for parents to choose a specific gender. Most symposium participants objected to such an approach if this is associated with the destruction of suitable embryos for reproduction and the need for repeated procedures to achieve a pregnancy with an embryo of the desired sex.

At present most research in human genetics is focussed on the elucidation of the molecular basis of disabilities and diseases. At the same time, however, our insight into normal cellular processes will increase and in the long run also our understanding of the molecular genetic basis of normal physical, mental and behavioural characteristics. Twin studies have already revealed a significant genetic background to a variety of normal human features. Although some experts do not expect the future development of this knowledge, others believe that in the long run combinations of DNA sequences will be linked to specific normal characteristics including sexual orientation, intelligence and certain aspects of social interaction. If such knowledge

were to become available, there was consensus at the symposium that this should not be used as a selection criterion in PGD or 'conventional' prenatal diagnosis. In addition to the arguments given above against HL typing and sex selection, large-scale selection for desired physical, mental and behavioural characteristics might have a dislocating effect on various important aspects of our society including education, employment, relationships and societal expectations and acceptance.

During the discussion it was pointed out that requests for selection against or in favour of a specific characteristic might depend on the societal context. For example, intolerant attitudes towards homosexuality might lead parents to seek selection against such sexual orientation to protect future progeny. Would such an attitude be morally different from the aim of preventing a disease?

At the end of this symposium one of the participants presented an overview of the procedures applied by Dutch advisory boards, which may be helpful in organizing public debates. After mapping out the problem area and questioning whether the use of a new technology already violates borderline values, the pros and cons of other relevant values and the aims that may be attained have to be defined, using checklists. Finally, the pros and cons have to be weighed and should result in a range of options for action.

Although a good procedure is helpful it does not guarantee a solution to ethical dilemmas. Major problems are moral, philosophical and religious pluralism between and within societies, a lack of shared morality, a variety of interests and a diversity of priorities and policies.

The last lecture dealt with the desirability of (international) legislation in matters of biomedicine. Although there is a strong tendency towards national or even private definitions of moral acceptability, the transnational nature of the problems (ease of travel, communication, etc.) means that the only way of regulating ethical dilemmas resulting from new technologies is through international agreement. Moreover, supranational organizations are important for supporting our moral values by international agreement.

It is however important to identify areas of bioethics which require international agreement. Examples are a need for consent, both in the clinical and research context, control of research, protection of the vulnerable and containment of severe risk. Areas where we must agree to disagree are the status of the embryo (both intended to develop into a human being and intended for research purposes in the test tube, for example embryonic stem cells); PGD and conventional prenatal diagnosis; and abortion.

In the past the European Union has stated that its member states should have the freedom to determine moral and social policy.

Within a given society, should people be left to make their own decision on moral issues as long as these do not compromise the health and safety of others? Prescriptive legislation may have the disadvantage of being too restrictive on individual autonomy and too inflexible to respond to changes in technology and in society. Self-regulation has the disadvantage that public morality may be violated and the interests of others infringed. Although (prospective) parents, in association with the clinicians,

should be given a good deal of freedom to reach decisions, there is a social interest in describing parameters for the exercise of particular choices. Regulation through agencies and codes of conduct gives us the flexibility to respond to changes and agencies may represent the prevailing range of (moral) positions.

In the UK (prenatal) genetic testing is not regulated by any specific piece of legislation. A special body, the Human Fertilisation and Embryology Authority (HFEA) regulates artificial reproduction while the Human Genetics Commission advises the government on ethical, social and legal aspects of genetics. A third body, the National Screening Committee (NSC) has stated certain general principles and emphasizes in particular that screening should aim at health risk reduction.

The international community is already acting to protect human rights. The UN Universal Declaration on the Human Genome asserts rights in relation to the human genome and genetic information and includes consent issues. People's right of access to genetic information about themselves is increasingly being recognized and there must be very good reasons for preventing people from obtaining this information. There are however also major differences between countries, with regard to reproductive rights, the status of the embryo, genetic testing, the use of embryonic cells and the termination of pregnancy.

Since bioethics is becoming increasingly global in its concerns, what is allowed in one country may influence the position elsewhere. The euthanasia debate and the abortion issue are examples of this. Can we achieve a balance which recognizes this fact but allows for diversity of approach?

In its 1990 recommendations on prenatal genetic screening, prenatal genetic diagnosis and associated genetic counselling, the Council of Europe recommends in brief:

- restriction of testing to serious health risks
- restriction of testing to state-approved institutions
- counselling made available before and after genetic testing
- data protection

In addition, Article 3 of the EU Charter of Fundamental Rights contains stipulations on:

- the right to physical and mental integrity
- the right to free and informed consent
- the prohibition of eugenic practices, in particular those aimed at the selection of persons.

The European Union appears to wish to create a new 'moral community' in Western Europe. If this succeeds, to what extent will this be a pluralistic community and to what extent will it involve the imposition of values? After all, no country is an island.

Lectures and discussions

Prenatal diagnosis and medical genetics – past and future

Historical introduction

The outstanding features of genetic information are its capacity to predict health effects far into the future, and the universality of the DNA sequence in virtually all cell types. Thus, a biopsy of the early placenta can provide information about a degenerative disease that will affect the brain four or five decades later. This is an awesome power, with potential for harm as well as benefit.

The development of methods for examining human chromosomes, and the discovery in the late 1950s that Down syndrome is due to trisomy of chromosome 21¹, put laboratory diagnosis in the hands of clinical geneticists. The technique of amniocentesis was already in use for another genetic disease, one of the least discussed but greatest triumphs of medical genetics, Rhesus incompatibility causing haemolytic disease of the newborn. Amniocentesis was used to test bilirubin levels in the amniotic fluid, as a sign of the severity of foetal disease. In 1966 and 1967^{2,3}, techniques for culturing living foetal cells from amniocentesis samples were developed, and the field of prenatal diagnosis was born. The presumption was that many people, given the knowledge that an early pregnancy would lead to a child with a severe and untreatable disorder, would opt to terminate the pregnancy and attempt another.

This concept and its developments have been in use for about 40 years.⁴ Literally millions of pregnancies have been tested, in many countries – not all of them from the developed Western world. Advances in genetics, and in obstetric techniques, soon broadened the scope of prenatal diagnosis to include a variety of different types of test aimed at many disorders.⁵ This progress still continues, and will do so in the future.

The techniques

Technical developments do not constitute ethical problems, but they do set limitations on what is realistically possible and therefore what needs more urgent ethical debate. Broadly, there are two classes of tests, with some overlap between them:

Diagnostic tests – these generally sample foetal material and give reasonably precise diagnoses. Because they are invasive, they inevitably carry some risk to the pregnancy.

Screening tests – these can be much more widely applied, and define higher risk individuals who then go on to be offered invasive tests. These carry no physical risk to the pregnancy, but there are various risks that derive from the information itself, and from action taken based on the information from the tests.

Diagnostic tests

These include: amniocentesis, chorion villus sampling (CVS), foetal blood sampling and pre-implantation genetic diagnosis. Amniocentesis, CVS and foetal blood sampling all carry a risk of around 0.5-2% of causing pregnancy loss.

Laboratory analysis – once a sample of foetal cells is available, it can in principle be tested for a wide range of chromosomal, biochemical and inherited disorders. The tests may involve microscopic examination for chromosome pattern, DNA tests looking for mutations known to cause disease, or biochemical analysis. Chromosome tests are predominantly still based on microscopic examination of the sample, but new DNA-based techniques for defining chromosome abnormalities are beginning to become available. Chromosomal disorders generally manifest during pregnancy; most metabolic errors declare themselves during childhood; but the multitude of inherited disorders, which can be detected by DNA tests, may manifest at any time of life.

Screening tests

These include, for example: serum markers, or maternal age, as a screen for high risk of Down syndrome and some other autosomal trisomies; serum markers for neural tube defects; family history is a screen for high risk of some inherited disorders; In the future, it may be possible to conduct tests on foetal cells isolated from the maternal circulation. I class this as a screen for now, but it could conceivably be developed as a diagnostic test.

Ultrasound examination – This is the most widespread modality for prenatal diagnosis of congenital disorder in use today, being applied to virtually every pregnancy in most developed countries. It is sometimes used as a screening test, for example for Down syndrome, with subsequent confirmation by amniocentesis or other invasive sampling method. Some practitioners however consider the ultrasound appearances alone to be sufficient, as a diagnostic test for Down syndrome. For many structural abnormalities of development laboratory confirmation is not possible, and so the diagnosis must of necessity be based on ultrasound alone.

Clinical application

The application of prenatal diagnosis involves both obstetricians and clinical geneticists. An individual patient may, depending on circumstance, consult either a geneticist, an obstetrician, or both. Both specialities espouse the paradigm of careful non-directive pre-test counselling, and freely informed patient choice. There is some evidence that in practice (particularly for less routine foetal conditions) pregnancy outcome is influenced by whether a woman is advised by a geneticist or an obstetrician.⁶

Some of the most difficult clinical problems result from test results showing unexpected or unusual abnormalities. With cytogenetic examination, a test that is primarily undertaken to screen for Down syndrome and other autosomal trisomies may unexpectedly show a balanced translocation or a sex chromosome aneuploidy. The clinical interpretation, and parental decision-making, can be awkward and insecure

in these situations and can cause much anxiety. It can be argued that these laboratory findings are best regarded as an 'unwanted side-effect' of prenatal diagnosis, an undesired but unavoidable by-product of cytogenetic examination. Newer techniques now being developed may allow more planned control over whether to include or exclude specific types of chromosome anomaly amongst those detected by the tests.

Despite evidence of some 'directive' counselling, particularly in the earlier days of prenatal diagnosis, I am not aware of any evidence of continuing significant abuse of the field of prenatal diagnosis to coerce people into terminating pregnancies against their better judgement.

Ethical aspects

Particularly in the context of misuse of the word 'genetics' by eugenicists and some political movements, those involved with prenatal diagnosis have from the outset been extremely careful to frame the practice in libertarian, non-coercive terms emphasising parental choice. This emphasis on pre-test counselling and parental choice has been widely endorsed by commentators.⁷

However, prenatal diagnosis does lead directly to the termination of pregnancies. Since all human life has ethical value, ending it is always distressing and problematic. To some, human life has full sanctity, from the time of conception, and these people cannot be reconciled to any process that terminates pregnancy. The majority of people in Western societies however clearly take a less absolute view of early pregnancy termination.

The most obvious fears of a 'slippery slope' towards adopting prenatal diagnosis for less severe conditions, for treatable conditions or for normal traits which are not disease-related have failed to materialise over the past four decades. However, there is every reason to remain alert and concerned, in order to prevent future slippage from these standards. For example, it has been argued by several commentators that selecting against individual pregnancies on the basis of characteristics within the normal range of variation would pose serious ethical problems.⁸

It has been argued that terminating abnormal pregnancies would lead to a diminution of respect and care provision for living persons with disabilities. This too has failed to materialise, perhaps due to an active and vocal disability lobby.

Future developments

Technical developments that are much under discussion today include: Pre-implantation genetic diagnosis – testing very early embryos resulting from in vitro fertilisation, in order to positively select which embryo to reimplant in the uterus. A biopsy of one or two cells from an eight-cell embryo can be examined cytogenetically, and for DNA markers of disease. It is known that such embryos can be reimplanted and develop normally after biopsy, and that reliable diagnoses can be made.⁹ However, the technical complexity of the procedures required and the extreme sensitivity of tests needed to work on such minute samples, make it in my view unlikely that this technology (which has clear and obvious benefits for some patients and families) will be very widely used.

Sperm selection – again for technical reasons, is in my view very unlikely to ever play a major role in medical genetics.

Testing foetal cells from the maternal circulation – it has been known for many decades that cells of foetal origin are present, in very small numbers, in the maternal circulation, and efforts have intermittently been made to isolate and purify these so that they have diagnostic utility.¹⁰

None of these techniques, in my view, raise new ethical issues in themselves. It is however possible that they would lead to less stringent control of the types of cases tested, since they dissociate the process of selection from the traumatic unpleasantness of terminating a pregnancy.

Although, as stated, I find it hard to see any of these techniques being widely used in the foreseeable future, the technical ability to perform them, combined with a much wider knowledge of the predictive value of DNA sequence changes for both disease and non-disease ‘normal’ variation, has already thrown up some contentious individual cases and will undoubtedly continue to do so.

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Case I: Prenatal testing for hereditary breast cancer

Introduction

The annual number of births in the Netherlands is about 200,000. The annual number of invasive prenatal diagnostic procedures is about 12,000 (6% of the total). The same standard indications are used in all 13 testing centres. One of these indications is: 'Pregnant women with an increased risk for an autosomal dominant, recessive or X-linked condition'. In 2001 prenatal testing for this indication was performed about 250 times. Prenatal testing for hereditary breast cancer was not listed in the conditions involved in this indication. However, since requests for prenatal testing for this condition rarely occur, we have reviewed the (limited) medical literature on this subject. Moreover we have reviewed Dutch policy statements on this subject. The result was published in 2002 (Dutch article with English abstract)¹, and it is on this article that this presentation is based.

Background

Of all women with Breast or Ovarian Cancer (BOC) about 5-10% have an autosomal predisposition. The genes involved are BRCA1 (on chromosome 17) and BRCA2 (on chromosome 13). Another 10-15% of these women have familial BOC without a distinct autosomal dominant predisposition. The clinical consequences of mutations in both genes are impressive. The average cumulative risks in BRCA1-mutation carriers by age 70 years are 65% (95% confidence interval 51%-75%) for breast cancer and 39% (22%-51%) for ovarian cancer. The corresponding estimates for BRCA2 are 45% (33%-54%) and 11% (4.1%-18%)².

The preventive options include either early detection by periodic examination of breasts and ovaries: self-examination (each month), physical examination (every 6 months), mammography (each year), gynaecological examination/ultrasound examination, CA125 in blood serum (both each year) or preventive surgery (bilateral mastectomy and ovariectomy).

The international literature on this specific subject is sparse. Lancaster et al.³ mention the prenatal testing for mutations in the BRCA1 gene 'an inevitable dilemma'. Wagner et al.⁴ give their article on prenatal testing for late-onset diseases such as mutations in the breast cancer gene 1 the subtitle: 'Just a choice or a step in the wrong direction?'.

Starting points

The following points are, in our opinion, relevant in ethical discussions on prenatal testing for hereditary breast cancer:

- Selective termination of pregnancy up to 24 weeks, if requested by the parents, is a legally, medically and socially accepted practice in the Netherlands.
- Female carriers of a pathogenic BRCA1 mutation have an estimated lifetime risk for breast/ovarian cancer of 65%. It is not yet clear whether or not they have an additional risk for other tumours as well.
- There are no indications that female carriers of a BRCA mutation have an increased risk of developing breast/ovarian cancer before the age of twenty years.
- Male carriers of a pathogenic BRCA1 mutation have a negligible (extra) risk of breast cancer; for males with a BRCA2 mutation the lifetime risk is about 5%. There is also a slightly elevated risk of prostate cancer in older age. In addition male carriers have of course a 50% chance of transmitting the mutation to their daughters, who will then have increased health risks.
- The possibilities for mortality reduction by means of early detection or prevention of breast/ovarian cancer are limited (periodic screening) or are decisions that are extremely difficult to make (preventive bilateral mastectomy).
- It is doubtful whether new developments will be available for the next generation of BRCA mutation carriers that could significantly improve prevention and morbidity and mortality by BRCA-related forms of cancer.
- In the available medical literature no arguments can be found that could qualify the prenatal diagnosis of BRCA mutations as ethically indefensible.

Considerations

For many – but not all – people, selective abortion is an acceptable option to prevent severe suffering of a future child and the parents. Whether or not a condition is judged as serious depends on objective and subjective factors. Objective considerations include the chance that a condition will manifest itself, the age at which a condition will manifest itself and the possibilities of prevention and therapy. A subjective consideration is for instance the experience of the future parents with the condition.

Conclusions

1. The decision to opt for prenatal BRCA testing and selective termination of pregnancy in the case of a BRCA mutation in the foetus cannot immediately be judged unacceptable from an ethical point of view.
2. Prenatal BRCA testing is morally defensible only in the case of a female foetus and if the parents at least have the intention of terminating the pregnancy if the foetus is a carrier; the final decision is up to the parents only.
3. Prenatal testing for a BRCA mutation should only be done after extensive counseling of the parents, during which not only the medico-genetic aspects but also the ethical aspects of prenatal BRCA testing are discussed.

Post scriptum

The above conclusions were discussed and adopted in a general meeting of the Dutch Society of Clinical Genetics (VKGN) in 2001. We feel that it is beneficial to have discussions (in a variety of forums) about this difficult issue in a setting in which there is no actual pregnant woman who is seeking prenatal diagnosis on this indication.

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Summary of the discussion on prenatal testing for hereditary breast cancer

Aspects which play a role in late-onset disorders include the later age at which the disorder manifests itself, the (un)certainly as to whether the disorder will in fact ever manifest itself and the uncertainty of the age at which this will occur.

A distinction is made between diseases which are certain to develop and for which no treatment has as yet been developed, and diseases where there is a risk of their development or for which a treatment exists. Some participants in the debate believe that prenatal diagnosis is intended primarily for the first category. The general view is that, where the future parents in the case of a disorder in the first category do not plan to terminate a pregnancy if the test produces a positive result, prenatal diagnosis will not be offered. However, some believe that the second category of disorders should also be eligible for prenatal diagnosis. For parents who have experience with a given disorder, either themselves or in their immediate social setting, it is less relevant whether or not a disorder manifests itself only at the later age or even whether there is a reasonable chance that the disease will never develop. Their concern is to protect their children against the life-threatening experience associated with these disorders.

An important focus of debate is the balance between parental autonomy and professional responsibility. How far do these extend and how can a balance be struck between them? In the Netherlands, the view of the parents plays a major role, although the role of the doctor should not be underestimated: the doctor can after all refuse to grant a request by the parents.

Not everyone accepts that parental autonomy should always be respected. Some believe that the focus should not be on the views of individual parents, but that the government should determine which disorders/risks are eligible for prenatal diagnosis and which are not. The number of people who use prenatal diagnosis cannot be used as a straightforward measure of the level of acceptance of this technique in society as a whole. Public morality also needs to be applied more as a principle for determining the indications for prenatal diagnosis. This will create the necessary supporting base for the regulation which will ultimately be based upon it.

There is a large group who feels uneasy in a society which decides on what parents are able to do, or not, in order to bring up a child with a serious disorder. Society generally lacks the experience of living with a disorder which those applying for prenatal diagnosis often do have. It is striking that during discussions on this topic, the need often emerges for the setting of a norm based on the preferences of a majority of society. However, this view takes no account of a minority who wish to move in an entirely different direction. Is it possible to give this minority the freedom to be heard, and to listen to those most closely involved? Is it necessary to draw a line and to decide that these late-onset disorders are not eligible for prenatal diagnosis?

Around 25,000 pregnancies are terminated in the Netherlands each year. In 2% of cases the reason for the abortion is the outcome of a prenatal diagnostic test. The remaining pregnancies are terminated for psychosocial reasons. The 500 abortions which are carried out because of a disorder discovered through prenatal diagnosis mostly concern disorders which will almost certainly cause an extremely serious disorder either during the embryonic development or during the early years of life. Anxiety about having to live with this, ignorance about coping with the disorder and the prospect of having to bring up a child with a serious disorder are adequate arguments for prospective parents to undergo prenatal diagnosis and potentially to end a pregnancy. It is striking that there is a greater inclination to consider the possibility of prenatal diagnosis for diseases which develop during childhood than for late-onset disorders.

These arguments appear to weigh less heavily for serious disorders for which it is only possible to test for the risk of developing them. To date virtually no interest has been shown in the Netherlands in prenatal diagnosis for BRCA gene mutations. The same trend is seen in the United Kingdom: although Huntington's disease is guaranteed to manifest itself in later life, the number of applications for prenatal diagnosis for this disease is one fifth of the number of prenatal diagnoses for Duchenne's muscular dystrophy, a disorder which will develop with equal certainty during early childhood. The reasoning may be that late-onset disorders only manifest themselves when the individual concerned is in adulthood and is capable of making a decision themselves. With regard to breast cancer, there is then the possibility of preventive measure.

Several participants in the debate indicate that, at least in our Western society, pregnancies are generally greatly desired and that to date no substantial demand for prenatal diagnosis for late-onset disorders has been noted, either for disorders which are guaranteed to appear or for disorders for which only a heightened risk can be identified. Only if the disorder is perceived as a serious threat to the parents or their offspring is a request made for PD.

Case II: Embryo selection and transplantation

Introduction

Pre-implantation genetic diagnosis (PGD) has an advantage over conventional prenatal testing. Using PGD, couples at risk who wish to prevent the transmission of a genetic disease to their offspring have the option of going through a medically assisted procedure like in vitro fertilization (IVF), with or without intracytoplasmic sperm injection (ICSI), followed by in vitro diagnosis of the resulting embryos after a few days' development. Only the disease-free embryos are transferred to the uterus and therefore couples are not faced with the difficult decision about pregnancy termination.

Over the last 10 years, PGD has become available for most of the monogenic and chromosomal disorders for which prenatal testing is available as well. Patients who prefer PGD to prenatal diagnosis and selective abortion may do so because the latter option conflicts with their fundamental beliefs. They may also select PGD after having one or more conventional prenatal diagnoses with unsuccessful outcomes. Finally, they may opt for PGD because they require medically assisted reproduction (IVF or ICSI) anyway because of infertility.

PGD takes place between fertilization and implantation, but in most cases on the third day of early embryonic development. To obtain access to this early development stage, in vitro fertilisation (IVF) with or without intracytoplasmic sperm injection (ICSI) is necessary, although the women undergoing this treatment are usually normally fertile. ICSI is preferred over conventional IVF in monogenic disorders requiring DNA diagnosis to prevent contamination from sperm still attached to the zona pellucida. After hormonal stimulation on average about 10 oocytes are obtained, of which on average 6 or 7 become fertilized following the medically assisted procedure. On the third day one or two blastomeres are biopsied from embryos, which have reached about the eight-cell stage. FISH (fluorescent in situ hybridisation) is used to detect the sex and chromosomal abnormalities. PCR is used to diagnose autosomal dominant, autosomal recessive and X-linked monogenic disorders. Although technically more difficult, the detection method at the single cell level is principally that applied to other tissues, although working with blastomeres has specific difficulties including lysis, multinucleation and allele dropout. Allele dropout means that just one of the two alleles under study is (selectively) amplified by PCR. Other diagnostic problems are caused by embryonic mosaicism or contamination. For these reasons it is advisable to diagnose two cells. Only those embryos of which both cells have been shown to be free of the disease would then be considered unaffected and used for transfer to the uterus or cryopreservation for transfer at a later date. A maximum of

two unaffected embryos are transferred to the uterus, because of the risks of multiple pregnancy.

The prospective and retrospective collection of data on availability, accuracy, reliability and effectiveness of PGD, has been one of the major aims of the ESHRE (European Society of Human Reproduction and Embryology) PGD Consortium. Since 1999 the results from three rounds of data collection have been published. Patients were referred for PGD because of sexing for X-linked disease, translocations and other structural chromosome abnormalities as well as monogenic diseases. The most frequently referred Mendelian disorders remain constant over the years: cystic fibrosis, thalassaemia and spinal muscular atrophy as autosomal recessive diseases; myotonic dystrophy, Huntington's disease and Charcot-Marie-Tooth disease as autosomal dominant and Duchenne's muscular dystrophy, Fragile-X syndrome and haemophilia as X-linked disorders.

The vast majority of couples have had one or more pregnancies prior to PGD. However, healthy children have been born in less than 25% of cases. More than a quarter of all couples have one or more affected children.

The success rate of PGD is expressed as the percentage of babies delivered per cycle and per transfer. On average this is about 1 in 6 and 1 in 5, respectively. The multiple pregnancy rate is about 30% and may be associated with premature birth and accompanying complications. The relatively low pregnancy rate and the high rate of multiple pregnancies are the main disadvantages of PGD. Other disadvantages are the complexity and psychological distress of the IVF procedure and the medicalisation of reproduction.

The most important factor hampering the pregnancy rates is the presence of chromosomal abnormalities in the oocyte. Therefore many centres are now trying to base their embryo selection on the results of aneuploidy screening.

The practice of PGD is becoming more and more established and more and more different applications are emerging.

Pre-implantation HLA matching

Among the new indications is pre-implantation HLA matching. In families with a diseased child having recessive genetic disorders such as Fanconi anaemia or thalassaemia or an acquired malignancy such as leukaemia, HLA-matched bone marrow is needed for stem cell transplantation. If no donor exists, HLA matching at the pre-implantation stage can be used to select a child as a donor, while PGD can be applied to exclude the presence of the genetic disorder. After birth of the neonate cord blood transplantation can be used to cure the diseased child.

On average, one in four embryos tested for a recessive disease needs to be excluded from transfer to the uterus. At the same time only one in four embryos will be HLA-identical. This means that on average no more than 3 out of 16 embryos tested will have a favourable genotypic combination and will be suitable for transfer to the uterus.

HLA matching at the pre-implantation stage is regarded by some as an extension of the already available arsenal of diagnostic methods which can be applied to improve

the diagnosis in situations where a strictly medical indication exists. Others regard this as a step further on the slippery slope towards the so-called 'designer baby', which is designed in terms of normal characteristics.

When PGD was started in Maastricht in 1995, the KEMO, a provisional central ethical review board, felt that the first clinical applications of PGD should be restricted to severe conditions for which no treatment was available because of the burden, the uncertainties and the risks of this still experimental procedure. It was decided to start with the diagnosis of some X-linked disorders such as Duchenne's muscular dystrophy and fragile X syndrome, cystic fibrosis and spinal muscular atrophy.

At the end of 1998 a Health Council Committee expressed the opinion that PGD had been introduced judiciously in the Netherlands. Furthermore it recommended that the inclusion and exclusion criteria did not need to be stricter than those used for prenatal diagnosis, with the exception of aneuploidy screening for risks related to advanced maternal age such as trisomy 21.

In January 2003 the Dutch Ministry of Health, Welfare and Sport issued the first and only Dutch licence for PGD to the Maastricht Centre for Clinical Genetics. In this licence it is stated that the application of PGD in combination with HLA testing is forbidden. Even before this decision of the Ministry was known, the PGD Working Group in Maastricht had decided not to offer pre-implantation HLA testing, since fewer than 20% of embryos tested will be suitable for transfer to the uterus. This percentage is much smaller than is usual in PGD and will have a negative effect on the success rate of the procedure. Normally not more than 8 embryos can be tested. This means that on average a total of only 1 or 2 embryos will be available for transfer and their quality will not necessarily be optimal. As a result, the 'take home baby rate' will be substantially reduced after this procedure. Furthermore, the Working Group has decided to follow the guidelines of the Health Council and to offer PGD only in those cases where prenatal diagnosis is also offered.

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Summary of the discussion on embryo selection and transplantation

The use of pre-implantation diagnosis for HLA matching raises a number of moral questions. First there is the question of whether it can be morally acceptable for a child to be a donor, since the child cannot take a decision on this itself. However, HLA matching using pre-implantation diagnosis ultimately involves the donation of umbilical cord blood, in other words a non-invasive procedure; using a child as a donor for umbilical cord blood then appears to be ethically justifiable. If an invasive procedure were involved (e.g. kidney donation, something which could play a role in the future), this argument needs to be revisited. Secondly, is it ethically justifiable for a child to be conceived purely to serve as a donor? Will that child henceforth be regarded by its parents as nothing more than a donor? And what will be the status of the donor child within the family if the intended healing of the first, sick child is unsuccessful? A third moral question is whether the procedure used in pre-implantation diagnosis is acceptable. Although the expectations for this procedure are high, the chance that an implanted embryo will actually lead to a pregnancy is small. In addition, the use of IVF in pre-implantation diagnosis means that unusable embryos are destroyed. In the Netherlands and many other countries, the discussion on the moral status of the embryo is an ongoing one. By contrast, IVF is an accepted technique in most countries, and this appears in any event not to be a valid argument against the use of pre-implantation diagnosis.

The possible instrumentalisation of the donor child which could be caused by HLA matching based on pre-implantation diagnosis is regarded as a major objection to this technique. There are fears that a child would be created purely to serve as a donor for a sick brother or sister. This argument is countered with the view that where there is no illness in a family, a second child is sometimes described as being desirable as a playmate for the first. Why is this argument for having a second child accepted, while the argument for saving a life is not? Applications for pre-implantation in HLA matching come from couples who have an illness in their family and are therefore at risk of passing this disease on to their future child. In addition they already have a sick child which they know would have a chance of survival if there were a suitable donor. Parents love their first child and are prepared to do anything for its cure. There is no reason to assume that they will love the second child less than the first. One of the participants in the discussion believes that many reasons can be cited why people want another child, but that it is impossible to ascertain whether this desire would also have existed if pre-implantation diagnosis had not been available.

The use of pre-implantation diagnosis forms an exception to the 'medical model'. This model implies that a medical technique or intervention will only be carried out on a person if that person stands to benefit from it. Critics argue that allowing an

exception to this medical model is the start of the slippery slope, which will end in the selection of embryos for all kinds of genetic properties with no medical grounds. The advantages of the technique are however considerable: in addition to the possibility of saving the life of a sick brother or sister, the very difficult decision of whether or not to end a pregnancy following a prenatal test is avoided.

A key objection to HLA matching based on pre-implantation diagnosis is that it takes away voluntary choice, because parents are given the opportunity to save their sick (living) child and will therefore opt to do so. The possible consequences for the donor child are likely to weigh less heavily. A side-effect of the IVF procedure which forms a necessary part of the pre-implantation diagnosis is an increased chance of multiple births and the associated potential complications. Based on experience, a number of participants in the discussion argue that future parents often give no thought to the fact that having and rearing multiple children is a very onerous task. The IVF procedure itself, and the relatively small chance of a positive outcome, is also often underestimated.

Some couples in the Netherlands who have a child with an incurable disease are aware that HLA matching using pre-implantation diagnosis is permitted in some EU member states. These couples find it difficult to understand that this opportunity is denied them in the Netherlands. Attempts by Dutch couples to take advantage of this technique in Belgium fail because Dutch health insurers will not cover the costs of this procedure. The question is whether it would not be more sensible to coordinate the different national legislations in the European Union. A ban in the Netherlands (or Germany, where HLA matching is also forbidden) on a particular medical act which is permitted in surrounding countries, can give rise to difficult situations. Because of the small number of centres which do carry out HLA matching using pre-implantation diagnosis, the waiting lists for this procedure are very long.

Although attempts have been made via the European Commission on the Ethical Implications of Biotechnology to address ethical issues associated with embryo research in a European context and to resolve problems between different countries on this issue, the Commission has been unable to bring about any major changes on this point. Its statements come down to the maintaining of existing national legislation so as not to become embroiled in complex political issues.

Finally, the question can be asked of how morally acceptable it is to ban a technique such as HLA matching using pre-implantation diagnosis, while the technique can save lives. It is odd in this connection that the Dutch government has introduced such a ban without conducting an ethical discussion first.

Case III: Sex selection and family balancing

A

As stated above, one of the reasons for referral for PGD is the presence of an X-linked disorder. X-linked inheritance is one of the three ways in which Mendelian disorders are transmitted to the next generation. Normally the patients are male, while females are carriers who will usually be symptom-free. Statistically half the sons of a female carrier will be affected. On the other hand all daughters of a male patient will be carriers. If a specific test is available, which it is in a minority of cases, these disorders are diagnosed like autosomal disorders and transfer of embryos is based on diagnosis of the disease. An example of this is the fragile X syndrome, which needs a specific approach since about one third of all female embryos having the mutation will also be affected.

B

If no specific test is available for an X-linked disease embryonic sexing can be applied. Almost all clinics performing sexing for X-linked disease use FISH. The most frequently referred couples are at risk for Duchenne's muscular dystrophy (DMD) and haemophilia. Although a DNA test is available, in both diseases many different mutations can be present and it is often very difficult to diagnose these at the single cell level. Therefore, in DMD as well as haemophilia, pre-implantation sex determination is most often performed. Since the phenotype of haemophilia is variable and therapy is available, some authors are not in favour of this type of approach. Furthermore selection on the basis of sex implies that statistically half the embryos are discarded without being abnormal.

C

A few years ago a questionnaire was sent to all members of the Dutch haemophilia patients' organisation. The answers showed that no fewer than some 50% of male respondents are in favour of sexing and negative selection of female offspring in order to avoid their daughters having to face difficult decisions with respect to their procreation in the future.

D

Some centres in foreign countries have included gender screening on pre-implantation embryos for social reasons. This practice meets widespread opposition; there are many arguments against. The most important indication is family balancing. This means that some couples wish to balance their families between boys and girls.

Social sexing can take on dramatic proportions, particularly in India and China, and many couples may resort to abortion, infanticide or abandonment of children of the undesired sex, especially girls. Sex selection by PGD is said to be preferable when compared to these alternatives.

During the last data collection of the ESHRE PGD Consortium, three centres sent in data after having performed PGD for social sexing. A survey of Consortium members showed that of the 21 centres that replied, 15 were against social sexing, while four were in favour (only one of the three centres performing sexing replied). Two centres did not clearly state their opinion. Among the arguments in favour of sex selection, the right of couples to self-regulation was mentioned. One respondent, who answered in a personal capacity and not for his/her centre and who was in favour of sexing, attached a few conditions to it: (1) it should be used for family balancing, (2) there should be a balance in the sex ratio within one centre and within one year (as many cases for boys as for girls), (3) healthy embryos (i.e. embryos screened for aneuploidy as well as gender) of the unwanted sex should be donated to other couples, (4) patients should pay for the treatment themselves. The main argument put forward by the one centre that is actually performing social sex selection and that responded, was that elimination of embryos of the unwanted sex was better than performing abortions. As arguments against sexing, it was mentioned that PGD and PD should only be used for serious genetic diseases, not for eugenics; one respondent called social sexing an abuse of child rights, another argument was the cost to society of social sexing, and finally the influence of social sexing on the sex ratio balance was mentioned.

Summary of the discussion on sex selection and family balancing

A person's sex should be counted as one of their normal personal characteristics, and should therefore be placed within the framework of the discussion of the potential future selection of embryos on normal characteristics. The fact that these two issues are often discussed separately may be attributable to the fact that sex selection is already possible, whereas selection on (other) normal characteristics is still hypothetical.

Sex selection via pre-implantation diagnosis was first employed in order to prevent the development of serious sex-related disorders by selecting embryos with the specific sex and not replacing them in the womb. One objection to this technique is that if the embryos with the 'unwanted' sex are destroyed, theoretically half of them would not have developed the disorder and have therefore been destroyed unnecessarily. This conflicts, at least for a number of people, with the moral value of the embryo. As remarked earlier, however, the IVF procedure, in which many healthy embryos are also destroyed, is accepted by a majority of the population in the Netherlands. This can therefore not be an argument for prohibiting sex selection using pre-implantation diagnosis in order to prevent serious sex-related disorders.

The other application of sex selection via pre-implantation diagnosis, for social reasons, has a general moral objection, which has to do with the medical model. Strictly speaking, sex selection using pre-implantation diagnosis is not intended for healing the person (in this case the embryo) who undergoes the intervention. This argument is countered by the view that medicine evolves and that its application could be extended. After all, sex selection for social reasons is also intended to guarantee the well-being and happiness of the family. However, the argument that sex selection for social reasons has nothing to do with preventing suffering, something which is the case in all other instances of prenatal diagnosis/pre-implantation diagnosis, appears to weigh more heavily in this discussion. Some participants wonder whether the desire to create a particular family composition can be an argument for intervening in Mother Nature. And if so, is it acceptable to use any means for this? According to this reasoning, having a particular sex can in no way be compared with having a serious disorder. If the human embryo has any value, it cannot be destroyed for social reasons in order to fit in with a lifestyle chosen by a parental couple. According to some, this is something of a 'luxury problem'. However, if it were possible to determine the sex of a baby using non-medical interventions, such as diet, sex selection might be more accepted. Where pre-implantation diagnosis is involved, however – a medical, invasive and expensive technique – this raises more moral objections. Is the decision to use pre-implantation diagnosis to select the sex of an unborn child a matter for individual parents, or should society decide on the use of a medical technique for a non-medical intervention?

In this discussion, the culture from which requests for sex selection for social reasons originates has a major influence: it makes a great deal of difference whether such a request comes from an Indian or a Dutch couple, for example. The cultural background and circumstances which form the backdrop to the question of whether something is morally acceptable or not are of great importance. Although demand for children of a specific sex is not common in Western society and is generally also not accepted, there is a growing group of ethnic minorities originating from non-Western societies for whom this question plays a major role. They have different preferences as regards their offspring from those that are generally customary in Western society. How should requests for family balancing by couples from different cultures be dealt with? The birth of a (or another) daughter can create great problems for them. Should requests be dealt with on an individual basis and the ban therefore be lifted, or should the boundaries of our moral acceptance be determined together, and the ban maintained?

Some participants in the discussion believe that both sexes should be treated equally, and feel that the use of medical techniques to make a distinction between them will ultimately lead to sex discrimination. The term 'family balancing' is seen by some as a euphemism for sex discrimination against women, including in other cultures. What is at stake is not family balancing but rather creating an imbalance in an entire society due to the creation of a very lopsided gender ratio. Poverty or ignorance are often cited as arguments for family balancing. However, most of the requests for prenatal sex selection in India come from the wealthier and better educated families, and the fact that this also occurs in the United States undermines these arguments.

It is worth noting here that during adoption, it is an accepted practice for the sex of the future child to be selected.

Participants in the discussion doubt whether sex selection would be widely used in the Netherlands if it were to be permitted. Many Dutch couples prefer a pregnancy which proceeds as naturally as possible. Only where it is necessary will they opt for artificial reproductive methods. However, the increased chromosomal analysis of all IVF embryos (during which the sex automatically becomes known) is highly likely to increase demand for sex selection. In the more 'traditional' forms of prenatal diagnosis, too, the sex of the embryo is known and is communicated to the future parents on request. There is a chance that a number of these healthy embryos are already being aborted because they are of the 'wrong' sex.

Prenatal analysis of normal characteristics?

Introduction

At present clinical genetics services, including genetic counselling, a large variety of laboratory tests and prenatal diagnosis are integrated into the health care system and funded from public resources. This, however, applies mainly for wealthy countries. It is a sobering thought that worldwide nearly 40 million women have no prenatal care at all and 55 million women deliver without professional help.

Globally approximately 50 million abortions are performed each year because of unwanted pregnancies, of which 40% are carried out illegally, often with severe complications. In Western countries, too, the number of abortions for social reasons significantly outweighs the number of pregnancies terminated following prenatal diagnosis.

Pro-life organizations and other opponents of abortion have for decades focussed on this negative aspect of prenatal diagnosis. It should however also be borne in mind that the technical possibilities of foetal testing enable parents with increased genetic risk to make an informed decision about their offspring. A study in our own centre revealed that about 50% of parents at high risk of having an affected child refrain from pregnancy if no prenatal test for the disease concerned is available. If there is a test 87% of couples opt for pregnancy. It may be that more children have been born thanks to the opportunity for prenatal diagnosis than the number of abortions due to an unfavourable test result.

In the Netherlands, 15,000 pregnant women undergo amniocentesis or chorionic villus biopsy each year, and another 10,000 are referred for ultrasound examination. Fewer than 1,000 pregnancies are terminated because of a severe foetal abnormality, equivalent to 4-5% of the number of abortions for socio-economic reasons.

New developments

During the past decade progress in human gene mapping and improved DNA analysis techniques have led to increased scientific interest in the molecular genetic background of multifactorial diseases which are clinically expressed in (late) adulthood. Examples of frequently occurring diseases believed to be caused by a complex interaction between several genes and environmental factors are cancers, cardiovascular diseases, diabetes, multiple sclerosis, some psychiatric disorders and Alzheimer's disease.

Specific DNA sequences are being identified which are associated with an increased risk of a number of these diseases. The most pronounced examples are gene mutations which result in a 60-90% risk of developing breast/ovarian cancer (com-

pared to a population risk of 10%) and DNA abnormalities which are associated with a 30-90% risk of colorectal cancer (compared to 1-3% population risk). There is little doubt that DNA testing in such high-risk families is of great value in cancer management of patients and genetic counselling of healthy relatives.

A question with a different ethical dimension is whether couples at increased risk are also eligible for prenatal testing. Professor Leschot has discussed this issue for the case of breast cancer and concluded that there are no arguments for a complete ban and that requests should be considered on an individual basis. So far there have been hardly any requests for prenatal testing despite the fact that in recent years thousands of women have undergone DNA testing and about one quarter of them were found to be carriers.

Apart from the difference between prenatal testing for a risk rather than for diagnosing with certainty a foetal abnormality, the question arises whether there are other limits to prenatal risk testing. For the cancers mentioned above the risk for carriers is very high both in absolute terms and in comparison to the risk in the general population.

For other diseases, however – such as Alzheimer's disease – certain DNA sequences are associated with a 1-3 times higher risk than that in the age-comparable population. Genetic studies on type-2 diabetes and psychiatric diseases such as manic depression suggest a similar risk increase. Would a risk of 2% that an unborn person will develop schizophrenia justify prenatal diagnosis and selective abortion when this risk is about 1% in the general population?

Another question is whether the availability of treatment should play a role in the acceptability of prenatal testing. Experience so far has shown that there is great diversity in the opinions of couples at risk. For instance, in the case of the treatable metabolic disease phenylketonuria, some couples still prefer prenatal testing, with the option of abortion, because they feel the lifelong dietary treatment and small risk of impaired intellectual development of an affected child should be avoided. Most other parents accept the result of newborn screening and expect sufficient benefit from available treatment.

The issues mentioned above have so far mainly been discussed among medical specialists but the debate needs to be extended to representatives of other disciplines such as ethicists, psychologists, sociologists and legal experts. The general public should be involved and politicians should be encouraged to participate in the debate without giving firm statements from the start.

Deciding on the necessity of national and international regulation / legislation seems to me to be a major challenge, given the great diversity in culture, religion and socio-economic status and the individual differences in perception of risk, severity of a disease and more generally of the value and quality of life at different stages of development.

The next step: normal human characteristics?

In an earlier contribution Professor Geraedts discussed the issue of sex determination and the testing of immunological characteristics in relation to pre-implantation

genetic diagnosis. In various parts of the world, especially Asian countries like India and China, prenatal sex determination is carried out on the basis of cultural and socio-economic factors. Recently the Indian geneticist Professor Singh estimated the annual number of abortions due to the female sex of the embryo at more than 50,000 in India alone. Preference for a particular gender also plays a role in Western societies, though on a smaller scale. In a recent report the International Bioethics Committee of UNESCO rejected prenatal sex determination for non-medical reasons. The Committee was divided on testing embryos for their ability to serve as bone marrow donors after birth in order to save the life of a sick sibling. Some members considered this to be an instrumental use of human embryos, while others would accept the procedure if it were performed in combination with testing for a particular disease.

Irrespective of the ultimate answers to these questions the cases discussed by Professor Geraedts show that prenatal testing of normal human characteristics has already started. The main question is whether this practice on a small scale will be followed by prenatal testing and selection for a wider range of human characteristics and on a large scale.

Scientifically there is little doubt that genetic factors play a substantial role in normal physical and mental / behavioural characteristics. In the era prior to DNA technology, twin studies and comparisons between biological and adopted children were the main indicators for the extent of a genetic background. In our country, the psychologist Professor Boomsma has for many years been building a register of twins. This facilitates comparison of identical and non-identical twins. Physical and mental characteristics for which a substantial genetic influence was found are summarized in tables 1 and 2. Although there has been criticism that statements like 'intelligence is at least 80% genetically determined' are based on statistical parameters only, there is little doubt that twin studies are a useful guidance for investigations of the molecular and cytobiological basis of normal physical and mental characteristics.

Table 1 Normal physical characteristics for which twin studies show a substantial genetic influence*

body length	apolipoprotein E
menarche	glucose level
menopause	nerve condition
brain volume	smoking
respiration rate	alcohol use
systolic and diastolic blood pressure	HDL and LDL cholesterol
	heart rate

*Data and references kindly provided by Mrs. Prof.dr. Boomsma. Dept. Biological Psychology, Free University, Amsterdam; see also Koopmans et al 1999, Boomsma (rev Nature Genet) 2002

Table 2 Mental characteristics for which twin studies show a substantial genetic influence*

intelligence	extraversion
cognitive features	disinhibition
performance cito test (12 yrs)	aggression
experience seeking	boredom susceptibility
adventure seeking	anxiety
somatic complaints	

*Data and references kindly provided by Mrs. Prof.dr. Boomsma. Dept. Biological Psychology, Free University, Amsterdam; see also Martien et al 1997; Boomsma et al 1999, 2002; Posthuma et al 2002

During the past decade DNA analyses have revealed gene linkage to a variety of human characteristics such as homosexuality in males, extreme aggression, social cognition in women, novelty-seeking / risk avoidance, suspicious / touchy behaviour and speech problems. Some of these linkages, such as that in homosexual men, could not be confirmed and other linkage studies have also been criticised. Unfortunately, as with the results of twin studies in the past, scientific criticism is often mixed with social / political points of view. For many people, especially those who have high expectations of the influence of education and socio-economic factors on human behaviour / accomplishment, it is difficult to accept that genetic factors sometimes play a crucial role as well. This is especially so for those who misunderstand genetic factors in a deterministic way.

Two major challenges lie ahead as far as the molecular genetic background of normal human qualities is concerned. First, in the years to come much research on neurobiology is necessary to provide scientifically sound data. Given the worldwide efforts on genomics and proteomics and the development of chip-DNA technology which allows the simultaneous analysis of gene expression of tens of thousands of individuals or the testing of thousands of genes in one individual, progress will be possible in acquiring reliable data on physical and mental characteristics.

The second major challenge for researchers in this area is to act with prudence in terms of discrimination and psychology of individuals and groups, to involve experts from different (social) disciplines and to inform the public in a timely manner about goals and results.

Once the molecular genetic basis of specific human qualities has been established, the next question will be whether prospective parents want to test their unborn child for desired or undesired characteristics. Although such developments seem far away and for some experts not even feasible, I believe the public debate must be conducted in time.

Ethics and politics

It is difficult to predict how long it will take to understand our normal physical and mental / behavioural characteristics in molecular terms. Whether this area of research will develop at all depends not only on basic science and new technology but also on the willingness of the public and politicians to support research in this area.

Most scientists agree that basic research is unpredictable in its applications and hence in its social implications. They also believe that research has its own dynamics and that maximum freedom and support is required to ensure adequate progress. The public wants science to address and solve their most important problems; most politicians believe that the priorities of specific disciplines and themes of research should be defined and steered by them via funding. It is no surprise that these different views clash.

In addition, cultural, religious and moral objections may influence the continuity or progress of specific types of research and practical applications. During the second half of the 20th century this was exemplified by the public attitude towards nuclear energy and during the past decade artificial means of reproduction, human embryo research and genetic modification of plants, animals and human germ cells have been the subject of emotional debate and disagreements up to the highest political level.

In biomedical research the status attributed to a human embryo plays an essential role in the support for or rejection of various types of research and applications, including prenatal diagnosis. Table 3 summarizes the view of some major religions on the status of the embryo; in many states legislation in matters of (selective) abortion, in vitro fertilisation, pre-implantation genetic diagnosis and embryo research is greatly influenced by the predominant religious-moral view. The Roman Catholic dogma, for instance, is reflected in the banning of abortion in all Latin American countries and its hedging in by very restrictive legislation in European countries like Ireland, Poland and Portugal. It is clear that in these countries neither prenatal diagnosis nor embryonic (stem) cell research will flourish.

Table 3 The status of the embryo in major religions

Catholic Church	the embryo is to be respected and treated as a person from the moment of conception.
Judaism	the full moral status of a human being is acquired after a period of post-implantation development
Islam	the embryonic journey to personhood is a developmental process where ensoulment takes place after 40 days after fertilization; before this period the embryo is not considered as human being.
Hinduism	reincarnation concerns the soul irrespective of physical elements, the embryo has no special status.

In many secular views the full human status is acquired gradually; although the basic principle is respect for human life, other values could justify an infringement of this respect.

At present prenatal diagnosis and selective abortion as well as pre-implantation genetic diagnosis are supported and funded in North America, nearly all European countries, Australia and New Zealand, but also in large Asian countries like India and China.

At international level UNESCO's Universal Declaration on the Human Genome and Human Rights (1998) has been adopted by all member states of the United Nations. This Declaration states that human reproductive cloning is considered a practice contrary to human dignity; it also states that genetic modifications in germ cells or early embryos intended to be used for reproductive purposes should be discouraged or prohibited.

The political leaders of France and Germany have proposed to the United Nations the establishment of a legal ban on reproductive cloning, but US President Bush wants this ban to be extended to all kinds of human cloning. This would imply that research on embryonic stem cells derived from nuclear transfer would no longer be possible (so-called therapeutic cloning). The latter is unacceptable for researchers and many patient organisations that have great expectations of embryonic stem cell research as a basis for future tissue transplantations for the treatment of diseases like diabetes, Parkinson's disease, Alzheimer's disease and perhaps even heart muscle failure.

At a national level there is presently a negative (legislative) attitude towards embryo research in the USA, Latin America, Germany, Switzerland, Australia, Ireland, Poland, Hungary and Norway. A positive attitude towards embryo research is found in the Netherlands, Belgium, Sweden, Spain, France, Canada and some states of Australia. The most liberal approach, including the creation of human embryos for research purposes and sometimes nuclear transfer, is found in the United Kingdom, Israel and Sweden.

I expect the support for embryo research to increase if practicable therapeutic results are obtained within the next decade, especially in view of the growing shortage of donor organs. Such support would of course be limited to countries without major cultural, religious or moral objections to the transplantation of human tissues and organs.

Similar considerations to those in the preceding paragraphs apply for the future of prenatal testing for normal human qualities. If a majority at national or international level raise moral objections to research on the molecular basis of behavioural characteristics, this will slow down progress in this area. Even if neurobiological research were to be encouraged, in particular in the hope of a cure for neurodegenerative diseases, it may well be that its application in the form of prenatal testing for mental and behavioural characteristics would be discouraged or even banned, as is now the case in several countries, including the Netherlands, for prenatal sex determination for non-medical reasons.

In the debate on this issue it must be realized that the societal impact of the large-scale application of prenatal selection for or against normal human characteristics would be considerable. In view of this possible impact 'preventive legislation' might need to be considered. Up to now, scientific advances in biomedicine and the first

practical applications have usually preceded the moral debate, with legislation only coming at the end of the sequence. By contrast, in the case of human reproductive cloning several countries have introduced legal bans before any actual experiments have been done.

The question of what will happen with the prenatal testing of human normal qualities is an open one. A quote from the British scientist Lewis Wolpert seems appropriate here: 'We just do not know what we do not know and hence what the future will bring'.

What I do know, however, is that our discussions on the ethical aspects of prenatal diagnosis concern a very limited proportion of the pregnant women in the world and an even smaller proportion of the global health problems. Table 4 is intended to put our discussions in a quantitative global perspective. Design or death? That is also an ethical question, but one that requires a separate debate from this interesting meeting on the future of prenatal diagnosis.

Table 4 The beginning of life

Wealthy countries approx. 10 million births	Developing countries approx. 120 million births
high contraceptive use	300 million children without access to education (2/3 girls)
most pregnancies wanted	30% unwanted pregnancies
app. 10% do not want child	20 million illegal abortions
postpone first pregnancy	half of women victim of violence
increasing number of IVF	in 41 countries 25-50% children < 5 year underweight
broader indications for prenatal testing	15 million children lost one or both parent(s) of AIDS
baby useful for others	14 million children die annually of infectious diseases and malnutrition, 40.000 children each day!
testing desired for normal characteristics?	
DESIGN?	DEATH?

* Data from UNFPA New York 2000, World Health Report 2000 Geneva, UN Development Report 2002.

Summary of the discussion on prenatal testing for normal characteristics

The views on this topic are fairly unanimous. Participants who believe that it will become possible in the future to carry out prenatal diagnosis for normal characteristics feel that this is not a good development and argue that the procedure should not be made possible or should be banned. However, if the cultural context and specific motives of the parents are brought into the discussion, outright rejection of selective abortion based on normal characteristics is less straightforward. Suppose the parents live in a society where homosexuality is not tolerated and that – assuming that this could be determined – their future child is found to have gene sequences which predispose it to a same-sex preference. Although sexual preference cannot be justified as an argument for prenatal diagnosis, parents want to ensure that their child has a happy life and wish to prevent it suffering in any way. And whether the quality of the child's life is reduced by social prejudices and discrimination or by physical disabilities makes little difference to them. However, if prenatal diagnosis is carried out for homosexuality, the prejudices and discrimination against homosexuality are likely to remain. What is then more important: the individual interests of the child or the interests of society as a whole? For whose benefit will the tests actually be carried out?

There is also a view that testing for normal characteristics will not be a possibility in future. In his paper, Professor Bobrow expressed the view that it is and will remain impossible to elucidate normal characteristics on a molecular basis and thus to test for them. The ultimate characteristics that a person possesses are the product of many different factors. In his view, the inherent variation of genes can only come to expression when there is a very large number of offspring. This is simply not possible in humans, and only a small proportion of the potential genetic variation in characteristics is therefore expressed. A technique is under development whereby egg cells are allowed to mature *in vitro*, making it possible to produce a very large number of embryos for a single couple, all of which could be tested. Even then, however, a large number of offspring would be needed in order to ensure that the diagnosed characteristic was actually expressed in one of them in the desired form. Other participants in the discussion feel that much greater insight will be obtained in the future into the molecular basis for normal human characteristics and behaviours.

The more possibilities are created, the more difficult it becomes not to use them. There are limits to the freedom of choice of parents/women. The increase in choice can lead to excessive social pressure from the immediate environment or from society to take part in prenatal diagnosis or pre-implantation diagnosis and ultimately to terminate a pregnancy. It is not only the demand which drives up the number of tests, but also the supply. In addition, the organisation of medical provisions in a given country influences the decisions taken by women/future parents. There is

every chance that in the future this social pressure, which will be based among other things on economic motives such as claims by insurance companies and employers, will also be exercised in respect of normal characteristics.

In general, the participants in this debate question the ever-increasing control over medically non-essential personal characteristics, the ever heavier financial and medical burden this greater control brings and the growing demand on limited medical resources. Nevertheless, the general belief is that prenatal diagnosis will not be used in Western society in the short term as a general solution for the most diverse problems. Virtually all pregnancies in the Netherlands are highly desired, and only when there is a serious threat to the health of the parent or unborn child will the pregnancy be terminated. The fear of developing a serious disease and/or transmitting such a disease to one's offspring imposes a heavy burden and it is this fear which often fuels the demand for prenatal diagnosis. In such a case, parents prefer an abortion to carrying the pregnancy to its full term. A situation where these extremely difficult decisions have to be taken in respect of a characteristic which will have little effect on the quality of the child's life is regarded as extremely unlikely. It should be noted here that 'quality of life' is a subjective notion which has a different meaning for different people and also changes in time.

No country is an island

All mankind is of one author, and is one volume; when one man dies, one chapter is not torn out of the book, but translated into a better language; and every chapter must be so translated... No man is an island, entire of itself...any man's death diminishes me, because I am involved in mankind; and therefore never send to know for whom the bell tolls; it tolls for thee. John Donne, London, 1572-1631

Implications for bioethics?

At this moment Europe, and especially Western Europe, is facing some fundamental questions concerning bioethical matters. The main problem surrounding these questions is the difference between nations and the different points of view people have. Bioethical issues are after all matters of universal concern. But are we inevitably affected by the way in which our neighbours approach moral issues? Is it necessary to reach consensus on those moral issues, or is it possible to live with moral pluralism? Perhaps it is better for bioethical issues to be determined by 'local moral communities'. Why do we need a Council of Europe Convention on Human Rights and Biomedicine and try to solve these questions at an international level? Because these kinds of organizational structures are important for supporting our moral values with international agreement. Essentially, the transnational nature of the problems (ease of travel, Internet, etc.) means that the only way of regulating these issues is through international agreement. An example is paternity testing, which is available on the Internet. It is hardly possible to isolate many of these things and therefore it is hard to regulate them nationally. On the other hand, there is also a tendency towards moral imperialism – a desire to ensure that others observe one's own standards, what one believes to be right, should be right for other people. We need, therefore, to identify in which areas of bioethics there may be international agreement and in which we need to agree to disagree. Areas of agreement are for instance the need for consent, both in the clinical and in the research context, control of research (within reason), protection of the vulnerable and containment of severe risk. Areas of disagreement are for instance abortion, embryo status issues (including in relation to embryonic stem cell research) and prenatal genetic testing/pre-implantation genetic diagnosis.

There are two regulatory dimensions. The first is national, but how are we to regulate at national level? The second is regional/international regulation. But, as we asked before, is this desirable? Is it feasible? In particular, is it desirable that we in the European Union should arrive at a single approach? Should the European Union

dictate to its members how they should approach these issues of moral and social policy? In the past the EU has said that its members should have the freedom to determine moral and social policy themselves. A single dictated approach would affect countries like the Netherlands, which will perhaps be out of step with some other members, which may wish to impose their view on the Netherlands.

Some fundamental issues concerning regulation

Should there be a presumption against regulation in a liberal society? Should people be left to make their own decisions on moral issues as long as these do not compromise the health and safety of others? There is a strong argument for this. In a liberal society people should be able to make their own personal decisions as far as possible and criminal law and other regulatory mechanisms should be used with the lightest touch possible. But in my opinion bureaucrats and moralists have an inherent interest in regulation. They may also have a tendency to impose uniformity.

Preferable is a system that recognises the diversity of views, but is it possible to have this? Different kinds of regulation are possible. We can think of self-regulation – leave it to the individual – where medicine responds to individual wishes. But in reality this is unacceptable, in that the interests of others (e.g. the future person in this context) are involved. While this is therefore not a realistic option, there should nonetheless be some room for self-regulation. When leaving wide scope for parents to reach decisions in association with the clinicians involved, however, we have to be aware that there is a social interest in describing some parameters for the exercise of that particular choice. Another possibility is professional regulation – leave it to the clinical and moral judgment of the medical profession. This is politically unacceptable in the light of anti-professional sentiment: the general view nowadays is that professions should not be entitled to regulate themselves on these crucial issues. A third option is to regulate through agencies and codes of conduct; these will leave us more flexibility because these create the possibility of responding quickly to changes in views in society. Moreover, agencies can contain representatives of all the existing variety of positions. Finally, there is the option of regulating through prescriptive legislation, but this option is possibly too tied because there is no possibility for responding to changes in society.

The UK position

In the United Kingdom, genetic testing is not regulated by any specific statute or piece of legislation. General principles of common law apply to the obtaining of genetic information (consent to testing). In addition, administrative guidance issued on screening and testing issues is quite an important element in the regulation. This system also means it is possible to respond very quickly to changed circumstances in society. A special authority, the Human Fertilization and Embryology Authority (HFEA), regulates artificial reproduction.

Ethical regulation

The UK government wishes to encourage appropriate genetic screening as a means of improving health and acknowledges the ethical issues originating from it. The British government has established a variety of bodies to advise on ethical issues. There is the Advisory Committee on Genetic Testing, (ACGT) which was dissolved in 1999; its work has now been taken over by the Human Genetics Commission (HGC; it advises the government on ethical, social and legal aspects of genetics). The Human Fertilization and Embryology Authority (HFEA) regulates all aspects of artificial reproduction in the UK and issues licences for that purpose. To some extent the work of the HFEA overlaps the Human Genetics Commission. The National Screening Committee (NSC), a third body established by the government, has stated certain general principles like: 'screening has been developed as a public health service to improve the health of populations' and 'screening programmes should offer choice to individuals: each individual should appreciate the risks and benefits of the screening programme for them as an individual' (Source: NSC, Second Report). This Committee particularly stresses the fact that screening means risk reduction. The intention behind this is to reduce psychological damage due to unrealistic expectations as to screening's potential. In order to regulate screening activities, the NSC endorses screening criteria such as:

- the condition should be an important health problem;
- the condition should be adequately understood and there should be a detectable risk factor; all cost-effective primary prevention interventions should have been implemented as far as possible
- tests should be simple and safe and should be acceptable to the population
- there should be an agreed policy on further diagnostic investigation and on choice available to individuals
- the benefit from the screening programme should outweigh the physical and psychological harm and the screening programme should have been ethically assessed and found to be ethically acceptable.

When translated into practice, however, standards in screening programmes are not always the same and there is some criticism of the inadequacy of counselling: not all patients receive the requisite level of advice. However, there have been attempts to ensure that people are able to make an informed choice – the NSC, for example, publishes leaflets on a number of conditions, in which the choice factor is stressed.

Other issues that play a role in the UK are pre-implantation genetic diagnosis (PGD), genetic testing for late-onset disorders, and 'over the counter' genetic testing. PGD has evoked objections from the disability movement, which is afraid that this will allow eugenic measures and directly diminish their social value. The HFEA has said that PGD should only be used for very serious, life-threatening conditions, not for minor genetic abnormalities. This raises problems as to what constitutes a serious condition. But it is very difficult to go beyond these kinds of general statements and it is impossible to prevent discussions about whether a disease or a condition is serious or not. However, there has been general opposition to listing diseases/ conditions, stating which will be considered for PGD and which will not.

The HFEA recently announced that tissue typing may be used on a pre-implantation embryo in order to allow for the use of cord blood for therapy in an existing child. The HFEA Ethics Committee approved this using arguments such as the complexity of parental motivation – parents in such a case may still be highly motivated to bring up their child well. The Committee did not feel this was a form of instrumentalisation of the future child at all, because nobody can say why parents want another child. There is no evidence that the donor child will simply be used and not appreciated for itself; parents should at least be given the benefit of the doubt. Furthermore, it could be in the interests of the future child to be able to save the life of a sibling. Finally, this is not a eugenic technique: the aim is to cure an existing condition, not to prevent its future occurrence.

As regards genetic testing for late-onset disorders, the Advisory Committee on Genetic Testing has issued guidelines on the genetic testing of both adults and children. The Advisory Committee thinks that report on this issue stresses the need for specific consent, for caution in the administering of such tests and it recognises the importance of counselling.

‘Over the counter’ genetic testing means that genetic tests may be provided directly to the public. This practice is likely to become more common. Should suppliers of genetic testing services be allowed to offer them directly to the public? The *arguments against* are inadequate counselling; increased public anxiety; and the possibility that excessive claims will be made by suppliers. The *argument for* is that individuals have a right to know. The Advisory Committee on Genetic Testing has issued guidelines for these direct tests and these are now overseen by the Human Genetics Commission. The guidelines recommend voluntary compliance with a Code of Practice, that tests should be submitted to the HGC for approval (some tests will be unsuitable for this direct offer) and that clients should be offered genetic advice. But problems are foreseen with this kind of testing in the future, because the nature of tests may change (lifestyle use of genetic information); it will also be difficult to control tests conducted outside the country (e.g. paternity tests); and there could be conflicts with human rights issues (e.g. Article 8 of the European Convention on Human Rights).

International regulation

What international interest is there in regulating this area of activity? The international community already acts to protect human rights. There is an emerging concept of genetic rights at international level: the UN Universal Declaration on the Human Genome asserts rights in relation to the human genome and genetic information, and this includes consent issues. In addition, the right of access to genetic information about oneself is increasingly being recognised; there must be very good reasons for preventing people from obtaining this knowledge (the paternalist position). And what about reproductive rights? Some reproductive rights are recognised (for example, many countries disapprove of or would restrict sterilisation of those who cannot consent to it). Some countries recognise the right to decide whether or not to terminate a pregnancy (in the early stages). By extension, this has some implications in terms of the abortion right: if a right to abortion is recognised in certain circumstances, then genetic testing, which affects this decision, must surely also be allowed.

The problem, though, is the extent to which genetic testing will push out the frontiers of the accepted grounds for abortion – the ‘abortion right’ may be a qualified one (only in relation to specific factors). This pushing out of the frontiers of the abortion question raises a policy issue: should we specify the parameters or limits of individual choice? In other words, should we regulate testing in order to protect other values (e.g. diversity, tolerance of disability, etc.)?

No country is an island

Bioethics is becoming increasingly global in its concerns. What is allowed in one country will influence the position elsewhere (the effect of permission); the euthanasia debate demonstrates this. Can we achieve a balance, which recognises this but allows for diversity of approach? The Council of Europe states the following:

Recommendation R (90) 13 on prenatal genetic screening, prenatal genetic diagnosis and associated genetic counselling (1990) covers antenatal testing during pregnancy, but also the testing of either sex before conception. In brief, its principles require:

- restriction of testing to serious health risks, but that counselling and testing services for those at risk of conceiving a child with a serious genetic disorder should be effectively publicized,
- restriction of testing to state-approved institutions under the supervision of a physician,
- free and informed consent of the subject,
- counselling – made available before and after the test, covering the purposes of the tests and their risks, non-directive in nature, tailored to circumstances, and with both parents participating if possible,
- data protection, with data used only for health care and closely related research.

In addition, Article 3 of the EU Charter of Fundamental Rights, which in my opinion is becoming an important part of the EU constitution, states that:

1. Everyone has the right to his or her physical and mental integrity
2. In the fields of medicine and biology, the following must be respected in particular:
 - the free and informed consent of the person involved,
 - the prohibition of eugenic practices, in particular those aimed at the selection of persons.

The EU project appears to seek to create a new ‘moral community’ in Western Europe and if this succeeds, to what extent will this be a pluralistic community, or to what extent will it involve the imposition of values? The stem cell issue has been a case in point: disagreement has been profound, but genetic testing may be a new testing ground for tolerance and pluralism.

Comments by panel members

Setting the boundaries for prenatal testing

Prenatal testing for hereditary breast cancer

The availability of prenatal diagnosis (PD) can restore reproductive confidence for many couples at risk of transmitting a genetic disease in starting a pregnancy and thereby increasing their prospect of having a healthy child. A considerable proportion of these couples have decided before becoming pregnant that they would abort the foetus if prenatal testing shows a pathological outcome. They thus deliberately embark on what has been called a ‘tentative pregnancy’.

The widespread use of PD in such situations has frequently been cited as evidence for its moral acceptability. However, in ethical debates empirical evidence cannot serve as moral justification. Facts must not be confused with norms, which are constituted by ethical reasoning. Therefore the question remains of whether embarking on a pregnancy in such a situation is ethically defensible.

Some argue that the right of the couple to make their own decisions as to how to reproduce prevails over the right of the foetus to live. Others would argue that the foetus’ right to live makes the deliberate establishment of a pregnancy ethically indefensible if the intention is to terminate should the foetus be found to carry the genetic pathology. If the latter position were the general norm, exceptions could nevertheless be justifiable under specific circumstances, for example if other high-ranking norms, values or interests need to be protected.

One such value is the health of the future child and the threat posed to it by the inheritable disease. Most professionals regard abortion as ethically defensible if the future child will be affected by a serious disease. Serious, however, cannot be defined in absolute terms; the perception of a disease does not depend only on objective criteria, but also on the situation of the prospective parents. This perception is to a certain extent subjective, context-dependent and contingent. Therefore, genetic professionals favour individual patients as decision-makers, with the help of individual doctors. If we apply this paradigm of far-reaching patient autonomy to the case of inheritable breast cancer, there is no question that the ultimate decision regarding pregnancy outcome and management, including termination, belongs to the expectant couple.

As genetic knowledge advances, more and more mutations involved in polygenic or multi-factorial diseases and disease predispositions become detectable by genetic testing, in addition to a growing number of monogenic traits. This has led to considerable unease not only among the general public, but also among genetic professionals. The question arises as to how far parental autonomy can go in the context of prenatal decision-making, if not only more diseases but also other health-related traits become detectable at the molecular level.

One argument which needs to be critically examined concerns the wellbeing of the women concerned. For example, in Germany abortion is legal when the actual or future physical or psychological health of the woman is endangered. Having to care for a child with a severe disease – and therefore to give up one's own life plans – may be regarded as a threat to the wellbeing of the woman. Although it is admittedly difficult in practice to distinguish between eugenic and maternal indications, poor health of the future child as such does not constitute an indication for termination of pregnancy.

These considerations are relevant for the case of PD for inherited predispositions to breast cancer. In this case, the individual health risk of the future child differs from that posed by 'classical' inherited diseases, in that the person carrying the mutation will not be sick for many years or even decades. Since BRCA1/2 and other cancer genes are not completely penetrant, the disease may even never develop. Therefore a situation which may justify abortion in order to protect the interests and wellbeing of the women will not exist. The child does not suffer from a serious disease in early childhood (and perhaps never will), and the mother or parents will not have to care for the child intensively for many years, at least not on account of the inherited condition. Instead, the child may experience that its mother develops cancer early in life. Following this line of argument, there are serious objections to PD (and termination of pregnancy) in the case of predisposition to inheritable breast cancer and other late-onset diseases.

Embryo selection for transplantation and desired traits

Pre-implantation genetic diagnosis (PGD) allows selection of embryos which are HLA-compatible with an existing child. To date, HLA-selection has been performed only a few times, and no empirical evidence is therefore available on the impact of this intervention on the child and on the social interactions within the family.

Two categories of interventions have been distinguished. In the first category, the couple are themselves at risk of transmitting the disease. In this case the future child could benefit from PGD because, in addition of serving as a stem cell donor, it would be born free of the disease. In the second category, there is little or no risk of the future child contracting the sibling's disease. In this case he or she would derive no advantage from PGD and HLA-selection, which would be performed for the benefit of the existing sibling only.

Whereas many ethicists and a growing number of regulatory bodies regard the first category of interventions as ethically defensible, few ethicists hold the same view with respect to the second category. One of the central arguments which have been levelled against HLA-selection is the instrumental use of the future child. To rebut this argument, parents have claimed that they wanted another child anyway. But how can the motives of the couple be assessed? If they wanted to have another child, they could have had a (healthy) child by performing PD after natural conception. The assumption that selection does not serve purely instrumental goals is no better founded than the assumption that this is the case. In this situation, other criteria are needed. One is the risk of the medical interventions associated with PGD and HLA-selec-

tion. IVF as a prerequisite for PGD is by itself associated with some health risks for the future child; after IVF, more children are born prematurely compared to normal conception. This is mostly, but not entirely, due to the fact that twin and higher-order pregnancies are much more common after IVF (and ICSI) than after natural conception. Premature birth and low birth weight are associated with a higher incidence of premature death and neurological problems. There may be also a slightly increased risk of imprinting diseases.

If one accepts PGD as a method of embryo selection – not everyone does – these risks may be acceptable if the goal is to become pregnant or to avoid a more serious risk. But is it also acceptable when parents wish to select a desired trait? In medical ethics, interventions on persons not able to consent may only be performed if it is for their direct benefit. Where the embryo/child is not itself at risk, such a benefit is at best very indirect. The child may or may not benefit from being born to help another child. Furthermore, it is debatable whether, how and to what extent non-health-related benefits can and should be included in the risk/benefit assessment of a non-necessary, highly invasive medical treatment and serve as its sole justification.

Parents may consent to treatment on behalf of their sick children as proxy decision-makers. However, it is considered unethical to consent to interventions which are not for the direct benefit or interests of the child. There is therefore neither an ethical nor a legal justification for non-therapeutic interventions. This prohibits not only selection by PGD for a desired trait only (including sex selection), but also poses questions as to the legitimacy of additional HLA-selection where there is a risk of an inherited disease. At least where parents do not refuse abortion for reasons of principle, the child could have been born healthy without PGD and the additional risks posed by it.

Future perspectives

If selection for desired traits is accepted, the next step can already be foreseen: DNA micro-array analysis is rapidly evolving. Embryos could then potentially be tested not only for several disease susceptibility traits loci, but also for one or more desired traits. At present, technical limitations and the cost of producing appropriate micro-arrays hinder their application in PGD. However, the rapid advances in molecular genetics are likely to prompt further use of PGD and to encourage a substantial change not only in the way in which genetic conditions in the offspring of certain patients are prevented, but also in how people approach procreation and how they perceive their future children.

In the long term, PGD has the capacity to establish new expectations and duties for families. Although women are part of this development, men and women are affected differently, not only by the treatment itself, but also by the social expectations and consequences associated with it. PGD not only fosters the idea that health is a matter of previous selection, it also makes it feasible. Expectations with respect to what a woman is obliged to do in order to guarantee the birth of a health controlled child may consequently increase.

In the context of PGD, women's bodies are not only used for the purpose of creating a healthy child, but also – in the case of pre-implantation HLA matching – to

select children who may be helpful for others and possibly to select children of preferred sex. In a liberal society, it is unlikely that women will be forced by the state to undergo PGD for any reason. However, in some societies or social groups it may be regarded as a duty to undergo PGD in order to conceive a child of a specific sex, or to avoid abortion. Especially where her own child or a close relative is affected by a disease which can be treated by cord blood stem cells, a woman may feel obliged to undergo PGD for HLA-selection in order to help the person in need. When the technology is available, she will inevitably be confronted with the desire to produce a potentially life-saving embryo.

Once established, such medical technologies and services develop their own dynamics. The challenge will be to restrict the use of PGD technology to medical purposes and the direct benefit of the future child and to prevent its use for other purposes.

Prenatal testing: a critical overview

Introduction

Prenatal diagnosis of foetal congenital and hereditary diseases first became possible with the introduction of amniocentesis approximately 35 years ago. Later, chorionic villus sampling and to a lesser extent foetal blood sampling was added to the armoury of invasive diagnostic techniques. Attention was primarily focussed on Down syndrome and other chromosomal abnormalities. In the Netherlands antenatal invasive testing for Down syndrome is offered to pregnant women aged 36 and over. With advances in biochemistry and molecular medicine it became possible to establish an increasing number of disorders antenatally at metabolic and DNA level.

Progress in genetic testing

The completion of the human genome project will allow a better understanding of the genetic basis of disease. Genetic tests for diseases and disabilities are becoming increasingly available. These provide couples who have a family history of genetic disease with the opportunity of having healthy offspring. Insight into gene mutations relative to increased risks of disease later in life has opened the debate on the justification for presymptomatic prenatal testing. Such a debate would span a wide range of issues varying from highly penetrant, late-onset, potentially lethal and non-lethal diseases (colorectal cancer, BRCA, autosomal dominant form of Alzheimer's disease) to minor disorders or disabilities with a nearly normal quality of life.

Diagnostic ultrasound examination currently allows the early detection of a wide range of foetal anomalies. The early diagnosis of a minor anomaly seldom results in a request for pregnancy termination. Instead, obstetric management may be aimed at delivering the affected infant in a well-equipped perinatal centre.

On the other hand, a serious anomaly detected by ultrasound beyond 24 weeks of gestation, which represents the legal upper limit of pregnancy termination, may deprive the woman of any choice regarding the future of her pregnancy. Since there is no officially recognized routine scanning at 18-21 weeks in the Netherlands, more than half of all foetal anomalies are detected beyond 24 weeks.

The potential of biotechnology to offer society the possibility of selecting against abnormal children has been subject to a great deal of discussion for some time. What was not foreseen was for instance the selection in favour of disability through the birth of a deaf child deliberately created by a sperm donor with five generations of deafness in the family. This raises questions as to whether the profession should participate in this, where the boundaries of parental autonomy lie and what constitutes 'the best life prospects'.

Recent developments in early embryo research, in particular diagnostic procedures at blastomere level (pre-implantation genetic diagnosis; PGD) have given this debate some urgency. Based on these developments changing attitudes can be observed in society towards expectations concerning the characteristics of offspring. New PGD issues have been reported, notably screening embryos for susceptibility to cancer, for late-onset disease, for HLA matching for existing children and for gender. These extensions of PGD raise questions about their acceptability and the effectiveness of regulatory structures to assess these new applications. It has been argued that, except for sex selection of the first child, most current extensions of PGD are ethically acceptable.

Recently the Human Fertilization and Embryology Authority (HFEA) in the United Kingdom found PGD for HLA matching to be acceptable when infants born after PGD were themselves at risk for the condition to be treated in the existing child. However, disorders unconnected to a known genetic mutation were not included. Of interest, therefore, is the recent action by the High Court in the United Kingdom to overturn a decision made by the HFEA not to grant permission for an HLA-matched embryo to be transferred in a case in which an existing sibling suffering from thalassaemia was in need of a compatible donor of haematopoietic stem cells.

The debate on non-medical sex selection is a continuous one. The ESHRE Ethics Task Force makes a clear distinction between non-medical sex selection and human rights and non-medical sex selection for family balancing. Particularly regarding the latter, the Task Force seems to have adopted the view that sex selection is morally acceptable. However, such selection is not allowed for the first child or when there is an equal number of both sexes.

By analogy with past debates on abortion and embryo status, one can argue for or against embryo selection. There are two issues: (1) the procedure of embryo selection itself; (2) the need to create and subsequently select embryos which are chromosomally normal or free of genetic disease. The first issue could be considered redundant on the basis that there seem to be no biological grounds for considering the early embryo to represent a person; the embryo is too rudimentary in its development at the time of embryo selection. The second issue can be justified on the grounds that similar indications are valid at the time of chorionic villus sampling and amniocentesis.

Presymptomatic prenatal diagnosis

A step further takes us to prenatal diagnosis for susceptibility to conditions, in this case BRCA 1 and BRCA 2 susceptibility for breast cancer. The aim is to prevent the birth of infants who are healthy at the time of birth but run a considerable risk of developing cancer later in life. If one takes the position that there should be room for prenatal diagnosis or embryo selection to prevent the delivery of a child with a high risk (but not 100%) of late-onset disease, then there are a number of issues which ought to be considered: (1) the risk of the disease developing; (2) the seriousness and age of onset of the disease; (3) possibilities for prevention and treatment; (4) the basic right of the foetus to be protected; and (5) parental autonomy. I do not share

the view that arguments in favour of presymptomatic prenatal testing are similar to the arguments for preventing the birth of infants with severe genetic disease. If one were to accept presymptomatic testing for late-onset disease, it should be limited to disorders which have a near certainty of becoming clinically manifest at a relatively early age, with limited or no treatment modalities, poor quality of life and reduced lifespan. FAP (Familial Adenomatous Polyposis) could serve as an example. For the moment, the general approach should be not to offer presymptomatic testing, unless arguments are presented by the couple that convincingly support such a procedure. In that instance, there must be adequate pre-test counselling, which includes verification by the counsellor that the request has been made voluntarily and not under pressure from family members. Moreover, the women will undergo an abortion if it has been established that the foetus is a carrier. It should be noted that requests for presymptomatic testing are still rare, suggesting that couples do not as yet consider such testing a major option. Perhaps with IVF programmes becoming less intrusive and less costly, embryo selection may one day become an acceptable means of avoiding the delivery of children who are very likely to develop cancer sooner or later.

HLA matching

Pre-implantation diagnosis for HLA matching raises questions about the acceptability of the donor child (love and care) and the potential risks involved for the donor child. Whereas treatment of the disease of the existing child is the motivating factor in creating an additional child, there is no reason to believe that parents would ignore the needs of that child. There are however two conditions to be met before embarking on PGD for HLA matching. Firstly, the ultimate intervention should not involve a physical intrusion on the donor child. This is the case when stem cells are harvested from umbilical cord blood. Secondly, there should be a connection to a known genetic mutation. This should prevent interventions such as an organ transplant from a donor child to an existing sibling with an incurable organ disorder.

Sex selection

The debate on sex selection for non-medical reasons is closely related to the issue of human rights. In this context, one cannot ignore the fact that for socio-economic, political or cultural reasons, 70-80% of the world female population still have insufficient or no access to good-quality medical care; for example, more than half a million women die in relation to pregnancy every year. PGD for non-medical sex selection should not be used unconditionally as long as there is social injustice towards women or where a person is considered to be of the wrong gender in the eyes of their family, an attitude that still prevails in some parts of the world. Whether or not sex selection for family balancing (selection for the 'other' child) is seen as morally acceptable depends on the socio-economic and/or culturing setting in which selection is requested. First the question as to why a couple wish to have a child of the other sex needs to be addressed. If sex selection for family balancing were to be accepted, parents would need to be psychologically counselled and made aware of the intrusion of the preceding IVF procedure and related cost burden.

Other issues

A development which may have a considerable impact on the perception of prenatal diagnosis is the introduction of so-called risk indicators for Down syndrome and other chromosomal abnormalities. Current studies are increasingly directed towards establishing the predictive value of early combined biochemical (PAPP-A and beta HCG) and sonographic (foetal nuchal translucency) testing, providing a risk assessment for the disorder. This could lead to the replacing of maternal age-related prenatal diagnosis by all-age screening for Down syndrome.

This development brings up the issue of how women perceive a potentially two-step procedure of risk assessment, possibly followed by an invasive diagnostic test, as opposed to the one-step procedure of an invasive diagnostic test. The former demands specific counselling strategies so that women understand the meaning of test results, allowing them to make informed choices. To determine the acceptability of prenatal risk assessment, the possible consequences for both individuals and society on a whole need to be known. Obstetric care-providers must take collective responsibility for developing and delivering such a screening programme according to well-defined guidelines. This may pose a problem in the Netherlands, which has a decentralized obstetric care system with care-providers having limited or no experience in antenatal risk assessment. Currently, the country is in a state of confusion as to what should be offered, by whom and when. A document on prenatal screening including the pros and cons of risk assessment was produced by the Dutch Health Council more than two years ago. The Health Minister recently decided not to include prenatal screening in the health insurance funding, but encouraged doctors to inform pregnant women adequately about the possibilities and limitations of such screening.

Ethical problems in parental decisions

Prenatal testing for severe early-onset diseases with a view to termination of the pregnancy is a widely accepted practice in most developed countries. The aim of the procedure is to prevent the birth of children who will be affected by diseases for which no cure is available. Prenatal testing for late-onset diseases is still controversial within the professional community, but less so to people who belong to families at risk and who opt for this solution after thorough genetic counselling. Even if only a minority of couples ask for prenatal diagnosis in the case of, say, Huntington's disease, either through direct mutation testing or via indirect exclusion testing, the counsellor should accept this because, in my view, the patient at risk knows the problem best and must have chosen the best solution to avoid transmitting the disease to his or her offspring. This is also the case for at-risk members of breast cancer families, although the problem here is more complex since inheriting a BRCA1 or BRCA2 mutation means an increased risk but not a certainty for breast or ovarian cancer. Moreover, the risk of developing cancer varies according to the gender: males carrying a BRCA1 or BRCA2 mutation have almost zero risk to low risk of developing breast cancer compared to female carriers. This means that at prenatal diagnosis, one could first karyotype the foetus and subsequently genotype the female foetuses in order to terminate the pregnancy only in the case of a female mutation carrier. Another, more straightforward practical approach at prenatal diagnosis would be to propose mutation analysis and termination if the foetus carries the mutation, without at that point knowing the sex. This would also avoid transmission of the mutation and thus the disease to the next generation. However, for practical reasons this approach may not hold for pre-implantation genetic diagnosis; developing a mutation-specific assay at the single cell level is labour-intensive and time-consuming. Embryo sexing based on fluorescent in situ hybridisation with transfer of XY embryos is more readily available at this point. But males have a risk, although small, of developing cancer. The question is how much residual risk we accept, especially if complex and costly technology is used to avoid the disease.¹ Besides, who are we – the patient or couple or the professional team – to make these decisions? In any event, I personally believe there is no reason for rejecting PD or PGD if couples confronted with such diseases in their family request it.

Most couples asking for embryo HLA-typing are also at risk for genetic diseases such as β -thalassemia or sickle cell disease. They have an affected child who they want to save and the only way to do this is by transplantation of hematopoietic stem cells from an HLA-matched donor who is not affected by the genetic disease. If no HLA-matched healthy sibling or other donor exists, the sick child cannot have the

transplantation and will die. In some of these families the parents had planned to have another child anyway. Others had not, but have changed their plans because one of their existing children is seriously ill and faces death. The parents can decide to become pregnant and wait for the HLA-typing at birth. Or they can become pregnant and, as has happened in practice though probably very rarely, request prenatal diagnosis followed by termination if the foetus is not compatible. Pre-implantation genetic diagnosis, avoiding the need for termination of pregnancy, offers a new option for families who are at risk for genetic diseases. However, the technique is neither easy for the family, especially the mother, nor for the physicians, scientists and lab technicians, because as many oocytes as possible have to be harvested from the mother's ovaries after ovarian stimulation. After fertilization, as many embryos as possible have to be carefully examined in order to detect the three out of sixteen that can, if they implant, lead to the birth of the expected donor. The age of the mother, the relatively low birth rate after IVF and PGD, the fate of the healthy but 'incompatible' embryos and the possible failure of the transplantation treatment all have to be taken into account and discussed with couples requesting PGD for pre-implantation HLA matching.

In addition to these more technical aspects in the clinic and the laboratory, this technique has ethical aspects as well. Is the donor child more of an instrument than another child which was made to create a playmate for his sibling? Probably not, as long as it is not made solely in order to save the sick child, and as long as it is accepted and treated like any other child that happens to be a compatible donor and therefore could help to cure a sibling. It is difficult to maintain the argument of instrumentalisation against this procedure if one thinks of all the current reasons why people want to have children. Moreover, PGD demands a lot of effort from the parents, who started the procedure because they love their affected child. There are many reasons for believing that they will also unconditionally love the new child. Finally, one has to take into account the fact that harvesting stem cells from cord blood or even bone marrow from one sibling for transplantation to another, causes no or very little harm and is therefore acceptable. Moreover, the procedure of bone marrow transplantation is acceptable when performed between existing children – therefore the intention to make a child to become a donor cannot be wrong. Too much should not be expected from the donor child, since there is no guarantee of a successful procedure, and the sick child may not be saved. Again, however, this would also be the case if bone marrow from an existing child were used. These are, in my view, arguments in favour of accepting requests for pre-implantation HLA matching.²

It is not wrong to hope for a boy when one already has a girl, or vice versa. One child of each sex is a dream for many parents. The reasons for this may be the difference between the two genders; bonding may be different; the interaction between children and parents and between siblings is different; and their roles in society are different. For many people life is incomplete without children, for others life is incomplete without at least one child of each sex. But does all this permit active interference with nature? It could be argued that this is permissible as long as one sex is not favoured over the other, but can any means be accepted?

Probably no-one will be against hoping, and many people would probably accept sex selection by means of a diet or intercourse timing. In other words, people doing this would not be considered immoral. What about the use of selected sperm enriched to 90% X-bearing sperm or 70% Y-bearing sperm combined with IUI, IVF or ICSI? And what about the use of PGD, a complex, costly procedure reliable as far as sex selection is concerned but with a relatively low success rate with regard to pregnancy and live birth? Should one consider this as a private matter, possibly available to well-off people only, or should society decide on the use of medical technology for non-medical indications? And although sex selection is a non-medical indication it is, apparently, linked to the wellbeing and happiness of a family.

Having thought about and discussed these questions a great deal, I continue to find sex selection, even in restricted conditions such as family balancing for a third child, to be a step too far. I suppose this is because boys and girls are both 'normal' and equal, and the price to be paid should be the same for both – not more expensive for one or the other. For me, using medical technology in this situation leans towards discrimination. This holds true for normal characteristics as well, but society may have changed when this becomes possible. At the moment I would say: dreams may come true, but not at any price.

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Prenatal testing and selection: proceed with caution

Introduction

There is wide consensus that both prenatal diagnosis (PD)/selective abortion and pre-implantation genetic diagnosis (PGD)/selective transfer can be morally justified if they are used to prevent the birth of children suffering from serious handicaps and disorders. In the Netherlands, this view – the ‘medical model’ – is reflected in various regulations, including the ‘Planning decree on clinical genetic research and heredity counselling’ (*Planningsbesluit klinisch genetisch onderzoek en erfelijkheidsadviesing*) and the Embryo Act (*Embryowet*).

New applications of PD/PGD are constantly being introduced or considered. Some of these raise new ethical issues and challenge us to reconsider whether or not the (ethical) guidance is adequate. Here I will concentrate on the four cases presented at the symposium: PD of hereditary breast cancer, PGD/pre-implantation HLA matching, PGD/sex selection for family balancing, and PD/PGD of normal characteristics.

Controversies within the medical model

Late(r)-onset disorders

Even though people rarely request PD of late(r)-onset disorders, PD of late(r)-onset disorders is especially controversial. While some commentators and the regulations in some countries consider PD/termination of pregnancy for this category of disorders to be unjustified, a differentiated judgement is needed, as one should take into account various morally relevant aspects, including the age of onset of the disorder, its severity, treatment possibilities, the penetrance of the respective mutations, and the implications for the people directly involved. Needless to say, ethical balancing is not a mathematical exercise.

In view of these variables, a distinction may be made between various types of late(r)-onset disorders, including the following.

First, there are untreatable, autosomal dominant disorders, like Huntington’s Disease (HD) – the paradigm case. Critics argue that a child carrying the HD mutation will have many decades of good and unimpaired living, that the parents of the child are not immediately affected in the way they would be in the case of an early-onset disease, and that we should acknowledge the moral ambiguity of the quest for ‘perfect’ babies.¹ In view of the fact, however, that HD is a midlife-onset, highly disabling, lethal disease, and that the penetrance of the mutation is total, PD aimed at terminating an affected

pregnancy can be considered to be morally justified. It is insensitive, if not an insult, to (dis-)qualify this as symptomatic of 'genetic perfectionism'.

The ethics of PD of Huntington's Disease cannot be reduced to the issue of aborting a foetus carrying the HD-mutation. The *conditions* under which PD may take place should be given due attention as well: what about PD of HD 'just for the reassurance' of (prospective) parents who do not intend to terminate affected pregnancies (risking a violation of the future child's 'right not to know'); what about prenatal exclusion testing (taking a 50% risk of aborting a healthy foetus); what about direct testing of the foetus of persons at 50% risk (risking double bad news for the prospective parents); and finally, how are we to handle requests from women for PD of HD when their male partners are at risk and do not want to know their genetic status?^{2,3,4}

PGD for untreatable later-onset disorders like HD raises specific questions concerning the doctor's responsibility to take into account the interests of the future child.³ After all, in view of the fact that a carrier will inevitably get HD, parental competence will steadily erode. Furthermore, serious behavioural problems may develop. A case-by-case approach is preferable in this light. With regard to 'non-disclosure' PGD, one may ask whether this approach can effectively protect the at-risk parent's right not to know his/her genetic status – and if so, at what financial, medical and psychological costs.^{5,6}

A second category of late-onset disorders concerns monogenic variants of multifactorial disorders which may be preventable and/or treatable. An example is hereditary breast/ovarian cancer (HBOC). PD of mutations in BRCA (case 1) is even more controversial than PD of HD, because the penetrance of these mutations is incomplete (the lifetime risk is 50-80%) and preventive interventions may effectively reduce morbidity and mortality in carriers. Again, however, we should resist premature conclusions. While the penetrance of the mutations is indeed incomplete, the lifetime risk is still very high. Furthermore, morally relevant questions concern the effectiveness of available preventive and/or therapeutic measures, and the burdens imposed by the respective medical interventions. Unfortunately, the effectiveness of medical surveillance (mammography) is currently far from optimal. Though the effectiveness of prophylactic bilateral mastectomy appears to be high, long term follow-up studies and study of more carriers are necessary in order to establish with certainty the protective value of this procedure.⁷ Furthermore, prophylactic surgery may have major implications for women's quality of life. In view of this, it may well be argued that the fear of prospective parents that their future daughter(s) may inherit a BRCA gene mutation is far from unreasonable, and that termination of pregnancy in the case of a female carrier foetus is not unjustified.^{6,8} The view that PGD is the only prenatal testing option that could be morally justified seems to be too restrictive.

Thirdly, there are late-onset, untreatable, multifactorial disorders. An interesting, though still hypothetical, case would be PD of the susceptibility for the common type of Alzheimer's disease (AD). While most of us would consider prenatal testing for this susceptibility to be rather bizarre, Steinbock claims – but does not convincingly argue – that procreative freedom includes the right (apparently: an unqualified right) to have *all* the information prospective parents deem relevant for deciding about termination of

pregnancy.⁹ As a consequence, she fails to present a proper balance between procreative autonomy on the one hand and professional responsibility on the other. To argue that doctors should ultimately comply even with bizarre requests for PD effectively makes a mockery of medical ethics.

Beyond the medical model?

There is an ongoing debate about the question of whether the medical model is too restrictive. The alternative model, which would allow, at least in some cases, selection of embryos/foetuses for traits which are not relevant for the health of the future child concerned, is usually called the 'designer' model – a rather misleading term. Three cases presented at the symposium are examples of this non-medical type of selection, and illustrate the hybrid character of the alternative model.

PGD/ HLA typing

For the ethical analysis, it is important to distinguish between three questions, the first two being preliminary.^{6,10} First, can it be morally justified to use a child as a source of a transplant, and if so, under what conditions? Clearly, it will be crucial to evaluate the risk for the donor. The example of donating umbilical cord blood for the treatment of a child suffering from Fanconi anaemia (FA) is the 'simple' case, as this procedure does not entail any medical risk for the donor child at all (a premature or very low birth-weight baby may be the exception to the rule). Secondly, is it ethically justified to conceive a child (partly) in order to obtain a transplant? Critics object that this would amount to treating the child as a means to an end. Kant's famous prescription, however, is against using people *solely* as a means. What matters, then, is whether the parents will value the child only as a transplant source or whether they will also love this child for itself.¹¹

What, then, about the third question: can it be morally justified to perform PGD to (prevent the conception of an affected child and simultaneously) select an HLA-matched embryo for transfer? A first, practical issue concerns the 'take home baby rate' (THBR). In most cases, a combination test will be required to select healthy, HLA-matched embryos. As a consequence, the numbers of embryos available for transfer and the THBR will decrease substantially. The fundamental ethical issue concerns the testing and selection of embryos for the required HLA type. On the one hand, this selection does not fit into the medical model for pre-implantation selection, as the HLA type is not relevant for the health of the prospective child itself. On the other hand, the aim of the procedure is clearly health-related, as it serves a vital health interest of a sibling. Critics may argue that even though this aim is not trivial, to allow exceptions to the medical model creates a slippery slope ultimately leading to the selection of embryos for whatever non-medical traits prospective parents prefer (athletic genotypes, etc.). The slippery slope argument, however, is questionable as it can be reasonably argued that the current case is a special one in view of its intermediate character (the parents are not designing a child) and should be evaluated on its own merits. One could object, finally, that 'mismatched' pre-implantation embryos will be destroyed. This objection, however, is rather weak given both the low moral status of pre-implantation embryos and the life-saving aim of the procedure.

It has not been convincingly argued that PGD/ HLA typing is necessarily morally wrong. The banning of this procedure in the Netherlands is therefore problematic. At the same time, the risks involved should be taken seriously. Parents may feel pressurized to opt for PGD while they cannot afford any more children, the affected child may die before the birth of the HLA-matched donor, and the transfusion may not save the child. Evaluating the risks and uncertainties on a case-by-case basis and providing adequate counselling are crucial prerequisites for PGD/ HLA typing. Clearly, it would be misleading and even dangerous to present this procedure as an easy way out of the parents' dilemma.

Questions for further debate include the issue of PGD/ HLA typing in order to save a child suffering from a non-hereditary and/or a non-lethal disorder. And what about PGD/ HLA typing in order to obtain non-regenerating tissues/organs? In any event, the 'slippery slope' argument – 'PGD/ HLA typing in order to obtain matched cord blood stem cells is unjustified because it results in and/or morally justifies the abhorrent practice of extirpating a kidney from live-born babies' – is invalid.

PGD: sex selection for family balancing

Sex selection for non-medical, psychosocial reasons is controversial.¹² *Deontological* objections include the claim that this type of sex selection is inherently sexist, and that it is at odds with both the goals of medicine/the task of the doctor and (in the case of post-fertilization sex selection) the moral status of the embryo/foetus. *Consequentialist* objections include the argument that sex selection for non-medical reasons may result in a disturbance of the sex ratio, that it will discredit PGD as a whole, that it may set a precedent for positive eugenics, and the firstborn argument. There is considerable disagreement, however, about the validity and implications of these objections.

Making an abstraction, for the moment, of the specific method used for sex selection, there seems to be growing support for allowing sex selection for family balancing. Family balancing seems to circumvent (or at least to weaken) some of the objections to sex selection for non-medical reasons, namely the firstborn argument, the possibility of a skewed sex ratio and the presumed sexism.

With regard to sex selection in the context of IVF/PGD, various cases can be distinguished; for example:

- A the patient learns the sex of embryos as part of or as a by-product of IVF/PGD carried out for medical reasons;
- B the patient requests IVF and PGD solely for the purpose of sex selection for family balancing.

The international debate concentrates on case B. Many countries, including the Netherlands, prohibit this procedure – but what about the ethics? Let me briefly comment on the major moral objections:

- 'This practice would be disproportionately burdensome and risky for women'. This objection smacks of unjustified paternalism¹³;
- 'This practice conflicts with the moral status of the embryo'. This objection is debatable in view of both the relatively low moral status of pre-implantation embryos

- and societal acceptance of the use of intra-uterine devices;
- ‘This practice is at odds with the goals of medicine’. One may argue that this objection reveals a questionable ‘medical essentialism’. After all, doctors regularly offer medical solutions for non-medical problems. Clearly, the issue at hand is not whether physicians should (be obliged to) offer this procedure, but whether they are free to do so. The current objection may be symptomatic of an uneasiness about the risks of making exceptions to the medical model (cf. the next objection). In that case, it is a disguised consequentialist objection;
 - ‘This practice sets a precedent for positive eugenics/enhancement, i.e. the generation of designer babies’. Sex selection for balancing is not itself a form of enhancement. The validity of this slippery slope argument is questionable. One may for instance reasonably argue that the selective generation of children with enhanced capacities would raise completely different moral questions, both from the perspective of the child and from a societal point of view.
 - ‘This practice could discredit PGD as a whole’. The fear that people who need PGD for medical reasons could be indirectly harmed by a backlash against PGD is neither ill-founded nor irrelevant.

Clearly, a further debate is needed about the validity of the cons regarding case B. In any event, the categorical legal prohibition of this procedure seems to be a premature position.

It is important to discern questions regarding the acceptability of PGD for family balancing on the one hand and the question ‘Who should pay?’ on the other. Undoubtedly, *if* IVF/PGD for family balancing were to be allowed in the future, it should not be reimbursed. Furthermore, medical indications for IVF/PGD should have priority over non-medical reasons. It would be unacceptable if IVF/PGD centres were to become overloaded by performing IVF/PGD for family balancing and had to postpone clients with a medical indication for PGD.¹⁴

In the future, there may be regular requests for sex selection in the context of pre-implantation screening for aneuploidy. For this reason, a discussion about case A above is especially relevant. The Ethics Committee of the American Society for Reproductive Medicine (ASRM) considers case A to be the simple case, as it is free of the problems of fairness in the allocation of scarce resources and appropriateness to the practice of medicine.¹⁵ The Health Council of the Netherlands takes a similar view.¹⁶ Case A, however, may not be that simple.¹⁷ A first question is whether sex selection should be restricted to family balancing (as in case B). Furthermore, if doctors take the (Health Council’s) principle ‘that doctors should not perform any additional actions for the purpose of sex selection’ seriously, there is little room left for sex selection, since doctors should then give priority to embryological criteria in deciding which embryo(s) to transfer. Clearly, starting a new IVF treatment while there are still embryos of the non-preferred sex available for transfer would blur the distinction between case A and case B. Modifying the transfer policy for family balancing would raise problems of fairness in the context of case A as well.

Prenatal testing for normal characteristics

This category is rather heterogeneous as it includes, apart from HLA typing and sex selection for non-medical reasons, the ‘dysgenic’ selection of embryos/foetuses for disabilities (e.g. non-syndromal deafness), positive eugenic selection (e.g. athletic genotypes), and testing for normal behavioural traits (e.g. IQ, sexual orientation, and anti-social behaviour). I will concentrate on a single case belonging to the latter sub-category: PD/PGD for sexual orientation (SO). While there are presently no genetic susceptibility tests for SO, in the future such tests may become available. Therefore, a proactive ethical reflection is needed. Assuming for the moment that genetic research into SO is justified, at least the following issues require ethical scrutiny:

a. Selective abortion because of SO?

The Nuffield Council on Bioethics takes the view that abortion merely on the basis of information about behavioural traits in the normal range is morally unacceptable.¹⁸ Should we really *categorically* reject selective abortion because of SO, irrespective of the cultural context, the specific motive of the prospective parents, and the penetrance of the predisposition? Let us assume that a test with reasonable predictive value were to be developed. Clearly, a homophobic motive for PD would be problematic. But take the case of prospective parents who live in a homophobic society, and who want to protect their future child from harm. Critics may object:

- that selective abortion can only be justified on the basis of the impact of future disease/disabilities on the child’s quality of life;
- that abortion because of SO would reinforce and perpetuate prejudices and discrimination against gays and lesbians.¹⁹

With regard to the first objection one may argue that, from the future child’s perspective, it makes little difference whether his/her quality of life is diminished by prejudices and discrimination or by a disability/disorder.²⁰ The second objection illustrates the potential clash between a micro-ethical and a socio-ethical perspective. Which perspective should prevail? How should the potential conflict be handled between one’s responsibility as a prospective parent to promote the best interests of your future child and one’s responsibility as a citizen to fight societal prejudices? Clearly, this moral conflict may resemble the conflict inherent in preventing the conception/birth of daughters ‘in their own interests’ in sexist cultures. Another issue would be the use of PD in order to select a gay/lesbian child.

b. What about PD ‘just for reassurance’?

PD as such is not morally indifferent, as it could harm a future child carrying a susceptibility gene for same-sex preference and violate its right not to know.

c. Is PGD really different?

According to the Nuffield Council, ‘the issues raised by the use of PGD are different. (...) Hence, the moral prohibitions which apply in the case of PD, do not apply in the same way in the use of PGD.’ The Council concludes that it might turn out

that there are possibilities for 'modest applications' of PGD in relation to behavioural traits in the normal range. Well, even if one accepts (as I do), that pre-implantation embryos and fetuses have a (somewhat) different moral status, it does not necessarily follow that selecting for behavioural traits is categorically unjustified in the context of PD but may be justified in the context of PGD. After all, it is not just the status of the embryo/foetus that matters morally.

A final question concerns (the implications of) potential future environmental modifications aimed at controlling the development of SO. Suppose, for the sake of argument, that parents could prevent the development of same-sex preference by promoting the practice of specific hobbies and/or by minimising the exposure of their children to specific kinds of music/odours. Should we blame parents who take preventive steps because they want to maximise their children's chance of leading a happy life? If not, what, from a moral point of view, are the relevant differences between environmental and medical/genetic preventive strategies?

Conclusions

PD/selective abortion and PGD/selective embryo transfer are controversial and ethically complex practices, partly because of their dynamics. The view that applications that can be subsumed under the medical model are always justified, whereas any selection on the basis of non-medical traits is necessarily wrong, demonstrates a misleading simplicity. Applications which go beyond the medical model are, from an ethical point of view, rather diverse, and should each be evaluated on their own merits, taking into account the interests and motives of the prospective parents, the interests of the future child and existing siblings, and the potential societal consequences. An ethical framework for applied behavioural genetics is urgently needed.

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Ethical dilemmas in prenatal testing

New developments in science and technology are morally relevant not only because of their effects on the human predicament but also because they imply an increase of power and therefore of responsibility. That is certainly true in the field of prenatal testing, especially where IVF, genomics and gene technology are combined. We are confronted with an increase in the power to influence human life from the very beginning, and with ethical dilemmas in the wake of that power.

Four of these ethical issues are:

- Prenatal testing for diseases that reveal themselves not before an individual is grown up;
- Prenatal testing for risk factors of diseases in adulthood (e.g. breast cancer);
- Prenatal testing in order to create a child as a donor for a living sick child;
- Prenatal testing for qualities like criminal behaviour and homosexuality.

I could add a fifth, closely related, issue, which is discussed in the first study of the Centre for Ethics and Health¹, namely prenatal testing with a view to enhancement, under the title 'Man in the making'.

As far as I can see, these dilemmas are not mere incidents, but signs that we have entered a new era, where we have the human embryo in our hands, as it were, and where we can manipulate human life from its very beginning. The question is not whether this ought to be the case or not, for it is the case. The question is how to cope with it in a responsible way.

In order to find an answer to this question we need at the very least a framework to assess the ethical dilemmas mentioned above. In 2002 the Dutch Parliament asked for an integral framework for ethical and social assessment of developments in biotechnology. The Commission on Genetic Modification (COGEM) has been given the task of doing the preparatory work. In a recent discussion paper² the COGEM proposed a step-by-step design in order to tackle ethical dilemmas in biotechnology. As it may become a trend-setting model for organizing the discussion in the Netherlands in the near future, I want to take it as a structuring principle for the main part of this paper. As it is more or less process-oriented, I will combine it with two other designs that are more case-oriented, one developed by the Centre for Bioethics and Health Law (CBG) at Utrecht University, and the other by the Commission for Animal Biotechnology (CBD). In combination, these designs offer at least a formal possibility of getting a grip on the ethical dilemmas mentioned above.

The COGEM design is a 'gate and balance model'. What this means will be made clear in the course of this paper. Mapping the problem area and creating the conditions for a fair discussion is the first step. This is the phase of problem definition, involving the drawing up of an inventory not only of scientific and technical details, but also of opinions and arguments, for and against, in society. To underline the importance of this first step in applied ethics, every CBD advisory report devotes one chapter to mapping out the problem. The CBG design asks four questions in order to define the ethical dilemma: (1) What is the moral question (in this case)? (2) Which possibilities for action are open at first sight? (3) Which factual information is lacking? (4) Who is involved in this moral issue? This last question is important because it tries to clarify what interests are at stake in a given case.

The second step is 'the gate'. It is the investigation into whether borderline values (i.e. values that are absolutely not to be violated) are violated, for instance scientific quality, safety regulations, (national or international) law, human rights, the precautionary principle, and so on. If the answer to this investigation is affirmative, the 'gate' will be closed and there will be no further treatment of the case. A check is also carried out as to whether the case has already been subjected to a comparable ethical assessment. If so, the procedure can be discontinued to avoid duplication. In the CBG design two questions are relevant in the context of this and the following steps: (1) Which arguments are relevant for answering the moral question? (2) What is the importance of these arguments for this case? In the CBD procedure, the questions as to whether the aim of the project is of substantial interest, and whether there are alternative ways of achieving the same aim, fulfil this role of 'gateway' to the rest of the procedure. It is interesting to note that this latter question about possible alternatives is absent in the COGEM design.

The next two steps in the COGEM design are the attempts to describe pros and cons, respectively, in terms of (other) values that could be violated and aims that may be attained. In order to facilitate this analysis a checklist of about 35 values and aims is offered, not merely to enable a 'yes' or 'no' answer to be given, but to create an opportunity for comments on the content and context of these values and aims in the case at hand. This checklist is not intended to be complete; on the contrary, it is recommended that as many (relevant E.S.) values and aims as possible be considered. There is also a questionnaire focusing on the usefulness and risks of specific projects. These two steps come close to the procedure of the CBD, where questions like 'Is the aim substantially to overcome the 'no, unless' criterion of animal biotechnology?', and 'What are the effects on animal health and welfare and on animal integrity?' are vitally important. These two steps come down to the questions 'What is (the value of) the aim?' and 'What is the price to be paid?' That is why I think that steps three and four in the COGEM design should change places.

The fifth and final step is weighing the pros and cons, resulting in various options for action. The proportionality principle plays an important role in this phase of the procedure. In the CBG design, this step is divided into three questions: (1) What is the importance of the arguments for and against for this case? (2) Which possible action is preferable in view of the weighing of the arguments? (3) Which actual steps

follow from it? According to the COGEM, decisions should be taken by the institutions with political responsibility. These decisions may contribute to jurisprudence and to the formulation of future borderline values in the sense of step two. In other words, the COGEM rightly underlines the dynamic character of its assessment framework and the importance of increasing the insight into social and ethical matters.

In short, the COGEM framework for the assessment of ethical and social problems comes down to (1) mapping out the (moral) problem; (2) asking whether borderline values are violated; (3) describing the values at stake; (4) describing the aims; and (5) weighing the pros and cons in order to come to a conclusion. This framework creates the necessary conditions for the handling of ethical dilemmas (in a biomedical context).

However, creating a procedure to cope with ethical dilemmas is not the same as creating a solution for them. This does not mean, of course, that I wish to deny the importance of a framework for assessment. On the contrary, having agreed to that, much work remains to be done. In view of (1) moral, philosophical and religious pluralism in society, resulting in (2) the lack of a shared morality, (3) the variety of interests involved in science and technology, resulting in (4) a variety of priorities and policies, each step in the framework brings its own difficulties. This is not intended to instil a pessimistic attitude, but rather, a realistic one: bioethical dilemmas are complex.

Take one of the cases presented earlier: prenatal testing for hereditary breast cancer. Mapping the moral problem depends on whether this is a scientific or technical problem (for instance as regards the predictive value of the test), a policy problem (should we do it in this hospital?), a patient-oriented problem (should we tell the results although we have nothing to offer in terms of a therapy?), a medical philosophy problem (should this sort of testing still be seen as medicine?), a so-called 'meta-question' (do we want this sort of testing and why (not)?) or a combination of these questions. A general adage in this context is the Latin saying 'Qui bene distinguet bene docet' (roughly: 'A good ethicist is (s)he who makes the right distinctions'), which means that at the least we should pinpoint what it is that we are talking about.

Suppose, however, that we know what we are talking about and that the moral problem is clear. We could then go on to the next step and try to find out whether borderline values are being violated. That the patient's autonomy should be respected in this case of testing for breast cancer seems to be clear, but what about the moral status of the human embryo? Is abortion an option? The question marks here suggest a possible difference between public and private morality. In Dutch public morality, abortion is morally acceptable under certain conditions, but individuals (patients and physicians) may not agree to it and may be opposed in principle. In Ireland, for example, it may be the other way around, illustrating the rather odd phenomenon from a moral point of view that borderline values (and thus morality) may differ geographically. But apart from this phenomenon, what I want to say here is that, in a medical setting, we are not only confronted with (borderline values in) law, EU regulations and public morality, but also with a variety of borderline values of individuals (as well as church-

es and other NGOs). This means that for some people the 'gate' will be closed, but not for others. Respecting the patient's autonomy then means that a patient's refusal to cross a borderline value will also be respected, and rightly so. In that case many other questions will arise: is an alternative option available and acceptable (for instance, if the woman in question is not already pregnant, PID and embryo selection)? If not, why should we offer the possibility of genetic testing? What is the value (!) of telling the truth? Does it contribute to 'the good life'? What about the right not to know? It goes without saying that in these cases the intake discussion is of paramount importance.

In this position paper, I do not want to elaborate further on the complexity issue. I think I have made my point, namely that structuring ethical dilemmas using an assessment framework is important but not enough. From a moral point of view, it represents only the starting point of the discussions that take place when the various steps are taken that are outlined in the framework. The final point I want to make here is that applied ethics is necessarily a multidisciplinary issue, which means that ethics not only cannot do without scientific and technological information, but also has to listen to it carefully. In more ethical terms, applied ethics cannot work without so-called morally relevant facts. In the case of testing for breast cancer, for instance, this disease only becomes manifest later on in life, which means that a child can live for decades before it will fall ill.

Here, however, I want to give another example of the moral relevance of new developments in science and technology, namely the far-reaching relevance of IVF and cryopreservation for the discussion about the moral status of the embryo. This discussion has been (and still is) dominated by the traditional position that has developed over millennia in the context of the problem of abortion. This position can be phrased in the words of Tertullian (2nd Century): 'homo est et qui est futurus', meaning: 'a future human being (i.e. a human embryo or foetus) is (to be treated as) a human being as well'. However, this traditional position presupposes that an embryo is an embryo in the womb. But nowadays, thanks to IVF technology and cryopreservation, we have to face the fact that there are embryos not only in the womb but in vitro and in the freezer as well. They cannot be considered as future human beings unless they are transferred into a womb and nidation has taken place. In other words, these embryos are potential human beings but the potentiality to become (perhaps) an actual human being depends on external factors; theirs is therefore only partly an inherent potentiality. This means that, through IVF technology, we are obliged to make a distinction between two categories of embryos: (1) embryos in the womb that are human beings-to-be and (2) embryos that are not, unless some external conditions are fulfilled. It is an open question whether these two categories of embryos have the same moral status. As far as I can see they do not. It is precisely because of these examples of morally relevant facts, created by developments in science and technology, that applied ethics is necessarily a multidisciplinary endeavour.

To conclude, ethics is about three 'A's: Articulating, Analysing and Arguing in morality. In this sense it reflects on morality in a systematic way. In this context I like to use a Platonic metaphor for philosophy, namely that of a midwife. A midwife does

not give birth herself to a child but helps another woman to do this. Likewise, ethics does not create or invent morality but helps us to find, to clarify and to apply morality (principles, norms, and values) which is, sometimes in a hidden form, already present in our society, or in a profession such as the medical profession. Moral problems will always be present as long as there are new developments in science and technology. That is why technology (as applied science) and ethics should be married forever.

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Programme 18 June 2003

- 10:00** Registration and coffee
Chair: Prof. J.H. Koeman, chairman of the Science and Ethics Committee of the Royal Netherlands Academy of Arts and Sciences
- 10:30** Opening remarks
Prof. J.H. Koeman
- 10:35** Introductory lecture 'Prenatal diagnosis and medical genetics – past and future'
Prof. M. Bobrow, head of the Department Medical Genetics, University of Cambridge, United Kingdom
- 11:15** Presentation of case I 'Prenatal testing for hereditary breast cancer?'
Prof. N.J. Leschot, head of the Department Clinical Genetics, Academic Medical Centre Amsterdam, the Netherlands
- 11:25** Reactions and discussions of an expert panel followed by a general discussion with the audience
- 12:00** Presentation of case II 'Embryo selection and transplantation'
Prof. J.P.M. Geraedts, head of the department Clinical Genetics, Academic hospital Maastricht, the Netherlands
- 12:10** Reactions and discussions of an expert panel followed by a general discussion with the audience
- 12:45** Lunch
Chair: Prof. N.J. Leschot
- 13:45** Presentation of case III 'Sex selection and family balancing'
Prof. J.P.M. Geraedts
- 13:55** Reactions and discussions of an expert panel followed by a general discussion with the audience
- 14:30** Lecture 'Prenatal testing for normal characteristics?'
Prof. Hans Galjaard, Department of Clinical Genetics, Erasmus Medical Centre, Rotterdam
- 14:50** Reactions and general discussion with the audience and the expert panel
- 15:15** Coffee
- 15:45** Lecture 'Ethical diversity and legislation'
Prof. A.A. McCall Smith, School of Law, University of Edinburgh, United Kingdom
- 16:25** Closing remarks
Prof. J.H. Koeman
- 16:45** Drinks

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