Pre-implantation genetic diagnosis

Gezondheidsraad
Health Council of the Netherlands

To the State Secretary of Health, Welfare and Sport
P.O. Box 20350
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Subject : Presentation of advisory report *Pre-implantation genetic diagnosis*
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Our reference : 1721/PB/IV/755-D
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Dear State Secretary,

In line with your request, as summarised in the request for advice dated 7 November 2003, I enclose an advisory report on the genetic diagnosis and screening of embryos produced by in vitro fertilisation, performed prior to implantation in the uterus. The report was compiled by a specially convened Health Council Committee and has been reviewed by the Standing Committee on Genetics and the Standing Committee on Health Ethics and Health Law.

The Committee regards pre-implantation genetic diagnosis as a viable alternative to invasive prenatal diagnostic testing for serious hereditary conditions.

The Committee regards the in vitro diagnostic testing of embryos with a view to ascertaining whether they carry serious hereditary conditions to be acceptable only if carriership constitutes a serious disadvantage.

In practice, life-threatening conditions occasionally occur, for which stem cell transplant is the only therapy, but no donor is available. The Committee recommends that, in such situations, the in vitro genetic testing of embryos should be permitted only under strict conditions with the aim of making the donation of umbilical cord blood stem cells possible.

The Committee regards pre-implantation genetic testing for non-medical characteristics as undesirable. The Committee indicates that the permissibility of such testing is not an exclusively medical question, but that when considering whether such testing should be permitted, the adverse aspects of in vitro fertilisation procedures should be taken into account.

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In certain circumstances, testing for a hereditary disease also yields information about an embryo's gender. In such circumstances, it is acceptable for a decision regarding which embryo to replace to be made in consultation between the treatment provider and prospective parents, provided that no additional procedures are required.

The inclusion of pre-implantation genetic screening as a standard element of the in vitro fertilisation process could increase the prospects of a successful treatment outcome. However, insufficient information is available regarding the effectiveness and safety of such screening. The Committee accordingly advises that only scientific research into the effect of such screening should be permitted for the time being.

I endorse the Committee's recommendations.

Yours sincerely,
(signed)
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to:

the State Secretary of Health, Welfare and Sport

No. 2006/01E, The Hague, January 18, 2006

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, Agriculture & Innovation, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

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Summary

Pre-implantation genetic diagnosis

Pre-implantation genetic diagnosis (PGD) is the examination *in vitro* of an embryo (or an egg cell prior to fertilisation) in order to exclude a genetic condition in case a very high risk of that condition is known. PGD can only be used in combination with *in vitro* fertilisation (IVF). If a genetic abnormality in the form of a monogenetic disease such as Huntington's disease or cystic fibrosis occurs in a family, then it is often possible to find out whether an embryo also has that abnormality. The same applies to structural chromosomal abnormalities, such as translocations, that are often associated with serious conditions.

PGD as an alternative to prenatal genetic diagnosis

Because PGD is carried out prior to pregnancy, it can be seen as an alternative to prenatal genetic diagnosis (PND), where the detection of abnormalities may result in an abortion being performed. But as IVF is an invasive procedure and PGD is generally associated with embryo selection, PGD should not be automatically preferred to PND. In the Netherlands, the indication consists of serious conditions for both diagnostic methods, while PGD is also carried out in the context of less serious diseases in some other countries.

The choice of method depends on individual preference and feasibility. With regard tot PGD in particular the feasibility of the IVF procedure and the technical

diagnostic options can restrict the choice. There is also a difference in the responsibility of healthcare professionals, who become involved in the creation of the child in the case of PGD (as this method is always associated with IVF).

The acceptability of various applications of PGD

The Health Council has, in previous advisory reports, discussed the *a priori* acceptability of PGD. This report concentrates on certain applications.

One of the questions dealt with in this report is about the acceptability of selection on the basis of an embryo being a carrier of a genetic condition. Being a carrier means that a future child is at greater risk of disease, although carriers themselves are not affected (or are affected to a lesser degree). Parents may request selection for carriership in cases where diagnosis for a serious condition has already been carried out and no additional investigations or treatments are necessary. There is little reason not to comply with the parents' wishes in this situation. Embryo selection in different situations is only acceptable if carriership presents serious problems. One example is carriership of Duchenne muscular dystrophy.

Another question relates to the situation where a parent runs a high risk of contracting a serious hereditary condition that becomes manifest later in life, but does not want to know whether he or she actually has that genetic abnormality. It is difficult to justify the use of methods where an individual's genetic status is determined, but not revealed to that individual. After all, healthcare professionals would then sometimes be called on to perform IVF knowing that there is no increase in the risk of producing a child with the abnormality in question. The Health Council's Committee on Preimplantation genetic diagnosis and screening, henceforth mentioned the Committee, regards as acceptable the use of methods whereby the parent's status is not determined, but where investigation focuses solely on finding out which grandparent passed on the relevant gene to the embryo. In both cases, it may be that IVF and PGD are carried out unnecessarily because the parent in question is not a carrier of the disease, and in both cases it can happen that healthy embryos are not used. The two cases differ in that in one case the doctors and laboratory staff know that the treatment and diagnosis are being carried out unnecessarily, while in the other case they do not know whether this is so.

Another question to be considered is whether it is responsible to carry out PGD in cases of hereditary conditions where not all individuals with the mutation contract the diseases, such as hereditary breast cancer and some forms of intestinal cancer. The answer to this question depends on the severity of the

condition, the therapeutic options and the likelihood of the condition becoming manifest early in life. Investigation of specific mutations sometimes allows this to be predicted. PGD can be acceptable in serious cases where no (or very invasive) treatment is available.

It is important for all the above-mentioned indications that the future course of events is discussed in detail with the prospective parents and, as is standard procedure with IVF, that this is confirmed in writing.

The scale of need for PGD is unknown

Little information is available as to the quantitative need for PGD in the Netherlands. In the Netherlands, the number of referrals is about 100 a year, but the need might be 300 or more patients a year. Factors affecting the number of PGD procedures include objection to induced abortion, knowledge of its availability among potential users, access (waiting lists, distance from hospitals and availability of diagnostic tests), the invasive nature of IVF procedures, and the likelihood of conception via IVF. Investigations into any parental preference between PND and PGD showed little difference, with at most a slight preference for PGD. But the fact that PND is much more common indicates that the availability of PGD is a limiting factor. Because of the uncertainty about the quantitative need, the Committee does not recommend designating a second centre for PGD in the Netherlands, but the Committee recommends keeping open the option of setting up a second centre in the future.

Pre-implantation genetic screening

Pre-implantation genetic screening (PGS) involves *in vitro* investigation of embryos to detect numerical chromosomal abnormalities (aneuploidies). Most numerical abnormalities are not compatible with life. Foetuses that are miscarried are often found to have an aneuploidy and this abnormality is also common in embryos created by means of IVF. Genetic testing is necessary to detect aneuploidy. Clinical research is currently being conducted to find out whether PGS can increase the likelihood of pregnancies resulting from each implanted embryo being carried to term (thus increasing the success rate of IVF) and whether this would more often allow one embryo to be implanted instead of two. This would reduce the chance of multiple pregnancy and the associated health risks to the children. The purpose of PGS is therefore both to increase the likelihood of conceiving a child as well as to reduce the likelihood of complications following IVF. PGS could also be an alternative to prenatal

screening for numerical abnormalities in women aged 36 or over who undergo IVF. At present, this diagnostic method is performed on a few hundred women who conceive following IVF. It seems likely that many would prefer *in vitro* selection.

Little useful research data is available on the effect, reliability and safety of PGS. Small-scale studies of cases of high maternal age, repeated implantation failure and repeated miscarriage do not point to any marked improvement in the likelihood of pregnancy. It also remains unclear whether determination of numerical abnormalities is an alternative to prenatal diagnosis. More data is needed before PGS can be carried out or offered as a matter of routine. If further research shows that PGS increases the chance of a healthy child from each IVF procedure that is started, then it is important to clearly establish the indications and to guarantee the quality and safety of the procedures followed.

The quantitative need for PGS is known only partially. The potential need for PGS as a way of improving the success rate of IVF and/or reducing the chance of multiple pregnancies following IVF is high, as many thousands of women are treated for fertility problems every year. It is estimated that at least a few hundred of these women would prefer PGS to prenatal diagnosis.

Embryo selection for reasons other than PGD or PGS

This advisory report also looks at selection based on the HLA system and selection for non-medical reasons, though these types of selection do not fall within the above-described aims of PGD.

The question of selecting a future child on the basis of its HLA system can arise if a child already born to the couple has a life-threatening condition that needs stem cell therapy, but no suitable donor is available. Stem cells are rejected if the HLA systems of the donor and recipient are too different from one another. The required stem cells can be obtained from the navel cord blood of a brother or sister with a matching HLA system. The conditions for which this treatment is carried out include certain forms of leukemia and hereditary anemia that are associated with a severely diminished life expectancy if a transplant is not performed. This embryo selection may be an instrumental use of the child, but the child can also be a welcome and wanted child, irrespective of the reason for which he or she was created. In the latter case, the life-threatening nature of the disease can justify HLA typing. Careful counselling is vital, first with regard to the intention and the capability of parents to take care and to foster the child, but also because there are practical limitations. On average, only one in four embryos is suitable. The success rate of IVF procedures is another limiting

factor. The question of whether the condition is hereditary and whether IVF and PGD have already been carried out for that reason is not of critical importance. Opting for an IVF procedure in the case of a non-hereditary condition can be acceptable in view of the interests of the sick child. Selection then has an indirect medical reason; curing the previously born child. Furthermore, in view of the practical limitations and for other reasons, it is also desirable to encourage the availability of stem cells from non-related donors.

The literature does not only report medical reasons for carrying out *in vitro* genetic research on embryos. Parents might be able in the future to choose from a wide variety of characteristics that they want their children to have. Although the applications discussed above are all carried out with a view to reducing suffering from disease, these choices would be directed at a particular desirable characteristic or ability (for example, muscle strength or gender). Some people take the view that such choices result in a less 'open future' and may be experienced as damaging by the child. The embryos' right to protection and the invasive nature of IVF procedures are also reasons for objection to selection. Furthermore, sex determination with no medical indication may also amount to discrimination. Other people offer parental autonomy as a counter-argument, believing that their freedom of choice should carry greater weight. The Committee does not assess the aforementioned arguments in this advisory report, but it is of the opinion that the invasive nature of IVF procedures is an important argument for restricting pre-implantation investigation to the indications referred to above. The Committee notes with this that the debate on embryo selection for non-medical reasons reaches beyond the boundaries of healthcare. A special situation arises when the sex is known as a result of the PGD or PGS procedure (which was carried out for a medical reason) and a choice is possible without further interventions being required. In 1995 the Health Council issued a report stating that there was little objection in that situation to respecting the parents' wishes. The Committee also now has no weighty objections against this, provided that indeed no further interventions are carried out (no additional diagnostics or IVF cyclus).

Legislation and regulations

The legislation and regulation of genetic testing of embryos vary considerably from country to country. Some countries have no rules, others prohibit such action, and some countries impose certain conditions on PGD and PGS. Some countries prohibit these procedures while permitting abortion, while others

prohibit abortion but allow PGD. HLA typing with a view to stem cell transplantation is permitted in some countries.

PGD can be carried out in the Netherlands at Maastricht University Hospital. HLA typing with a view to stem cell transplantation is prohibited, but the Committee is of the opinion that it should be acceptable under the conditions discussed above. Regulations (the planning decree) should provide an opportunity for this. The term PGS refers to screening, but the procedure is not strictly speaking screening in the sense of the Population Screening Act as it is not carried out on people and as, when performed as a result of impaired fertility, it is performed in the context of a medical complaint. Scientific investigation of embryos with a view to improving treatments for impaired fertility is permitted under the Embryo Act. The Central Committee on Research involving Human Subjects (CCMO) has issued permits for PGS trial protocols to four centres.

Chapter 1

Introduction

1.1 The development of pre-implantation genetic diagnosis

In vitro fertilisation (IVF) is used to increase the likelihood of pregnancy in cases of impaired fertility. Soon after the procedure's viability was clinically demonstrated, people began to point out that IVF could also enable the testing of embryos for genetic abnormalities prior to their transfer to the uterus. That would require the development of ways of performing diagnostic tests on very small quantities of cell material (Ser04). Much of the pressure to develop such tests came from the parents of children with serious hereditary diseases, who were reluctant to accept the *abortus provocatus* risk associated with prenatal diagnostic testing. The first instance of such testing was in 1990, when embryos were gender-tested and selected in vitro in order to exclude the possibility of serious X-chromosomal conditions (adrenoleukodystrophy and X-linked mental retardation; Han90). Since then, many hundreds of pre-implantation diagnostic tests for hereditary diseases and chromosome abnormalities have been performed on embryos around the world (Ger01, Ver02, ESH02; see also Table 1 in 2.1).

The two main pre-implantation genetic diagnosis (PGD) techniques are fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR). The former is used almost exclusively to detect chromosome abnormalities, and the latter to detect DNA-level mutations.

Chromosome abnormalities may be structural, as with translocations, which involve segments of different chromosomes being interchanged. Alternatively,

the abnormalities may be numerical, in other words, involving the presence of an abnormal number of chromosomes. Such abnormalities frequently lead to miscarriages and are believed to influence the likelihood of an IVF procedure being successful. Numerical abnormalities can be detected using FISH, which enables up to ten chromosomes to be viewed in one cell. The possibility of making all chromosomes readily visible by means of so-called comparative genomic hybridization (CGH) or using a PCR panel is currently being investigated. Which chromosomes can be examined for numerical abnormalities using FISH depends on the estimated prevalence of those abnormalities and on the technical possibilities. Where structural abnormalities are concerned, it is necessary to know what chromosome abnormality to look for. Testing for DNA mutations is always preceded by family research. The diagnostic test methods for detecting mutations that have been thoroughly described in the scientific literature, such as those frequently associated with cystic fibrosis (CF), have been defined in detail. However, methods for the detection of some rare mutations still need to be developed and tested before PGD can be used.

1.2 Terminology: diagnostic testing and screening

If someone has health problems, and a test is performed to ascertain whether he or she has a particular disease, one speaks of diagnostic testing. If the same test is made available to everyone, or to everyone in a particular population group, without the people concerned seeking medical assistance, that is usually referred to as screening. Depending on the type of condition tested for and the nature of the test, a licence may be required under Population Screening Act 1992 (WBO). In practice, however, the term ‘screening’ is not restricted to screening as defined in the WBO, but is also applied to any large-scale test programme.

If, at the request of the parents, a pre-implantation test is performed on an embryo to ascertain whether the embryo is affected by a genetic condition that is known to be present in the family, the procedure may be regarded as testing in connection with a health problem. The test may therefore be described as a form of diagnosis: pre-implantation genetic diagnosis. Such testing may relate to a monogenetic Mendelian inherited disease (caused primarily by a mutation in a particular gene) or to structural abnormalities in the chromosomes. Diagnostic testing is PGD in its narrowest sense.

The situation is more complex if it is not clear whether there is any elevated risk of a genetic abnormality. In an IVF process, more embryos are usually created than are transferred to the uterus. From those embryos, a selection is made on the basis of morphological criteria, with a view to transferring those that

are thought most likely to lead to pregnancy and birth. There is reason to believe that testing for numerical chromosome abnormalities (aneuploidies) may increase the prospect of a successful outcome (see Section 3). Furthermore, better embryo selection would make single-embryo transfer viable in more cases. Such testing is sometimes described as 'pre-implantation genetic screening' (PGS). The term 'screening' is used in this context because the procedure is performed without any prior indication that there is an elevated risk of a particular abnormality. However, if one considers impaired fertility to be a health problem *and* to be indicative of the potential presence of an aneuploidy, testing for the abnormality is not strictly screening, but a diagnostic procedure inherent to good medical care.

In the USA, the term PGD is applied to both types of testing (Asr01). In the UK, both terms are used. The European Society of Human Reproduction and Embryology (ESHRE) uses the terms PGD and PGD-AS, where AS stands for aneuploidy screening (ESH02), and has recently also adopted the term PGS (ESH05b). In the Planning Decree on Clinical Genetic Testing and Heredity Counselling, the terms PGD and PGS are both used. In the latter context, PGD refers to testing in the case of an individual at elevated risk of having a child with a serious genetic condition or disease; PGS is the routine examination of embryos ahead of transfer (Pla03). The latter distinction is applied in the context of the report now before you.

As well as the qualitative distinction between PGD and PGS, there is also a quantitative distinction. Internationally, PGS is more commonplace than PGD. In the USA, thousands of pre-implantation tests are performed every year, an estimated three quarters of them for aneuploidies (Kul02, Ver04). In the Netherlands, PGD tests are performed between fifty and a hundred times a year; while PGS takes place only in the context of scientific research. There are about 14,000 IVF cycles performed a year, with one in every sixty-one children now being the product of IVF (Kre02). Consequently, the number of PGS procedures is potentially far higher than the number of PGD procedures.

In this report, testing to determine the genetic characteristics of embryos in vitro for reasons other than those described above, which does not qualify as diagnostic testing or screening, is referred to as pre-implantation genetic testing.

1.3 Issue addressed

Recent developments could lead to significant qualitative and quantitative changes in the use of PGD and PGS. The State Secretary of Health, Welfare and Sport asked the Health Council to report on the possible applications of such

procedures (Annex A). The Committee has accordingly deliberated on the following issues and problems:

1 Medical science is identifying the DNA mutations associated with an increasing number of conditions. The identification of pathogenic mutations, combined with the development of reliable and sensitive detection methods, is leading to increasing demand for PGD. Under the Planning Decree, diagnostic testing for such conditions may be carried out only at one particular designated centre (Maastricht University Medical Center; Pla03). In due course, a second centre may be designated. It is not clear how quickly the demand for PGD will develop, and whether it is necessary to designate a second centre.
2 In other countries, PGD is indicated for less serious conditions. That brings the criteria applied in the Netherlands – and the consistency of those criteria with those applied in the context of prenatal diagnostic testing – into question.
3 Another pertinent question is what to do about the potential for detecting recessive hereditary disease carriership. The carrier of such a disease does not normally develop the disease him/herself. Is it ethical, therefore, to select non-carrier embryos for transfer ahead of otherwise identical carriers, on the basis of diagnostic testing?
4 If there is a risk of a serious hereditary disease that does not manifest itself until later in life, prospective parents may wish PGD to be undertaken, but not to be told whether they themselves are liable to develop the disease. There is debate regarding the acceptability of methods that might make this possible.
5 In some countries, pre-implantation genetic testing is allowed for the purpose of determining embryonic HLA type, thus enabling in vitro selection of embryos that may eventually provide a source of umbilical cord blood for the donation of stem cells. This gives rise to the question: are the interests of the sick child sufficiently great to justify the use of IVF and selection on the basis of HLA type, both in circumstances involving a hereditary disease where the birth of a second child with the same disease can be avoided by the use of PGD, and in circumstances where it cannot.
6 In the international literature, there has been debate regarding selection on the basis of gender or on other non-medical grounds. One topical aspect of that debate is the acceptability of including additional selection criteria in circumstances where PGD is medically indicated or IVF performed due to impaired fertility.

7 In the Netherlands, PGD for a serious potential condition is relatively uncommon. Influential factors in that regard include the prospects of IVF being successful and the adverse aspects of the IVF procedure. Whether demand is likely to increase therefore depends partly on developments in the field of IVF. PGS is one such development. Numerical chromosome abnormalities are quite common in embryos. Selection for embryos with the correct number of chromosomes might increase the chances of IVF being successful. If so, the demand for PGD could well increase. However, it is not clear whether and, if so, to what extent there is likely to be a positive influence on IVF outcomes.

8 The use of PGS may serve various purposes. First, it may influence the likelihood of having a child. If it boosts the probability of pregnancy, it may also mean that multiple embryo transfer is not necessary in as many cases. That would be desirable insofar as multiple pregnancies more commonly involve health problems for mother and child. Furthermore, for women undergoing IVF, PGS may serve as an alternative to prenatal screening for trisomy.

9 It is vital to know how reliable and safe the PGS technique associated with each of the above-mentioned applications is.

10 In the literature, a great deal of attention is devoted to the ethical and legal aspects of PGD and PGS. The ethical discussions concerning PGD tend to centre on the indications for which this form of diagnostic testing may be considered acceptable. Where PGS is concerned, one of the key issues is whether any ethical distinction should be made between the in vitro selection of embryos on the basis of genetic characteristics and selection on the basis of morphological criteria. From a legal perspective, it is important to decide whether PGS falls within the scope of the Population Screening Act (WBO).

1.4 Methodology of the Committee

Current scientific knowledge and thinking in this field and the questions raised by the State Secretary of Health, Welfare and Sport were discussed by the Committee that compiled the report now before you. The Committee included experts active in various fields of science and health care relevant to PGD and PGS. The members of the Committee are listed in Annex B. The Committee consulted scientific literature on PGD and PGS via PubMed and scientific journals (see Literature). This advisory report has been reviewed by the Standing Committee on Genetics and the Standing Committee on Health Ethics and Health Law. In the preparatory phase, Ms. A. Knaapen contributed to the

compilation of the report during her internship at the Department of Scientific Dynamics at the University of Amsterdam.

Chapter 2

Pre-implantation genetic diagnosis

This Section deals with the technique of PGD and its application in connection with monogenetic conditions and chromosomal translocations (2.1), and contains an analysis of the ethical issues associated with various applications (2.2).

The quantitative demand for PGD and the possible expansion of capacity to two centres in the Netherlands are discussed in 2.3.

2.1 Monogenetic conditions and chromosomal translocations

This Section provides a summary of the PGD technique, which is considered in more detail in Annex C. The information leaflet published by the Maastricht University Medical Center is appended (Annex D). Before PGD can take place, an ovum has to be fertilised by an in vitro procedure. The IVF procedure is preceded by hormone stimulation and surgical puncture for the purpose of ovum collection. Thereafter, a sperm cell has to be introduced to the ovum. In the context of PGD on the basis of polymerase chain reaction (PCR), introduction is by means of intracytoplasmic sperm injection (ICSI), in order to minimise the risk of diagnostic errors caused by the presence of sperm cells clinging to the ovum. The success rate in IVF is relatively low (20 to 25 per cent per initiated cycle) and the procedure has adverse implications for the woman concerned. When the embryo is at the 6 to 10-cell stage, one or two cells are removed for biopsy. This very small quantity of cellular material quickly undergoes genetic diagnosis involving one of several methods, such as PCR and FISH. If this

analysis indicates that the embryo possesses the relevant genetic characteristics, and if the morphological characteristics are also positive, the embryo is transferred to the uterus in the hope that it will implant and that pregnancy will follow.

Research into the risks associated with PGD (and PGS) indicates that the main problems are inherent to the related IVF procedures. Hormone stimulation and ovum collection have adverse implications for the woman. ICSI and cell biopsy do not appear to have any negative effect on embryo development, but relatively little research has been done in this field (Vos01, Mag04; see also Annex C). Neonatal morbidity and mortality are more common following IVF than following natural fertilisation. This is due mainly to the increased frequency of multiple pregnancy associated with IVF (Fau05). Perinatal mortality is at least four times as high for twins as for single foetuses and the risk of premature birth is 7 to 40 times as high. The prevalence of disabilities in twins and triplets is, respectively, 1.5 times and twice as high. Table 1 contains a summary of the monogenetic conditions for which PGD is undertaken in various countries. The summary disregards blood group testing (Rhesus, Kell; ESH05a). The conditions in question include those that result in a strongly reduced life expectancy and diseases such as phenylketonuria and medium chain acyl-CoA dehydrogenase deficiency, which are considered treatable if detected in good time, and Charcot-Marie-Tooth disease, which does not bring any reduction in life expectancy.

PGD can be used for the detection not only of monogenetic conditions, but also of structural chromosome abnormalities (ESH05a). Such abnormalities may be deletions (where a segment of chromosome is missing), translocations (where segments of chromosomes switch places) and translocation-related partial trisomies (where a segment of a particular chromosome occurs three times instead of two). Distinction is made between reciprocal translocations, where terminal segments are interchanged, which occur in roughly one in every five hundred people, and Robertsonian translocations, where two whole chromosome arms are interchanged, which occur in one in a thousand people. If the interchange does not involve any genetic material being lost, the translocation is said to be balanced. Generally speaking, the carriers of balanced translocations are phenotypically normal. However, 50 to 70 per cent of the gametes of translocation carriers exhibit unbalanced combinations (Gar96), resulting in repeated miscarriages or in offspring with congenital abnormalities. Translocation may also be associated with a higher prevalence of numerical chromosome abnormalities in the ova (Puj03). If chromosome testing reveals that a parent carries a structural abnormality, it is usually possible to test the associated embryos for the abnormality in vitro. This generally involves using the FISH technique (see Annex C).

Table 1 Monogenetic conditions that are the subject of PGD testing. (Sources: Bra02, Har02b, Hel02, Rec02, Tho02, Gir03, Rec03, Ver03a, Ver03b, Die04, Dru04, ESH05a, Hej04, Hel04a, Alm05, Kul05, Ste05a, Sim05.)

Adrenogenital syndrome	Familial adenomatous polyposis coli	NARP[b]
Adrenoleukodystrophy	Familial amyloid neuropathy	Neurofibromatosis types 1 and 2
Agammaglobulinaemia	Fanconi's anaemia	Osteogenesis imperfecta
Alzheimer's disease	Fragile X syndrome	Ornithine transcarbamylase deficiency
Alport syndrome	Gaucher's disease	Phenylketonuria
Angelman syndrome	Gorlin syndrome	Retinitis pigmentosa
Ataxia telangiectasia	Haemophilia A	Retinoblastoma (hereditary)
Barth syndrome	Haemophilia B	Rhizomelic chondrodysplasia punctata
Becker's muscular dystrophy	Brain tumour (hSNF5), familial	Sanjad-Sakati syndrome
Beta-thalassaemia	Holoprosencephaly, familial	Sickle cell anaemia
Breast cancer, hereditary	Holt-Oram syndrome	Spinal muscular atrophy (Werdnig-Hoffmann disease)
Canavan's disease	Hunter's syndrome (MPS II)	
Central core disease	Huntington's disease	Spinocerebellar ataxia
Ceroid lipofuscinosis	Lesch-Nyhan syndrome	Stickler syndrome
Charcot-Marie-Tooth disease	Li-Fraumeni syndrome (p53)	Tay-Sachs disease
Crouzon syndrome	Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency	Thalassaemia alpha
Currarino syndrome		Thalassaemia beta
Cystic fibrosis	Marfan's syndrome	Tuberous sclerosis
Duchenne muscular dystrophy	Medium chain acyl-CoA dehydrogenas deficiency	Tyrosine hydroxylase deficiency
Dysautonomia, familial		Von Hippel Lindau syndrome
Ectodermal dysplasia	MELAS[a]	Wiskott-Aldrich syndrome
Epidermolysis bullosa	Myotonic dystrophy	

[a] MELAS: mitochondrial myopathy, encephalopathy, lactate acidosis and stroke.
[b] NARP: neurogenic muscle weakness, ataxia and retinitis pigmentosa. MELAS and NARP are caused by mitochondrial DNA mutations.

Table 2 Maastricht PGD results for the period 1993-2003.

Condition	Patients	Cycles started	Births	Multiple births
Huntington's disease	20	46	11	2 sets of twins
Myotonic dystrophy	8	20	0	
Spinocerebellar ataxia type 3	4	5	2	
Tuberous sclerosis type 1	1	2	0	
Polyposis coli	1	1	0	
Cystic fibrosis	17	45		1
Spinal muscular atrophy	7	8	3	1 set of twins
Fanconi's anaemia	1	1	1	
Tyrosine hydroxylase deficiency	1	1	0	
Fragile X syndrome	5	9	3	1 set of triplets
Gender-related conditions[a] (FISH method)	33	77	21	5 sets of twins
Structural chromosome abnormalities	22	45	6	
Total	120	260	48	8 sets of twins, 1 set of triplets

[a] Fragile X-syndrome, Duchenne or Becker muscular dystrophy, haemophilia A or B.

However, if the abnormality is of maternal origin, the diagnostic testing may also be performed on the polar bodies (Mun98; see Annex C).

At Maastricht, PGD is carried out in connection with various conditions (Die04; see Table 2). The list of conditions is defined partly by demand from parents and partly by the technical possibilities. The number of referrals has stabilised in recent years at approximately 100 a year (Die04).

2.2 Ethical aspects of PGD

PGD prompts ethical questions of various types. First there is the question of whether it is acceptable to perform PGD at all; then there are questions regarding the acceptability of particular applications. The inherent acceptability of PGD has been discussed in various earlier Health Council reports (GR89, GR98, GR01a, GR03). In those reports, the Council cites various arguments and considerations, on the basis of which PGD is considered acceptable in certain circumstances. In this report, two of those considerations – the moral status of the embryo and the respect and care for people with a medical condition or handicap – are briefly re-stated. Thereafter, the moral points that need to be taken into consideration in order to decide whether a particular application is acceptable are covered. The moral acceptability of the various applications is then addressed in the Sections that follow.

2.2.1 Moral considerations concerning the acceptability of PGD

Moral status of the embryo

There is a wide range of opinion regarding the status of an embryo and therefore the protection that should be afforded to it. Some commentators suggest that an embryo deserves complete protection; others that it is not entitled to any special protection. In an earlier Health Council report, three schools of thought regarding the moral status of the embryo were characterised (GR98). First, there is the view that an embryo in vitro deserves the same protection as a person after birth. Second, there is the view that an embryo in vitro deserves no protection. It is worth noting that the latter view does not imply that absolutely anything can be done with embryos in vitro; their ‘symbolic value’ alone may be sufficient to preclude certain uses. Finally, the third view is that an embryo in vitro has a relative status and therefore deserves some protection. That third view is also set out in other Health Council reports: an embryo in vitro does have a status, but

that status is relative and may be outweighed by other interests (GR01b). The Embryo Act is based on the same belief (Emb02). Opinion differs as to whether an embryo/foetus deserves more protection as it develops (Rei93).

If one holds the religious or philosophical belief that an embryo has an absolute right to protection throughout its development, and one therefore rejects the use of IUDs ('coils') and IVF, it follows that pre-implantation genetic diagnosis is also unacceptable. The Roman Catholic Church is opposed to artificial reproduction and believes that human life begins at the time of conception. For these and other reasons, the church condemns IVF (Con87) and therefore the use of PGD. The Greek and Russian Orthodox churches take a similar stance. On the other hand, various Protestant churches, including the Anglican Church and some Lutheran churches, consider IVF and PGD to be acceptable, subject to certain conditions (Sch00). The procedures are also acceptable within Islam and Judaism, because these religions subscribe to the view that an embryo does not acquire the essential characteristics of a human being until some time after nidation (Sch97, Ser01, Daa01). It is argued by some that protection should be afforded to cells extracted from embryos in vitro for diagnostic testing, since such cells could in theory become embryos (Hoe03). Such cells are referred to as totipotent, i.e. capable of developing into any type of body cell, including gametes (Alb02). However, medical science is not yet able to develop embryos in vitro from extracted totipotent cells.

The Committee subscribes to the view set out in earlier Health Council reports, namely that an embryo has a relative status, which may be outweighed by other interests.

Respect and care for people with disabilities

Opposition to PGD has also been voiced on the grounds that it is indicative of a lack of respect for people with disabilities (Ste02a). From this so-called 'disability rights' perspective, the practice of PGD is perceived to imply that people with certain diseases and/or disabilities are unwanted. People who subscribe to this view are opposed not only to PGD, but also to invasive prenatal diagnostic testing. The counterargument is that considering a medical condition to be undesirable does not imply any lack of respect for the individuals who exhibit that condition (GR01b, Ste02a). What is unwanted is not the person, but the impact of the health problem on the person who has it and on his/her family. In an earlier report, the Health Council stated that objections based on disability rights were not persuasive in relation to a parent's desire not to have a child with a serious medical condition (GR01b).

In addition, concerns have been expressed regarding the possibility that less care might be available to people with (hereditary) diseases and disabilities if their conditions were perceived to be preventable by screening. However, the Committee does not regard such a scenario as plausible. No reduction in the availability of care occurred following the introduction of invasive prenatal diagnostic testing. On the contrary, the amount of care provided (in the Netherlands and in the USA) increased in the period after those test techniques became available (Gal01, Ste02a).

The Committee is not persuaded by objections to PGD based upon the moral status of the embryo or perceived discrimination against people with disabilities. Nevertheless, the Committee would not wish to see a situation in which the availability of PGD gives rise to social pressure to make use of it. Furthermore, as indicated in earlier Health Council reports, the retention of solidarity should remain an important focus (GR94, GR01b).

2.2.2 Moral considerations determining the acceptability of PGD applications

In this Subsection, the Committee identifies the considerations that determine the moral acceptability of PGD applications. The considerations in question are used to assess the acceptability of various applications in the following Subsections.

An embryo's relative entitlement to protection

In the previous Section, the point was made that opinion differs as to whether the relative entitlement to protection of an embryo/foetus increases as it develops (GR98, Wer99). The view one takes on the latter question has an important bearing on the question of whether the indications for PGD should or should not be the same as the indications for PND. If an embryo's status prior to implantation is less than that of a foetus, should the restrictions on the use of PGD be less strict than those that apply to PND? This question is addressed in Subsection 2.2.3.

The advantages and disadvantages of IVF/PGD

An IVF procedure is necessary for PGD. The strain and risks associated with IVF are important factors to be taken into account when considering the acceptability of an application. The moral principle of non-maleficence requires that no injury is caused or harm done to others and the principle of beneficence that action is taken to prevent or alleviate injury or suffering and to promote the welfare of

others. Where IVF/PGD is concerned, account has to be taken of the possibility of the woman suffering complications (infection, ovarian hyperstimulation syndrome, increased likelihood of *sectio caesarea* being required in a multiple pregnancy), the adverse aspects of the treatment and the elevated risk of neonatal morbidity and mortality (see also Annex C). The prospects of the woman becoming pregnant with a child that does not have the relevant genetic condition needs to be weighed up against the risk of complications and the strain associated with the treatment. Those prospects and that risk are influenced by various factors, including the woman's age, and are therefore case-specific to a large extent. The assessment also needs to consider the advantages of PGD over PND. The use of PND often results in the parents having to decide whether to abort a pregnancy. With PGD, parents are generally spared that particular decision, because embryos are examined in vitro (although it should be noted that, following PGD, PND is still needed in 4 cases out of 45 (Die04)). Hence, PGD prevents the psychological and moral difficulties and physical risks associated with abortion. Furthermore, the use of PGD reduces the period of uncertainty regarding the genetic status of the embryo.

Respect for the client's entitlement to make an autonomous choice

As indicated in Subsection 1.1, much of the pressure to develop PGD came from the parents of children with serious hereditary diseases. However, little research has been done into the views of couples faced with a choice between invasive genetic diagnosis and PGD. The aspects of PND highlighted as particularly hard for prospective parents to deal with included the possibility of abortion and having to wait a long time (during the pregnancy) for the results of the invasive diagnostic tests; the most difficult thing associated with PGD was the IVF procedure. Women in the USA and Scotland at elevated risk of having a child with a genetic condition expressed a slight preference for PGD (Per91, Mie93). However, amongst beta-thalassaemia carriers in Italy, a substantial majority (73 per cent) preferred PGD (Pal94). By contrast, couples in England were more likely to opt for invasive diagnostic testing, although this may have been partly attributable to the long waiting list for the alternative (Sno97). Researchers in the UK and Spain sought the views of couples that had gone through the PGD procedure. Most (76 per cent) said that they would choose PGD again (Lav02). Couples that wish to have diagnostic tests performed and also require IVF due to impaired fertility understandably tend to prefer PGD.

A survey by the Association of Cooperating Parents' and Patients' Organisations found that the parents of patients had a slight preference for PGD. However, only a small number of people were interviewed (Lig04).

The principle of respect for clients' freedom of choice has an important bearing on the moral acceptability of particular applications. However, that does not imply that freedom of choice should be unlimited. Earlier Health Council reports made the point that the objective was not to maximise the autonomous reproductive decision-making per se (GR01b). The primary reason for making PGD available is the prevention of serious suffering.

Professional responsibility of the doctor and other care providers

PGD is possible only in combination with IVF, which requires the involvement of a doctor and other care providers. A doctor who provides IVF treatment does so with the aim of bringing about pregnancy and thus the birth of a child. The doctor consequently shares a degree of responsibility for the welfare of the unborn child. The doctor is also professionally responsible for the welfare of the client. Hence, IVF entails a double professional responsibility: the doctor is responsible for the consequences of his/her actions not only for the welfare of the client(s), but also for the welfare of the unborn child (GR97, GR98).

The existence of this double responsibility constitutes an important distinction between IVF/PGD and PND. Where PND is concerned, if prenatal testing is indicated, the couple or the woman is free to decide whether to proceed and, if so, what to do in light of the results. The provision of PND respects the principle of non-directivity, i.e. the principle that a genetic counsellor should not advise the client and or guide the client towards a particular course of action. By contrast, a doctor providing IVF/PGD shares responsibility for starting a pregnancy, implying that he or she has to consider the interests of the child when deciding whether it is appropriate to proceed.

In the ethics literature, different opinions are expressed as to the extent of the doctor's responsibility for the welfare of the unborn child. Three standards are recognised (Pen99, Wer99, Bol04):

1 the maximum welfare standard: one must not contribute to a child being brought into the world under non-ideal circumstances
2 the reasonable welfare standard: medical reproductive assistance is acceptable if the resulting child has a reasonable chance of a reasonable quality of life (Arr90, Wer99)
3 the minimum threshold (or welfare) standard: a child is harmed only by being born into an intolerable existence.

In its report *In vitro fertilization (IVF)*, the Health Council states that it should be a criterion for the provision of IVF that the doctor sees no significant risk of the child suffering serious harm (GR97). The Committee considers that the application of this criterion strikes the best balance between the potentially conflicting professional responsibilities to respect the autonomy of the prospective parents and to protect the interests of the child produced by IVF. Hence, medical reproductive assistance may be withheld in the interest of the child, if there is a significant risk of serious harm. This implies a degree of constraint on prospective parents' freedom of choice concerning PGD. Difficult situations can arise if Huntington's disease is observed in a prospective parent: is it in the interest of the resulting child to provide PGD if he or she is going to grow up with a parent who has a serious untreatable disease with behavioural implications? And what if a prospective parent is considered liable to behave in an aggressive or uncontrolled way, e.g. because he or she is at risk of frontal lobe dementia. With late-onset diseases, such as Huntington's disease, this question is also relevant to the assessment of non-disclosure tests (see 2.2.5). Finally, problematic situations can arise with embryo selection if, for example, there is disagreement between parents and treatment providers regarding embryo implantation (e.g. if the PGD is inconclusive or if the parents have already been through several unsuccessful PGD cycles and have come to the point where they favour the implantation of an embryo that carries the mutation). In such situations, there is a moral obligation to consider the interests of any child produced by IVF.

2.2.3 *Indications for PGD and invasive prenatal diagnostic testing (PND)*

At present, PND is indicated where there is a substantially elevated risk of a serious condition (GR98). PGD is also indicated only for serious conditions: the prospective parents must be at elevated personal risk of having a child with a serious genetic condition or disease (Pla03).

The indication is limited to serious cases partly because of the embryo's protected status. However, there are sometimes compelling reasons for PGD, such as the prevention of serious suffering. Because PGD is performed at a relatively early stage in the development of the embryo, it has been suggested that the indication for PGD could possibly be defined more leniently, allowing its use in connection with less serious conditions than PND. However, any such relaxation is justified only if one accepts that an embryo acquires protected status progressively – in other words, if a foetus deserves protection more (possibly a lot more) than an embryo in vitro. The arguments made to support that viewpoint

have been set out in earlier Health Council reports (see GR98). If protected status is acquired progressively, PGD may well be preferable to PND. For the sake of completeness, it is pointed out that some authors suggest that, in addition to the qualitative considerations, a quantitative consideration should be taken into account, namely that the number of embryos lost in vitro in the context of IVF is greater than the number of abortions associated with PND (Bot98, Ste02a). Setting aside the question of the progressive acquisition of protected status, there are various reasons why the Committee concludes that both PGD and PND should be indicated only where there is an elevated personal risk of a serious disease. PGD necessitates IVF treatment, which has adverse aspects and entails risk for the prospective mother and the resulting child (see Annex C). Furthermore, the chances of a successful outcome to an IVF procedure are fairly low, especially if the treatment is followed by PGD: depending on the hereditary pattern of the relevant condition, either a quarter or half of the embryos created will on average be unsuitable for transfer to the uterus (GR03). This raises the question of what should happen if a woman needs IVF anyway, due to a medical indication such as tubular pathology: should PGD still be made available only if there is an elevated personal risk of serious disease? After all, the reasons for not making it available (the adverse aspects, the risks and the relatively poor prospect of success) cease to apply, because the PGD will not add to the disadvantages that will be experienced in the context of the medically indicated treatment. Notwithstanding these considerations, the Committee believes that the indication for PGD should remain unaltered in the circumstances described. The reasons being that, as indicated above, pregnancy is less likely to occur when PGD is used (fewer embryos are available for transfer), so it is more likely that additional IVF cycles will be required (with the associated adverse aspects and risks).

The information given to clients regarding the various indications for PGD should of course address the technical limitations of the procedure and the difficult situations that can arise in the context of embryo transfer (e.g. what will happen if the diagnostic tests are inconclusive and if numerous suitable embryos are identified). As in an IVF procedure (CBO03), in a PGD procedure agreement should be reached about what is and is not possible and the details recorded in writing. The agreement should cover the possible use of cryopreservation (the freezing of morphologically sound embryos without the relevant genetic abnormality, for possible subsequent transfer).

Restriction of the use of PGD and PND to serious conditions is liable to raise the question of what constitutes a serious condition. A precise definition of ‘serious condition’ is not possible in practice. There are sound arguments for not

defining a list of serious conditions: (i) a given condition can vary considerably in terms of both genotype (various mutations) and phenotype (various manifestations), (ii) perceptions of seriousness can vary from one family to the next, under the influence of psychological and socio-economic factors, and (iii) the list would need continual revision in line with scientific developments. As things stand, a decision is made by the professional practitioners in consultation with the parents as to whether a case involves a serious condition.

2.2.4 *Selection on the basis of carriership*

PGD can also reveal whether an embryo carries a particular gene. The male carrier of an autosomal recessive condition has a mutation on one of the two relevant chromosomes. In such cases, the condition is not usually manifest in the carrier. A female carrier of an X-chromosomal condition has the relevant mutation on one of the two X-chromosomes. Such a female carrier will not suffer from the relevant condition, or at least not as badly as her male counterpart. In the case of an autosomal dominant condition, someone with a mutation on one chromosome will be affected by the condition, and a person who carries the mutation on both chromosomes will suffer from it much more badly.

Prospective parents may sometimes ask for embryos to be selected on the basis of carriership because they perceive carriership to be a burden on a child. Selection on that basis is sometimes possible without any additional procedures being required. If, with a view to excluding the possibility of a serious autosomal condition, embryos are examined to identify those that have a mutation on both chromosomes, the procedure will also identify those that are merely carriers (i.e. have only one mutation). In most cases, the conditions involved will be autosomal-recessive conditions. Occasionally, however, the tests will be performed for autosomal dominant conditions. If, for example, both parents have a particular disease (e.g. familial hypercholesterolemia or Charcot-Marie-Tooth disease), they may want PGD because a child with two mutations would be very seriously affected. Similarly, if embryos are examined to identify those that will manifest X-chromosomal conditions, the procedure will allow the identification of carrier-embryos (female embryos with one mutation). In such cases, selection on the basis of carriership will be possible without any additional procedures being required. A further IVF cycle is amongst the procedures that need to be considered in this context; this is significant insofar as the prospects of pregnancy may be diminished by the selection process. If the embryos include both carriers and non-carriers with good morphology, selection does not influence the chances of pregnancy, provided that non-transferred,

morphologically sound embryos are put into cryogenic storage so that, if the first transfer does not lead to pregnancy, a further IVF cycle is not needed. A previous Health Council report (on gender testing for non-medical reasons) indicated that, in such cases, there can be little objection to complying with the parents' wishes (GR98). The Committee believes that the same applies in the circumstances described here.

In terms of the acceptability of the testing, there is in principle no difference between X-chromosomal and autosomal recessive or autosomal dominant inheritance. However, there is a significant statistical difference. Where an X-chromosomal condition is concerned, an average of one in three embryos in which the condition is not manifest will nevertheless carry the mutation. Where an autosomal recessive or autosomal dominant condition is concerned, the figure is two in three. This clearly has implications in terms of the scope for selection.

In the Committee's view, the acceptability of selection in circumstances where additional procedures are needed depends primarily on the extent to which carriership would be a burden on a child. The extent to which that is the case differs considerably, depending on the condition. Many people who know that there is a sizeable risk that they will pass on a serious condition to their offspring are troubled by that knowledge. With X-chromosomal conditions, such as Duchenne muscular dystrophy and adrenoleukodystrophy, there is a 50 per cent risk that the son of a female carrier will inherit the disease. Female carriers sometimes exhibit symptoms of the disease as well. Although such females suffer much less than males in whom the disease is manifest, the symptoms constitute a significant burden. Selection on the basis of female carriership may entail the female offspring of female carriers, or the female offspring of males with manifest conditions such as haemophilia (A or B). In the latter case, all female embryos will be carriers. Any associated pre-implantation genetic testing is therefore concerned exclusively with female carriership, and acceptable only if carriership of the particular mutation constitutes a serious condition.

With an autosomal recessive condition, it is much less likely that the child of a male or female carrier will inherit the condition. In the case of cystic fibrosis (CF), the risk is about 0.8 per cent, for example. With almost all other autosomal recessive conditions, the chances of inheritance are even smaller. Furthermore, most carriers of both sexes are usually asymptomatic. The associated burden is therefore much smaller and selection on the basis of the mutation in question is appropriate only in exceptional cases. Naturally, the conditions involved also vary in their seriousness and treatability, and the variations have a significant bearing on the associated burden.

The Committee believes that, in each case, the possibilities need to be discussed with the parents. In some cases, carriership will represent a serious burden sufficient to justify selection, even if this implies additional procedures.

2.2.5 *Exclusion tests and non-disclosure testing*

Where a serious, late-onset, untreatable condition is concerned, a prospective parent who requests PGD may not wish to be informed about his/her own genetic status (see also GR03; the acceptability of PGD or PND for such serious conditions is not in dispute). Typically, concern about the condition will have arisen because one of the prospective parent's own parents has developed it. Knowing that one is going to develop a disease of this kind is a major psychological burden and it is common for the sufferer's children to opt not to be informed of their own status. However, the wish to remain in ignorance of their own status can be difficult to reconcile with the wish not to pass the condition on to the next generation.

In some cases, however, those two wishes can be reconciled. It may be possible, for example, to determine the prospective parent's genetic status without telling him/her what has been established. This is referred to as 'non-disclosure testing'. The drawback of this approach is that it sometimes implies the 'unnecessary' use of IVF in cases where the care providers in the clinic or at the laboratory already know that the client does not have the genetic defect in question (Bra98, Ser02).

Another possibility is 'exclusion testing'. This is possible if it is known which embryos cannot carry the mutation because they have inherited the relevant gene from a grandparent who does not have the mutation in question. If only these embryos are transferred to the prospective mother, the possibility of a child with the condition being born is excluded (exclusion testing; Qua87, Bra98, Ser02). One drawback with exclusion testing is that it involves the rejection of embryos that have inherited a non-mutated gene from the grandparent with the condition (the chance of this happening is 25 per cent). Another problem is that the approach involves IVF/PGD treatment even in cases where the client is not in fact at risk. As indicated in Subsection 2.2.2, the interests of the child produced by IVF should also be considered. In that context, it is relevant that the ultimate outcome of the procedure may be that a child has to grow up in a family where one of his/her parents has a serious untreatable disease (Mou04). However, as explained in the latter Subsection, the Committee believes that medical assistance with reproduction is acceptable if any child thus produced has a reasonable chance of a reasonable quality of life (the intermediate standard;

Arr90, Wer99). The risk to the child is not sufficient to justify a categorical prohibition on exclusion testing. Rather, each case should be judged on its merits. If, for example, the prospective parent is liable to develop a serious hereditary disease, consideration should be given to how the other parent is likely to cope, given his/her social network, with the possibility that the carrier may develop and die from the disease in the near future, and the risk of serious behavioural problems (and their likely influence on the child) (GR03).

The Committee takes the view that, in the case of a serious untreatable condition such as Huntington's disease, the psychological burden of knowing about one's genetic status is sufficient to justify the use of exclusion testing. In this context, the Committee emphasises the importance of good information and counselling. Clients must be fully informed about what is possible, what the limitations are and what the drawbacks are (e.g. the adverse aspects of IVF treatment for the woman), so that both prospective parents are able to arrive at a free, informed decision.

2.2.6 Mendelian conditions with variable expression or incomplete penetration

With a monogenetic condition, the risk of a child being affected is either 25 or 50 per cent; geneticists refer to this as Mendelian inheritance. However, there can be major differences in manifestation, involving the seriousness of the disease and the age at which it develops. This phenomenon is known as variable expression. It is also possible for a monogenetic condition to manifest itself in only some of the affected individuals; this is referred to as incomplete penetration. Predisposition to cancer on the basis of a mutation in the BRCA1 or BRCA2 gene can illustrate both phenomena (Cob02). The same mutation can lead to both breast cancer and ovarian cancer (variable expression). The likelihood of an affected individual developing each of these two forms of cancer differs. Moreover, not everyone who carries the mutation will develop either form (incomplete penetration).

In practice, there is relatively little demand for PGD in connection with hereditary predisposition to cancer. Assistance is generally sought by families in which one parent has already been affected and the disease has also manifested itself in another first-degree blood relative (Rec02). Whether a Mendelian inherited condition with variable expression or incomplete penetration forms an indication for PGD (and prenatal diagnostic testing) depends on the likelihood of the disease, the age at which the condition usually manifests itself, the clinical seriousness and the adverse aspects of any available treatment. On the basis of experience with PGD for hereditary colorectal cancer, it has been argued that

requests for assistance should be assessed on a case-by-case basis (Edi04). The fact that one is dealing with the chances of disease and averages of seriousness is not a valid reason for precluding the use of PGD for this type of condition.

Whether PGD is indicated depends on the merits of the individual case. The maintenance of a list of qualifying conditions has been rejected for various reasons (see 2.2.3).

2.2.7 *Multifactoral conditions*

Multifactoral conditions are conditions that typically have one or more genetic components and are also influenced by environmental factors. The repetition risk is greater than the population risk, but smaller than the 25 or 50 per cent associated with Mendelian inherited conditions. However, variable expression and incomplete penetration (see 2.2.6) have the effect of rendering the distinction between monogenetic and multifactoral conditions somewhat arbitrary. Within the latter group, congenital abnormalities may be distinguished from late-onset conditions. Congenital multifactoral conditions include neural tube defects and heart defects. Cancer, cardiovascular disease and psychiatric conditions generally fall within the second category. Many multifactoral conditions are chronic. Sometimes, within a particular category, it is possible to identify a subgroup with a Mendelian inheritance pattern, as is the case with breast and colorectal cancer (see 2.2.6). It is only where such subgroups are concerned that PGD is a viable option, to which the criteria set out in Subsection 2.2.6 apply.

2.2.8 *Multiplex genetic testing*

In the request for advice, the Health Council was asked to consider the question of multiplex genetic testing. Although multiplex testing is a method and not a reason for PGD, it does raise ethical issues that may appropriately be examined in the present context, because of their potential future relevance to PGD.

Rapid advances both in understanding of the human genome and in technical capabilities have made it possible to screen several genes at once. A DNA sample can be amplified by PCR, then numerous characteristics can be simultaneously studied on a micro array chip. This form of testing is known as multiplex genetic testing. It can be used to establish which genes are expressed in a particular tissue. Whether it is possible to reliably screen individual cells in this way has yet to be established. Hence, it is unclear whether multiplex testing is viable for embryos in vitro. However, it is not efficient to perform a multiplex test with the very small quantity of DNA yielded by a single cell, if many times

as much material can be obtained from a drop of parental blood or a cheek swab. Multiplex genetic testing of parental DNA can establish whether there is a previously unrecognised risk of a child having a hereditary condition. This approach can shed light on the risk of various autosomal recessive and X-chromosomal conditions; autosomal dominant conditions will normally have already manifested themselves in the family. Consequently, multiplex genetic testing of embryos is not relevant. Multiplex test kits for hereditary conditions are already commercially available to parents, including kits designed to enable couples of Ashkenazi Jewish origin to test themselves for mutations that are common in that population group (Lei05).

The availability of multiplex testing raises questions about informed consent (Wer99). Can clients be expected to digest the volume and complexity of information needed to understand what is involved? Should the requirement that practitioners provide information be relaxed and should the information provided be more general? Some commentators argue that generic consent should be sought: general information should be given before the test, followed up with more detailed information only if the subject is found to be a carrier. Proponents of such an approach argue that explaining all the issues surrounding a multiplex test implies providing far more information than most clients can be expected to take in, and that a generic procedure would be more cost effective. However, the Committee considers such an approach to be inconsistent with the principle of informed consent, which requires that people must always be enabled to arrive at a considered decision.

The screening of parents for genetic conditions by means of multiplex testing requires careful assessment, like any other form of screening. The Health Council's report on genetic screening sets out criteria for the assessment of screening programmes (GR94). One aspect that distinguishes multiplex testing from other forms of testing is the volume of information that needs to be made available to prospective clients (see also GR03). The Committee emphasises that particular attention needs to be given to the question of informed consent under such circumstances (Wer99).

2.2.9 HLA typing

Pre-implantation genetic testing is used not only to detect conditions of the kinds referred to above, but also to establish an embryo's HLA type, with a view to enabling the treatment of a seriously ill older child by means of stem cell transplantation. For children with certain life-threatening diseases such as Fanconi's anaemia, a stem cell transplant is the only effective therapy. If no

suitable donor is available, parents may consider IVF followed by embryo selection on the basis of pre-implantation genetic testing as a means of having a child whose umbilical cord blood may be used after its birth for treatment of the older child (Ame99, Ver01a). If the condition affecting the older child is a hereditary disease, PGD can also be used to ensure that the implanted embryo does not have the condition as well. Under such circumstances, the testing has two purposes: to prevent disease in a child produced by IVF and to treat disease in a living child. However, where conditions such as therapy-resistant leukaemia are concerned, pre-implantation genetic testing serves only to determine whether an embryo's HLA type is suitable.

Scientific advances have brought substantial improvements in the methods used to replace malfunctioning stem cells with donor cells (as evidenced, for example, by the outcomes of transplants performed in the Netherlands to treat children with aplastic anaemias; Ste02c). To date, only a few thousand umbilical cord blood stem cell transplants have been performed anywhere in the world (mainly for the treatment of children with acute leukaemia or cancer; Ben04).

A significant practical problem is that the procedure often does not have the desired outcome. On average, only a minority of the embryos created will have an HLA type that is compatible with that of the sick older child. The chance of a tissue match between siblings is roughly 24 per cent (50 per cent per parent, corrected for the possibility of recombination; the chance of a tissue match between non-siblings is negligible). Where a hereditary disease is concerned, there is also the risk that the embryo in vitro will have the condition as well (with thalassaemia and comparable conditions, there is a 25 per cent chance). Another limiting factor is the likelihood of IVF leading to pregnancy, which diminishes as the mother gets older. Clients need to be fully informed about these chances.

In various countries, there is debate regarding the acceptability of HLA typing as described. Demand is driven mainly by the lack of donors. Action to reduce the donor shortage (e.g. increasing blood bank facilities) can therefore be significant in this context. The UK's Human Fertilisation and Embryology Authority (HFEA) and the Victorian Infertility Treatment Authority in Australia have both ruled that the HLA typing of embryos in vitro is acceptable in life-threatening situations (Hfe01, Spr02, Hfe04). HLA typing of this kind is permitted in various other countries as well (see 4.1). In the Netherlands, however, PGD for the purpose of securing the birth of a child that can be used as a donor for another child is deemed unacceptable (Pla03).

Setting aside the question of whether it is the mother or the child who acts as donor when umbilical cord blood is donated, interpretation of the rules that apply in the Netherlands depends to a significant extent on whether 'for the purpose of'

implies 'for the *sole* purpose of' (Pla03). Pre-implantation genetic testing may also have the purpose of diagnosis with a view to excluding the possibility of bringing into the world a child with a hereditary disease. Under such circumstances, the procedure has both a direct medical purpose (prevention of disease in a child produced by IVF) and an indirect medical purpose (treatment of disease in an older child). However, even if the former reason does not exist, as in the case of a child with therapy-resistant leukaemia, for whom no donor is available, the parents may want HLA typing and selection. If so, there is an indirect medical reason for the procedure, which is not strictly consistent with the classic medical model for PND and PGD, since the procedure does not entail the investigation of (the risk of) a health problem in a child produced by IVF. However, the purpose of the medical intervention remains the treatment of a child with a life-threatening condition.

Opponents of in vitro HLA typing argue that the procedure effectively involves using one child (the child produced by IVF) as a resource for the treatment of another child (the older sick child). However, this argument cannot justify a categorical prohibition. First, the parents may wish to have another child as well as wishing to preserve the health of their existing child. Second, donorship does not necessarily imply 'instrumentalisation'. Even if the desire to have another child stems initially from the wish to save an existing child, it does not follow that having another child will not be regarded as an end in itself or that the child will be cherished any less than the first (Wer03b). The inherently reasonable wish to enable the treatment of a sick older child by securing a source of umbilical cord blood for the transplantation of stem cells (GR02) is quite compatible with the wish to have another child for its own sake. What matters is that the additional child is wanted, regardless of the initial motivation for its conception (Mun04). Under such circumstances and subject to careful counselling, the in vitro HLA typing of embryos can be acceptable (Pen02, Wer03b, Hfe04). The Ethics Committee of the European Society of Human Reproduction and Embryology has also indicated that such typing is not unacceptable ('if parents intend to love the child'; She05). It has therefore been proposed that parents should be allowed to make their own decisions, in consultation with their doctors (Bre02).

The distinction between hereditary and non-hereditary conditions is defended on the grounds that, in the case of a hereditary condition, the parents could have opted for PGD anyway (Hfe01, Mun04). Because of the invasive nature of the procedure and the risks potentially associated with the biopsy, the HFEA initially authorised in vitro HLA typing only in cases involving serious genetic conditions. Furthermore, typing was restricted to cells that had already been

removed from the embryo for the purpose of genetic diagnosis. The latter restriction was withdrawn in 2004, however, after the HFEA concluded that there was no evidence that HLA typing entailed added risk to the embryo (Hfe04). The Committee similarly believes that the distinction between hereditary and non-hereditary conditions is not of decisive significance: the interests of the sick child are the same, regardless of whether the condition is hereditary, and the additional burden on the prospective mother stems from the adverse aspects of an IVF procedure, which, while not inconsiderable, are not disproportionately great.

An important consideration for practitioners is that the number of people likely to want in vitro HLA typing is likely to be small, given the prevalence of the relevant conditions.

The Committee is of the opinion that HLA typing for the purpose of enabling a stem cell transplant for the treatment of an older child with a life-threatening condition is justifiable. The acceptability of such a procedure is conditional upon the possibility of other suitable therapies having been considered, all reasonable steps having been taken to find a suitable donor through the donor banks around the world and proper counselling having been provided (in which context the relatively small chance of finding a suitable embryo is covered).

2.2.10 *Non-medical reasons*

In addition to the medical reasons for pre-implantation genetic testing discussed above, a number of non-medical reasons are referred to in the scientific literature. Embryos in vitro may be tested for genetic characteristics that are not related to disease, but to physical or psychological capabilities. Distinctions between health and ill health and between medical and non-medical reasons are not always easily drawn. In bio-medical terms, for example, health may be defined as the normal function of a typical member of a species. That definition requires the existence of a context, within which a particular physical function may be judged healthy or unhealthy. Colour-blindness, for example, is a neutral phenomenon; a social and cultural context is needed to attach a value to it (Hav98). It has also been said (in the context of the funding of IVF) that the concept of a ‘medical indication’ is not a well-defined criterion, but ‘a practical normative construct in which medical and social justifications are woven together’. However, the fact that no clear criterion exists for distinguishing between the medical and the non-medical does not of course imply that assistance should be made available through the health care system for all kinds of non-medical purposes. There is a difference between a request for medical assistance with a health problem and a request for assistance from parents who

wish to have a child that conforms to a particular ideal. However, it is important to specify the medical and normative considerations that determine whether a given application of pre-implantation genetic testing is justified. For example, parents who have a particular hereditary form of deafness may sometimes wish to have a child who has this characteristic (GR03). Such parents might wish to have pre-implantation tests performed in order to select embryos that have the relevant predisposition to deafness. Proponents of this application argue that deafness is not a medical condition, but a normal variation, which one may reasonably select in favour of (Rob03). On the other hand, it may be argued that deafness is a disability and that a doctor must not cooperate with the deliberate creation of a child that has a disability or an illness (GR03). Researchers investigating the effects of cochlear implants have concluded that deafness limits a person's ability to participate in social intercourse (GR01c). While that conclusion has been disputed, there is sufficient reason to be cautious about accepting deafness as a normal variation.

In the future, it might become possible to select in favour of, for example, intelligence or athletic ability. A few years ago, it was suggested that such forms of selection were not feasible, because the relevant characteristics were highly complex, only partially genetically determined and influenced by a large number of genes (Bot98). However, a lot has already been learned about the genes that influence characteristics such as memory and muscle power.

Pre-implantation testing and selection for non-medical reasons (outside a medical setting) are defended on the grounds that parents are autonomous and therefore free to choose what characteristics they wish their children to have (Rob92, Sav01). Proponents of this school of thought argue that objections to IVF are not decisive, particularly not in the case of a couple that requires the procedure anyway for reasons of impaired fertility. However, it is not only because of the need for IVF that people are opposed to in vitro selection for desirable characteristics. The possible development of a 'market', with parents as consumers and children as products, is seen as undesirable because of its impact on parent-child relations (Ann94). In such a scenario, a child might be perceived not to meet its parents' expectations. Some commentators have therefore contended that, while freedom of choice might be the corollary of parental autonomy, it does not respect the autonomy of the child produced by IVF (Cla02). Selection for particular forms of a gene might subsequently be perceived by the child to unreasonably restrict his/her freedom (Dav97, Bot98). Another objection to this form of selection is that it would exacerbate inequalities of opportunity for future children, with existing inequalities amplified by the fact that selection would be affordable only for wealthier

members of society (Ann94). Moreover, it is feared that the ability of some people to afford selection would tend to divert personnel and other resources away from health care. A publication by the Royal Dutch Academy of Science highlighted the (undesirable) possibility that, in the future, there could be social pressure to allow embryo selection for non-medical reasons (KNAW04).

In this report, no attempt is made to weigh up the relative merits of the arguments for and against selection on non-medical grounds. Nevertheless, the Committee believes that the adverse aspects of IVF amount to a strong argument for restricting pre-implantation testing to the indications mentioned earlier. Even if IVF is indicated for a couple on the grounds of impaired fertility, selection necessitates additional procedures and may reduce the chances of pregnancy. The Committee's standpoint does not imply that the other arguments set out above are invalid. Moreover, the considerations referred to in Subsection 2.2.2 are also relevant in this context. However, the Committee makes the point that the acceptability of embryo selection for non-medical reasons is an issue that transcends the health care domain.

As alluded to in the request for advice, a special situation arises if the gender of an embryo is already known from a PGD or PGS procedure. That is usually the case if PGD is performed in connection with an X-chromosome mutation. PGS could also reveal an embryo's gender, because it involves determining the number of X-chromosomes. If then a selection has to be made from a number of embryos that are deemed suitable for transfer, the questions arise: who may decide which embryos will be used, and on what grounds. Given that the embryos in the selection pool are deemed equally suitable in medical terms, the choice could be left for the treatment provider to make on a 'blind' basis. Alternatively, the prospective parents could be involved in the decision-making process, although there are no medical selection criteria that they could apply either. In a 1995 report, the Health Council indicated that, in such circumstances, little more was expected than that any preference that the parents might have should be respected (GR95). The situation is different if additional procedures are required, in which case the report advises caution (GR95). A further IVF cycle that could be avoided by cryopreservation is considered to be an additional procedure in that context. The Committee is of the opinion that, if (and only if) suitable embryos of both genders are available, it is acceptable for the choice of embryos for transfer to be made on the basis of consultation between treatment provider and prospective parents. In line with standard IVF practice, a written record should be kept of the agreed procedural arrangements.

2.3 Estimation of the demand for PGD

PGD is an important option for couples if there is a serious hereditary condition in the family and they have profound moral or other objections to *abortus provocatus*. As indicated in Subsection 2.2.3, there appears to be a preference for PGD ahead of PND, but the research data are sparse and involve small numbers of parents. Furthermore, the scientific literature suggests that there are certain categories of disease for which PGD is more often preferred to invasive prenatal diagnostic testing. The diseases in question tend to be those for which treatment is available, but which are nevertheless frequently associated with serious problems, such as haemophilia, and untreatable late-onset diseases, such as Huntington's disease. The PGD Centre in Maastricht is currently comparable in size to most other European centres. There are roughly a hundred referrals a year (Die04). Approximately fifty referred couples embark on IVF treatment each year, resulting in about a hundred IVF cycles a year. The other couples cannot be assisted for technical or ethical reasons, or IVF/ICSI is not possible, or the couples themselves decide against PGD (common reasons being the waiting time and the distance to the centre).

In relation to the question of whether it is desirable to have a second PGD centre in the Netherlands, the following considerations are relevant:

a The existing waiting time in Maastricht (a year; this is linked to the fact that there is as yet no policy directive on fulfilment of this function)
b The distance to Maastricht (non-central location)
c Possible technical limitations (Die04): the development of new diagnostic tests requires time and resources (see point a)
d It is not known how many couples in whose families there are serious hereditary conditions would in principle qualify for PGD in the Netherlands
e The number of couples who actually ask for PGD or information about it is also influenced by the extent to which PGD is mentioned, along with PND, as a possibility during clinical genetic counselling. Invasive diagnostic testing is performed in connection with a monogenetic condition or structural chromosome abnormality about 450 to 500 times a year in the Netherlands (Wpd00). Therefore, if parents do indeed have a (slight) preference for PGD, as suggested, the number of referrals could potentially increase to many more than the existing hundred a year.
f Another factor that influences the number of couples that request PGD is the acceptance of and familiarity with PGD within the associations representing patients with hereditary conditions.

Any estimate of the demand needs to take account of all the factors referred to above. All things considered, it appears possible that the latent demand is at least three hundred patients a year. The Committee considers it undesirable that waiting times and travel times should have a major bearing on prospective parents' decision-making when choosing between PGD and PND. The increase in capacity at Maastricht in line with the policy directive may be expected to reduce waiting times to an acceptable level and to at least partially satisfy the anticipated growth in demand.

The Committee explicitly wishes to defer judgement on the question of whether a second PGD centre should be created in the Netherlands. A conclusion regarding the desirability of another centre – which needs to take numerous variables into account, as indicated earlier – cannot be reached until it is known what influence optimisation of the PGD programme at Maastricht has on the volume of PGD care in the Netherlands. The Planning Decree allows scope for a second centre.

Chapter 3

Pre-implantation genetic screening

In quantitative terms, PGS is a more significant procedure than PGD (Kul02). In the USA in particular, it is increasingly presented as a 'normal' part of IVF, serving to increase the likelihood of pregnancy. However, the effectiveness of PGS in this regard is open to question, and it is not clear whether there are any particular circumstances in which it is indicated.

PGS usually involves the use of FISH, although also PCR and CGH can also be used. The various methods are summarised in Annex C.

This Section of the report considers the phenomenon aneuploidy and assesses the effectiveness and acceptability of PGS and the potential demand for it.

3.1 Aneuploidy

It has been known for a long time that aneuploidy, i.e. having an abnormal number of chromosomes, plays an important role in spontaneous abortion (Bou73). Aneuploidy often involves the presence of three chromosomes, or one, where there would normally be two. Such abnormalities are not usually compatible with life. Furthermore, research involving embryos available following IVF treatment has suggested that aneuploidy may explain the relatively low chance of human embryo nidation (20 to 40 per cent). To compensate for the low implantation rate, it is normal in IVF to transfer more than one embryo. It has been suggested that pre-implantation testing for aneuploidy and in vitro selection of embryos with normal chromosome counts

for transfer could increase the prospects of IVF leading to pregnancy (Mun93, Wil02). If the chance of nidation per embryo were higher, it would not be necessary to transfer as many embryos (ideally, embryos should be transferred singly). In this way, PGS could contribute to the prevention of perinatal mortality and morbidity associated with IVF-induced multiple pregnancies (Fau05). However, no randomised research has yet been published showing that this effect does in fact occur, generally or in certain patient groups.

Aneuploidy in an early embryo may be maternal, paternal or embryonic in its origin. Aneuploidy of maternal and paternal origin involves, respectively, the ovum and sperm cell being chromosomally abnormal prior to fertilisation, while aneuploidy of embryonic origin involves the occurrence of an abnormality during the division of embryonic cells. If the origin is paternal or maternal, all the embryo's cells will usually exhibit the chromosomal abnormality. If an abnormality occurs at an early stage in the division of embryonic cells, a so-called mosaic embryo can form, containing both cells with a normal chromosome pattern and cells with an abnormal pattern (mosaicism). The extent to which the prospects of IVF leading to pregnancy can be increased by using PGS depends on, amongst other factors, the frequency of aneuploidy or mosaicism, the influence of those phenomena on the morphology of the embryo in vitro, and any damage that may be caused to the embryo by the biopsy.

The risk of aneuploidy depends on the age of the woman (more precisely, how close she is to the menopause). In women under the age of twenty-five, aneuploidy is present in 2 per cent of identified pregnancies, while in women over the age of forty the rate is more than 25 per cent (sometimes a lot more). Research involving donated ova indicates that the cause of aneuploidy is related to the age of the ovum (Nav94, Has01). Because of the correlation between aneuploidy and aging, both the risk of miscarriage and the risk of having a child with a chromosome abnormality increase sharply with age. Conversely, the likelihood of pregnancy decreases sharply.

Studies of ova and embryos from couples registered with IVF clinics have revealed high but extremely divergent aneuploidy percentages (Ser04). One study of chromosomes in ova from women with an average age of thirty-eight found abnormalities in 52 per cent of the ova (chromosomes 13, 16, 18, 21 and 22, examination of first and second polar bodies; Kul03a). Another chromosome study, involving women aged nineteen to forty-six, found abnormalities in roughly 20 per cent of the ova (Pel03). Studies of embryos in vitro have indicated aneuploidy percentages ranging from 20 to 90 per cent (Jam94, Del97, Coo04, Kah04, Ser04, Sta04). Uncertainty as to the prevalence of aneuploidy is attributable to several factors. First, only a small number of chromosomes were

examined in each study. It is unclear how much higher the aneuploidy percentage would be if a larger number of chromosomes were examined. Also of significance is whether the chromosome patterns of one or two blastomeres were studied and how discordant results were interpreted in the light of possible mosaicism. Furthermore, some of the studies used embryos that had been judged unsuitable for transfer on account of their morphology. Such embryos exhibit an above-average rate of aneuploidy (Bal04). Most abnormalities occur at meiosis of the ovum, but the study of sperm cells from men who had been classified as infertile has also revealed above-average rates of aneuploidy (Tem04).

As well as generating uncertainty about the prevalence of aneuploidy, the occurrence of mosaicism has an important bearing on the reliability of PGS and on the influence that PGS has on the prospects of IVF leading to pregnancy (discussed in Subsection 3.2). If mosaicism is present, a studied cell is not necessarily representative of the chromosomal composition of the other embryonic cells (Baa05). Significantly, the removal of a cell also influences the numeric ratio between normal and abnormal cells. If an abnormal cell is removed, a higher proportion of the remaining cells will be normal, and vice versa (Los04). A study that involves the examination of two blastomeres will yield a statistically more reliable result, but discordance in the results is liable to arise (Baa04). Data on the prevalence of mosaicism are sparse (the ratio between chromosome abnormalities of meiotic and mitotic origin can only be estimated). Due to mosaicism, aneuploidy testing of a single cell is estimated to lead to erroneous diagnosis in 6 per cent of the examined embryos (Ser04). Further research is needed in order to reach firm conclusions regarding the reliability of PGS (Kat05).

The significance of aneuploidy (and mosaicism) for the likelihood of IVF resulting in pregnancy depends not only on the prevalence of aneuploidy, but also on its relationship with morphology. Embryos are selected for transfer on the basis of their morphological characteristics. Therefore, the closer the relationship between morphology and aneuploidy, the less influence PGS is likely to have on the outcome of the IVF process (Alm96, Bor05). Although aneuploidy does indeed appear to be less common in embryos with a morphologically normal pronucleus (26 per cent, compared with 73-83 per cent in embryos with anomalies; Bal04), the correlation is not sufficiently strong to make PGS superfluous. Another important factor is whether the PGS procedure itself, in particular the removal of a cell, has any (negative) influence on the outcome of IVF.

It is not known how much influence the described effects have on the likelihood of IVF resulting in pregnancy. If pregnancy has not been achieved

despite prolonged efforts, it is likely that other significant factors are also at work (Emi05). One influence that receives particular attention in the literature is the availability of the adhesion proteins required for nidation. A deficiency of these proteins may adversely affect the chances of pregnancy (Les02, Mac02, Gen03).

Researchers have reported that PGS increases the prospect of the nidation of a transferred embryo (Mun02b). The number of spontaneous abortions also appears to be lower following PGS (Mun02a). The process seems to be particularly beneficial for older women (Kul03b). The reader is, however, referred to Subsection 3.2.

The research into the relationship between aneuploidy and IVF raises certain questions. One is whether PGS leads to the exclusion of mosaic embryos, which could in fact have resulted in healthy pregnancies (the number of abnormal cells being small and selection against those cells being possible). Another pertinent question is at what stage of embryonic development it is best to investigate chromosomal make-up. It may be significant for the prospects of success that, when PGS is involved, the embryos are generally transferred to the prospective mother on day 4 or 5, compared with day 3 in conventional IVF. Furthermore, it is not clear what effect blastomere biopsy has on the cryopreservability of (surplus) embryos.

3.2 Effectiveness of PGS

In order to assess the effectiveness of PGS, it would be helpful to know the number of live births per treatment started. However, no value is clearly stated for that parameter in any of the published study reports. In most cases, no figure is reported for the number of ongoing pregnancies either. In this Section, therefore, reference is made mainly to the implantation rate (likelihood of nidation), pregnancies (hCG detectable) and clinical pregnancies per cycle, and miscarriages per clinical pregnancy. It is often unclear from the reported data whether the number of cycles equates to the number of treatments started (with hormone stimulation) or to the number of surgical ovum punctures performed (see Annex C; IVF procedure).

3.2.1 Elevated maternal age

Only two randomised studies into the effectiveness of PGS in older women are reported in the literature (Wer03a, Sta04). The first study involved just seven PGS patients and twelve control patients and yielded little useful information (Wer03a). The second, performed at the Free University in Brussels, involved

four hundred couples, 148 PGS cycles and 141 control cycles (Sta04, Pla05a). In the PGS group, eighty-one embryo transfer procedures were performed (involving an average of 2.0 embryos); in the control group, the figure was 121 (with an average of 2.8 embryos). No statistically significant differences in outcome were observed. The research did, however, shed additional light on the causes of infertility (Pla05a).

In addition, six non-randomised comparative studies have been reported (Gia97, Gia99, Mun99, Kah00, Oba01, Mun03). In some cases, the same data are reported in more than one publication (Gia97, Gia99, Mun99). The control group used by some researchers consisted of younger patients who had experienced repeated implantation failures; the results of the research in question are not therefore considered here (Kah00). Other researchers reported only data on patients who had progressed to the embryo transfer stage of the process; only the implantation figures and miscarriage figures from this source have been used (Mun99). The data from the other studies are included in the summary, regardless of any irregularities or weaknesses in the methodology. Hence, the data presented below exhibit inconsistencies in the minimum age for inclusion, which varies from thirty-five (Mun99, Mun03) to forty (Oba01). This may influence the results, because PGS may be more effective in older women (Gia99, Mun03, Oba01). Another methodological weakness is disparity between the PGS and control groups in terms of the number of embryos transferred. It appears that, in all the studies, the average number of embryos transferred was higher in the control group than in the PGS group.

If, despite the various problems referred to above, the data are collated (Tables 3, 4 and 5), PGS appears to result in significantly improved nidation in older women. However, this does not translate into an increased likelihood of (clinical) pregnancy, probably because, in the PGS groups, fewer embryo transfers were performed, as a consequence of the rejection of embryos following PGS and the phenomenon known as ‘unit-of-analysis error’. The latter entails statistical conclusions being drawn in the context of a randomised controlled trial, regarding a unit other than that which was randomised: a practice that is methodologically flawed. In this case, the error involved a trial in which the women were randomised (making the woman the unit of analysis), but conclusions were drawn regarding the embryo implantation rate.

PGS appears to be associated with fewer miscarriages per clinical pregnancy. However, no usable data are available on the number of ongoing pregnancies per cycle or the number of live births per cycle.

Subanalysis on the basis of age indicates that the PGS effects referred to above increase with maternal age (Gia99, Mun03, Oba01). PGS also appears to be more effective as the number of embryos available for analysis increases (Mun03).

Table 3 Effect of PGS - maternal age – comparative studies.

Outcome indicator	Ref.	PGS	%	Control	%	OR	RR
						CI 95%[a]	CI 95%
Implantation (per embryo)	Gia99, Mun99, Mun03, Oba01	150/781	19.2	170/1451	11.7	1.79 (1.40-2.29)	1.64 (1.34-2.01)
HCG+ (per cycle)[b]	No data						
Clinical pregnancy (per cycle)	Gia99, Oba01	28/100	28.0	44/153	28.8	0.96 (0.53-1.75)	0.97 (0.65-1.45)
Ongoing pregnancy (per cycle)	No data						
Miscarriages per clinical pregnancy	Gia99, Mun99, Oba01	8/70	11.4	22/79	27.8	0.33 (0.13-0.87)	0.41 (0.2-0.86)

[a] CI: confidence interval
[b] HCG+: positive pregnancy test

Table 4 Effect of PGS - maternal age – polar bodies biopsy (comparative study).

Outcome indicator	Ref.	PGS	%	Control	%	OR	RR
						CI 95%	CI 95%
Implantation (per embryo)	Mon04a	33/214	15.4	63/490	12.9	1.24 (0.76-1.99)	1.20 (0.81-1.77)
HCG+ (per cycle)	Mon04a	34/140	24.3	59/279	21.2	1.20 (0.72-1.99)	1.15 (0.79-1.66)
Clinical pregnancy (per cycle)	Mon04a	27/140	19.3	49/279	17.6	1.12 (0.64-1.95)	1.10 (0.72-1.68)
Ongoing pregnancy (per cycle)	Mon04a[a]	22/140	15.7	39/279	14.0	1.15 (0.63-2.09)	1.12 (0.69-1.82)
Miscarriages per clinical pregnancy	Mon04a	5/27	18.5	10/49	20.4	0.89 (0.23-3.3[b])	0.91 (0.35-2.38)

[a] HCG+: positive pregnancy test
[b] not accurate

Table 5 Effect of PGS - maternal age – randomised studies.

Outcome indicator	Ref.	PGS	%	Control	%	OR	RR
						CI 95%	CI 95%
Implantation (per embryo)	Sta04	28/164	17.1	39/338	11.5	1.58 (0.90-2.76)	1.48 (0.95-2.32)
HCG+ (per started cycle)	Sta04, Wer03a	32/207	15.5	42/212	19.8	0.74 (0.43-1.26)	0.78 (0.51-1.19)
Clinical pregnancy (per started cycle)	Sta04	22/200	11.0	30/200	15.0	0.70 (0.37-1.31)	0.73 (0.44-1.23)
Ongoing pregnancy (per started cycle)	Sta04	22/200	11.0	29/200	14.5	0.73 (0.39-1.37)	0.76 (0.45-1.27)
Miscarriages per clinical pregnancy	Sta04	0/22	0	1/30	3.3	-	-

3.2.2 *Repeated implantation failure*

The only outcome indicator used in the randomised study into the effect of PGS on repeated implantation failure (Wer03a) was pregnancy (hCG) and the number of patients involved was small. In addition, five non-randomised studies have been reported (Gia97, Gia99, Kah00, Peh03, Mun03). There is some overlap in the reported data (Gia97, Gia99). One study, in which PGS for patients with an average age of thirty following repeated implantation failure was compared with PGS for patients with an average age of 38 years has not been included in this summary (Kah00). Of the data from another study, only the implantation figures have been included (Mun03).

The data presented in Table 6 do not indicate that PGS has any clear effect on repeated implantation failure. However, the small number of cycles involved may be a factor. It appears that embryos may implant more readily following PGS, but some of this effect may be due to the high maternal age in one research (Mun03: average maternal age is forty, compared with thirty-one to thirty-three in the other study), and to the effect of the unit-of-analysis error once more (see 3.2.1).

Table 6 Effect of PGS - repeated IVF/ICSI failure.

Outcome indicator	Ref.	PGS	%	Control	%	OR	RR
						CI 95%	CI 95%
Implantation (per embryo)	Gia99, Mun03, Peh03	36/204	17.6	38/312	12.2	1.55 (0.92-2.61)	1.45 (0.95-2.21)
HCG+ (per cycle)	Wer03	2/10	20.0	0/9	0	---	---
Clinical pregnancy (per cycle)	Gia99, Peh03	16/59	27.1	9/39	23.1	1.24 (0.44-3.53)	1.18 (0.58-2.39)
Ongoing pregnancy (per cycle)	No data						
Miscarriages per clinical pregnancy	Gia99, Peh03	2/16	12.5	1/9	11.1	1.14 (0.06-37.8)	1.13 (0.12-10.8)

3.2.3 *Repeated miscarriage*

In the literature, data regarding the effect of PGS on repeated miscarriage are sparse (Pel99, Rub03, Wer03a, Pla05b). Again, there is overlap in the reported data (Pel99, Rub03). Although some researchers have reported improvements in association with PGS, the relevant study did not include a good control group. Following PGS, 139 embryos were transferred to fifty-eight women who had suffered repeated miscarriage; the procedures resulted in the birth of thirty-four children (Mun05). However, it is not possible to know how many children would have been born following IVF without the use of PGS. In another study, the sole outcome indicator used was elevated hCG (Wer03a). The influence of PGS both on implantation and clinical pregnancy and on the miscarriage percentage is reported in only one study (Rub03). PGS was not found to have any clearly discernible effect on the number of clinical pregnancies or ongoing pregnancies. It did appear that the implantation rate was slightly higher in the study group following PGS, but this effect was apparent only in patients aged thirty-five and above (Rub03), possibly due to the positive effect of PGS on implantation at elevated maternal age. In a prospective cohort study (49 women; ongoing pregnancy as outcome indicator), aneuploidy testing was not found to have any better effect (Pla05b).

The likelihood of spontaneous ongoing pregnancy following repeated miscarriage appears to be greater than the likelihood of pregnancy following IVF, with or without PGS (Bri99, Cli97, Str84). Repeated miscarriage does not therefore appear to be an indication for PGS.

Table 7 Effect of PGS - repeated miscarriage.

Outcome indicator	Ref.	PGS	%	Control	%	OR	RR
						CI 95%	CI 95%
Implantation (per embryo)	Rub03	28/100	28.0	12/56	20.6	1.43 (0.62-3.33)	1.31 (0.72-2.36)
HCG+ (per cycle)	Wer03	7/11	63.3	3/8	37.5	2.92 (0.31-30.8)	1.70 (0.62-4.61)
Clinical pregnancy (per cycle)	Rub03	23/86	26.7	9/35	25.7	1.02 (0.39-2.76)	1.02 (0.52-1.97)
Ongoing pregnancy (per cycle)	Rub03	9/86	10.5	4/35	11.4	0.91 (0.23-3.81)	0.92 (0.30-2.78)
Miscarriages per clinical pregnancy	Rub03	3/23	13.0	0/9	0	---	---

3.2.4 *Conclusion regarding the effectiveness of PGS*

The conclusion is that – although PGS is in increasingly widespread use – its effectiveness and safety are not yet proven. The few studies so far conducted into the effectiveness of PGS are hard to compare, because of terminological and methodological differences.

At higher maternal age, PGS has been found to increase the likelihood of embryo nidation – in practical terms, to increase the chance of pregnancy per transferred embryo. However, the increased nidation rate was not associated with an increased likelihood of pregnancy per started treatment (partly because fewer embryos are or can be transferred). The percentage of miscarriages per clinical pregnancy appears to decline following PGS. It has recently become clearer which subgroups benefit most from PGS, namely relatively old women (>37) whose IVF treatment leads to the creation of several embryos. Future research needs to be directed towards ascertaining how effective PGS actually is. Various randomised controlled trials are currently being performed with that aim in mind.

The data on the use of PGS to assist women following repeated IVF failure or repeated miscarriage are sparse and provide no clear evidence that the procedure is effective. More research is required. Nevertheless, it seems improbable that PGS might be indicated for repeated miscarriage, since the likelihood of a spontaneous ongoing pregnancy is greater than the likelihood of pregnancy following IVF (with or without PGS).

The Committee therefore considers it premature to routinely perform PGS or make it available. If further research should demonstrate that PGS increases the percentage of started treatments that lead to a live birth, it will be important to clearly define the circumstances under which PGS is indicated and to take steps

to assure the quality of the procedures performed. Such research is currently under way in four centres in the Netherlands, with the necessary consent from the Central Committee on Research Involving Human Subjects (CCMO). Information from one of those studies indicates that 54 per cent of the embryos produced using the ova of women aged thirty-five and above were abnormal, and that ongoing pregnancy was induced in 16 per cent of the women (Mas04).

In public health terms, the greatest benefit potentially attainable with PGS is a reduction in the frequency of obstetric and perinatal problems associated with multiple pregnancies. The Committee attaches great importance to procedural improvements that contribute to a reduction in the number of multiple pregnancies. PGS might make it viable to transfer single embryos to the prospective mother. Another possible reason for using PGS is to avoid the need for trisomy testing during pregnancy; this would principally involve women for whom IVF is indicated. However, it has yet to be shown that the technique is effective and reliable.

3.3 Ethical aspects

The acceptability of PGD was considered in Subsection 2.2.1. The PGD-related issues surrounding the protection status of the embryo are equally relevant in the context of PGS. However, it does not follow that, because PGD is acceptable, PGS is also acceptable, if only because the two differ fundamentally in their purpose. While PGD is intended to avoid the possible need for *abortus provocatus* in circumstances where an unborn child has a serious genetic condition, PGS is a means of increasing the likelihood of bringing about an ongoing pregnancy (Mun02a, Kul03b) and reducing the neonatal morbidity associated with multiple pregnancy (Mac03, Mon04b, Thu04). It is also possible to use PGS as an alternative to prenatal trisomy testing in women who receive IVF treatment. In that context, it is important to recognise that, if a screening test indicates an elevated likelihood of a chromosome abnormality and an invasive diagnostic test is later performed, there is a risk that the necessary surgical puncture will lead to miscarriage.

With regard to the acceptability of PGS aimed at increasing the likelihood of pregnancy, the question is whether that goal is sufficiently important to justify the genetic selection of embryos. In practice, IVF entails selection on the basis of morphological criteria, which is not in principle more or less ethical than selection on the grounds of genetic criteria. In fact, morphological and genetic criteria overlap to some extent (the number of pronuclei may be indicative of an abnormal number of chromosomes). Nevertheless, differences between two

techniques in terms of efficacy or safety may justify permitting one and not the other. Hence, the Committee takes the view that PGS-based selection with the aim of increasing the likelihood of pregnancy is no less acceptable than selection by established means, provided that the PGS technique used is effective and (where the biopsy element in particular is concerned) safe. The same principle applies to the use of PGS with the aim of making single-embryo transfers viable.

As well as considering the question of PGS's acceptability as a method for increasing the likelihood of IVF resulting in pregnancy or as a method for reducing the number of multiple pregnancies, it is important to recognise that the selection of embryos by means of PGS will generally yield information about the embryo's gender (see also Subsection 2.2.10) and about certain numerical chromosome abnormalities that do not always lead to spontaneous abortion. The risk of such abnormalities can justify prenatal screening (GR01b). Couples for whom IVF is indicated may prefer PGS to conventional prenatal testing, because they are against *abortus provocatus* and are concerned that invasive diagnostic testing may lead to miscarriage (see also Subsection 2.2.2). The Committee considers it acceptable to accommodate such a parental preference by performing PGS, provided that the effectiveness and safety of the procedure are assured. If that is the case, couples who undergo IVF should be informed about the possibility of using PGS in the way described. A pregnant woman has a right to information about prenatal screening (TK03). Therefore, assuming that PGS is demonstrably effective and safe, it would be wrong not to tell IVF couples about the PGS option in good time; that would be tantamount to denying them access to a less invasive option. In cases where PGS is used, clear agreements should be made and recorded regarding the procedures to be undertaken, as currently happens with IVF (GR97, CBO03).

However, as explained above, there is not yet sufficient evidence that PGS is effective. Consequently, it is not possible to reach any conclusions regarding the efficiency of PGS or regarding the precise form it might take. Similarly, little is known about the safety of biopsy. Various researchers have pointed out that the outcomes following biopsy give no reason to believe that the procedure is injurious to the embryo (Vos01, Pic03, Mag04). However, it is not possible to be sure that it is not injurious (Ver04). The Committee accordingly recommends that, for the time being, the use of PGS should be restricted to scientific research aimed at improving IVF treatment. As indicated in Subsection 3.2.4, such research requires the approval of the CCMO in the Netherlands.

3.4 Estimate of the demand for PGS

PGS has the potential to help couples where there is scope to improve the likelihood of IVF resulting in pregnancy. Improvement in that regard could make the transfer of single embryos viable. PGS may also play an important role in situations where there are objections to performing an abortion in the event of the discovery that an unborn child has chromosome abnormalities that could have been detected by prenatal diagnostic testing.

In the Netherlands, more than 14 000 programmes of IVF treatment are provided per year (Kre02). If PGS were demonstrated to be effective and safe, it is probable that a large number of PGS procedures would be performed. Even if the indication for PGS were relatively narrow (e.g. if the procedure were indicated only for women aged thirty-six and above), the number involved would be considerable. However, as indicated in Subsection 3.2.4, PGS is currently appropriate only in a research context.

The total number of invasive prenatal diagnostic test procedures performed in the Netherlands has remained fairly stable since 1995 (Wpd00). About 12 000 procedures are performed each year: approximately 9 000 amniocenteses and 3 000 chorionic villi sampling tests. The number of chorionic villi sampling tests is in decline. The age profile of the client population is also changing. The percentage of women over the age of thirty-six undergoing invasive diagnostic tests has gone down from approximately 45 to 35 per cent since 1995.

However, the number of diagnostic procedures currently performed serves only as a general guide to the potential demand for PGS. Of the women made pregnant by IVF at the AMC, 7.5 per cent agreed to undergo invasive prenatal screening. Extrapolated to the country as a whole, that equates to several hundred women a year. Given the choice, these women might well prefer PGS, in order to avoid the possibility of selective abortion. It is not known how many women who currently decline to undergo screening following IVF might opt for PGS as a means of reducing the risk of having a child with a chromosome abnormality. Nor is it known how often women who currently become pregnant without IVF would, for the same reason, choose IVF plus PGS, or how many women choose not to have a child because of concerns about the risk of chromosome abnormalities. Collectively, those various groups of women could generate considerable demand for PGS.

Chapter 4

Legislation and regulations

In the Netherlands, the principal legislation governing the use of PGD and PGS is the Embryo Act (Emb02). More detailed rules are set out in the Planning Decree on Clinical Genetic Testing and Heredity Counselling (Pla03). This Section of the report first describes the rules that apply in various countries, then goes on to pose a number of questions concerning the Dutch regulatory framework.

4.1 Regulations in other countries

The regulations governing IVF and PGD/PGS vary considerably from country to country (Gun01, Bra02, Hen04). Some countries have no controls at all, others apply certain restrictions, and still others prohibit the procedures altogether.

In the USA there are no restrictions; PGS is commercially available in connection with IVF. Japan has no statutory controls either (Tak04). In most European countries, however, PGD/PGS has to comply with certain rules. In France, PGD is permitted for serious conditions (Viv00). A central Committee has licensed three centres to perform the procedures (Men04). HLA typing is permitted in cases where an older child has a life-threatening hereditary condition (Ste05b). In the UK, the Human Fertilisation and Embryology Authority allows PGD for serious diseases, as well as PGS and, under certain circumstances, HLA typing (Hfe01, Hfe04). In Germany, PGD/PGS is prohibited, as are other procedures not to the particular embryo's direct

advantage; PGD of polar bodies is permitted, however (see Annex C; Gun01, Sch03). A majority of members of Germany's national ethics Committee have called for the law to be changed to allow PGD (Eth03). In Austria, PGD is not permitted. However, the ban on PGD does not mean that PGS is necessarily prohibited; in vitro embryo assessment and treatment procedures necessary to bring about pregnancy are permitted in Austria (Gun01). Belgium has no regulations on PGD/PGS. In Norway, PGD used to be permitted only for serious X-chromosomal conditions, but is now also allowed for certain other special purposes (such as HLA typing). In Denmark, PGD is permitted, but the procedures have to be approved by a central Committee. The Minister of Public Health can give permission for HLA typing. Sweden also allows PGD. In Italy, PGD/PGS is prohibited; moreover, the practical effect of the existing legislation is to make IVF difficult (Tur04). In some non-European countries, the legislation reflects the view that the status of an embryo in vitro is inferior to that of a foetus: abortion is prohibited, but PGD permitted (Haz99, Luc01).

In the Treaty of Oviedo, the Council of Europe has prohibited artificial reproduction techniques whose purpose is to enable gender selection (article 14; RvE97). This prohibition does not preclude the use of techniques whose primary purpose is not gender selection, but which nevertheless reveal the gender of an embryo, as described in Subsection 2.2.10.

4.2 The Netherlands

In the Netherlands, the Embryo Act provides the regulatory framework for in vitro procedures with embryos (Emb02). The Act lays down various requirements that must be satisfied by any research on embryos (whether for scientific or other purposes). It also contains a number of prohibitions and sets out rules on information and consent. The Embryo Act is not the only law with implications for PGD and PGS, however. Other significant legislation includes the Exceptional Medical Procedures Act, the Termination of Pregnancy Act, the Medical Treatment Contracts Act (WGBO), and the Population Screening Act (WBO).

The Embryo Act defines an embryo as a cell or a cohesive body of cells with the potential to develop into a human being. It is worth noting that an embryo with an abnormality that is incompatible with life does not fall within this definition, and that amendment of the Act is therefore desirable (Wer01, Dut03).

Procedures with embryos (and gametes) whose purpose is to enable gender selection are permissible under the Embryo Act only for the prevention of serious gender-related abnormalities. A special situation arises where an

embryo's gender is already known from diagnostic testing for such an abnormality or from screening for numerical abnormalities. As indicated in Subsection 2.2.10, the Committee does not believe that, under such circumstances, gender selection is inherently unacceptable, provided that no additional procedures are required. The Embryo Act would appear to allow scope for such selection (Section 26 of the Act prohibits procedures whose purpose is gender selection; a situation such as that described would not involve any procedures).

In this context, it is pertinent to consider whether the selection of embryos on the basis of gender constitutes discrimination against people of a particular gender. Although gender selection is not inherently sexist or otherwise instrumentalising, in international practice gender determination is driven by the wish to have a son. Doubt has been expressed as to whether further selection on the grounds of gender and carriership of recessive conditions does actually require statutory regulation if no additional procedures are required (see Subsections 2.2.10 and 2.2.4). If not, any difficulties could be satisfactorily resolved in the context of the doctor-patient relationship (Dut03).

The Act makes no further provisions regarding the non-medical reasons for the in vitro testing of embryos referred to in Subsection 2.2.10. However, restrictions may be imposed via the protocol that (under the Planning Decrees) has to be compiled by any establishment where procedures are carried out with embryos. The statutory basis for the Planning Decrees in which the rules on the licensing of particular medical procedures are set out is the Exceptional Medical Procedures Act.

The legal restrictions mean that PGD is an option only in situations where there is a substantially elevated risk of a serious condition. As explained in Subsection 2.2.3, there are sound reasons for not specifying the conditions that qualify as 'serious'.

The Planning Decree on Clinical Genetic Testing and Heredity Counselling (Pla03) excludes PGD for the purpose of HLA typing. In circumstances where a child has a life-threatening condition, selection on the basis of HLA type could facilitate the use of umbilical cord blood from a future sibling for stem cell transplantation. One reason for prohibiting HLA typing is to prevent the instrumentalisation of a child subsequently produced by IVF. However, as explained in Subsection 2.2.9, the Committee takes the view that, given the considerable interest that the sick child has in securing a donor and the probably minor nature of any negative implications for the child produced by IVF, PGD for the purpose of HLA typing may be acceptable under certain circumstances. It is important that the IVF child is not wanted purely to act as a donor, and proper

counselling must be provided. Further provisions should be made under the Planning Decree to cover this point. The Committee does not believe that it is necessary to distinguish between hereditary and other life-threatening diseases in this context (even though a hereditary disease may have been the reason for opting for PGD).

Under the Planning Decree, as an exceptional medical procedure, PGD is permitted in a designated centre (Maastricht University Medical Center). Thus, the Decree has brought to a close the period in which PGD had experimental status. Furthermore, the Decree allows scope for the creation of a second centre. The Committee advises leaving that possibility open for the time being (see Subsection 2.3).

In vitro procedures with embryos are additionally addressed by the Termination of Pregnancy Act. Preventing the nidation of an embryo does not qualify as the termination of pregnancy; because PGD and PGS take place before nidation, the other provisions of the Act are not relevant.

In the context of PGD and PGS, as in the wider field of IVF, clients must be properly informed and written consent must be obtained for any procedure undertaken (see Subsections 2.2.3-5, 2.2.9-10 and 3.3). These requirements stem from the WGBO, which gives certain general directions. The Planning Decree on In Vitro Fertilisation focuses mainly on how long surplus embryos are retained and what they may be used for (Pla98). If it is scientifically demonstrated that PGS is a safe and reliable alternative to prenatal screening for couples receiving IVF treatment, the information provided to such couples would need to highlight PGS as an option.

The Committee rejects the possibility that PGS might fall within the scope of the WBO, for two reasons. First, the statutory definition of screening covers only the examination or testing of people; it does not cover the testing of embryos. Furthermore, PGS may be viewed as a medical procedure performed in connection with a medical problem, namely impaired fertility. If PGS were carried out merely as an alternative to prenatal screening, only the first of those reasons would apply.

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Annexes

Annex **A**

Request for advice

The Hague, 7 November 2003
Reference IBE/E-2417401

Dear Mr Knottnerus,

Clinical genetic testing and genetic counselling form a rapidly developing field. Pre-implantation genetic diagnosis (PGD) was first used in the context of procedures leading to the birth of children in the early 1990s. PGD involves the in vitro testing or examination of ova or embryos with a view to detecting constitutional and hereditary conditions. Another possibility that is now available is pre-implantation genetic screening (PGS). In the Netherlands, this form of screening is currently used only in the context of scientific research.

The Centre for Ethics and Health addressed PGD and PGS in its 2003 surveillance report, highlighting various ethical issues on which policies should be defined.

The Clinical Genetics Regulations of January 2003 provide for PGD capability to be concentrated at a single centre, with the possibility of adding a second centre at a later date. I shall be pleased to learn whether you believe that a second centre is required to ensure the availability of (qualitatively and quantitatively) adequate PGD services.

It has become apparent that professional practitioners are unclear as to the circumstances under which PGD is indicated. As stated in the above-mentioned Regulations, the guiding principle is that PGD should be undertaken only in cases where there is a personal risk of a child being born with a serious hereditary condition or disease. Please let me know how you believe that that principle is best operationalised in connection with the following issues: additional selection on the basis of gender,

additional selection on the basis of carriership of a recessive condition, selection on the basis of late-onset conditions, selection on the basis of multifactoral conditions, and multiplex genetic testing.

In order to ascertain whether in due course the general application of PGS is desirable and acceptable, I need a coherent overview of the medical, ethical, medico-legal and social considerations that are relevant to decision-making in this field. I shall therefore be grateful if you will prepare such an overview and (partly by reference to the subsidiary questions listed below) formulate recommendations regarding the possible general use of PGS.

Subsidiary questions:

- What (which chromosomes) are studied in the context of PGS and why?
- How effective and safe is PGS? Does PGS lead to a (considerable) improvement in the prospects of success per transferred embryo?
- What volume of PGS services is envisaged (in terms of the number of procedures requested/ provided per year)?
- What are the potential applications of PGS and what is the primary target group?
- What should the general indications for PGS be?
- What ethical and social considerations are relevant to the application of PGS and is this form of diagnostic testing desirable? If so, subject to what conditions?
- What medico-legal considerations are relevant to the application of PGS?
- How is PGS regulated in other western countries?

I shall be grateful to receive your report no later than December 2004.

Yours faithfully,
Clémence Ross-van Dorp,
State Secretary of Health, Welfare and Sport

Annex **B**

The Committee

- Prof. B.C.J.M. Fauser, Professor of Reproductive Medicine, Utrecht University Medical Centre, *Chairman*
- Dr. L.L.E. Bolt, Ethicist, Ethics Institute, Utrecht University, Department of Medical Ethics and Philosophy, Erasmus MC, Rotterdam
- Prof. O.F. Brouwer, Professor of Paediatric Neurology, Groningen University Medical Centre
- Dr. J.M. Cobben, Clinical Geneticist, Emma Children's Hospital University Medical Centre, Amsterdam
- L.B.J. Geldof van Doorn, Ministry of Health, Welfare and Sport, *Adviser*
- Prof. J.P.M. Geraedts, Professor of Genetics and Cell Biology, University of Maastricht
- R.M. den Hartog-Van Ter Tholen, Ministry of Health, Welfare and Sport, *Adviser*
- Dr. G.C.M.L. Page-Christiaens, Gynaecologist, Utrecht University Medical Centre
- Prof. F. van der Veen, Professor of Reproductive Medicine, University Medical Centre, Amsterdam
- Dr. S.M. Weima, Clinical Embryologist, Utrecht University Medical Centre IVF Laboratory
- Dr. P.A. Bolhuis, Health Council, The Hague, *Secretary*

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

Methodology

The diagnosis of a genetic abnormality (or characteristic) in an embryo entails a combination of specialist techniques, whose application requires gynaecological, embryological and genetic expertise. First, an ovum has to be fertilised in vitro to create an embryo. Then one or two cells have to be biopsied from the embryo. The relevant genetic diagnosis is then made using this very small quantity of cellular material. If the analysis reveals the desired genetic composition and the embryo's morphological characteristics are good, it is transferred to the uterus, in the hope that nidation and an ongoing pregnancy will follow. These four steps are described in more detail in this Annex.

IVF Procedure

In vitro fertilisation (IVF) – literally meaning fertilisation in glass and also known as 'test tube fertilisation' – is the artificial fertilisation of an ovum in the laboratory, followed by transfer of the embryo thus produced to the uterus (in vivo) in order to bring about pregnancy. The success rate of this procedure is relatively low; 15 to 25 per cent of the attempts to achieve pregnancy in this way ultimately lead to a birth (per started cycle; GR98, Nyg01, Kre02). IVF treatment is generally provided at the same centre where the PGD is performed.

Hormones are administered to stimulate ovum maturation in the prospective mother, so that numerous ova come to maturity simultaneously. Under local

anaesthetic, between eight and fifteen ova are extracted from the ovaries by means of surgical puncture. These ova then undergo in vitro fertilisation.

Where PCR-assisted PGD is concerned, fertilisation almost always involves intracytoplasmic sperm injection (ICSI): the mechanical injection of a single sperm cell into the ovum (Geb02). ICSI makes PGD more reliable, because it ensures that there are no residual sperm cells around the embryo. DNA from such sperm can interfere with the genetic diagnosis by making it unclear whether a particular genetic characteristic belongs to the embryo or a surplus sperm cell.

The fertilised embryos are studied in the laboratory. Ensuring that transferred embryos are morphologically sound increases the likelihood of ongoing pregnancy. In many cases, therefore, embryos are selected partly on the basis of their morphological characteristics.

If several embryos are found to be morphologically sound, some undergo cryopreservation, i.e. are frozen under special conditions. Such embryos remain viable for a considerable time, enabling their implantation long after fertilisation.

Risks

The IVF procedure is not risk-free. Hormone stimulation can give rise to various problems and complications, including emotional stress and abdominal pain (Roe96). Harvesting of the ova also entails risk (GR98). The most serious problem that can develop is ovarian hyperstimulation syndrome, which affects 0.7 per cent of women who undergo hormone stimulation (Roe96, Ven01). It is estimated that one woman a year dies from the consequences of this syndrome in the Netherlands, and its long-term implications remain unclear (Fau99, Fau02). Research into the risks is complicated by the fact that IVF is typically provided to women in relatively good health (‘healthy patient effect’; Ven01). It is also important that steps are taken with a view to making the procedure safer, such as using a milder form of hormone treatment to reduce the incidence of hyperstimulation (Mac03b, Hui04, Fau04).

In the scientific literature, there has been discussion of the risk of congenital abnormalities following IVF (Mit02, Str02). An analysis of twenty-five studies from the period 1985-2002 revealed that the risk was indeed elevated: abnormalities were more common in children born following IVF (Hel04b). Researchers in Australia found one or more serious congenital abnormalities in roughly 9 per cent of IVF children: twice the percentage in the control group (Han02a). However, this research has been criticised because separate lists of congenital abnormalities were not given for the study and control groups and because various conditions of dubious relevance, such as hip luxation, were

included. It is not disputed, however, that some of the abnormalities were associated with multiple pregnancies, which are more common following IVF. There is also a significant risk of low birth weight in multiple births following IVF, albeit no greater than that linked to natural multiple births. Low birth weight is generally associated with a higher risk of abnormalities. It is therefore considered preferable that embryos should be transferred singly to the prospective mother's uterus (Bra03, Hel04b, Gor05).

However, even in single births, the average birth weight following IVF is significantly lower. A small proportion of the elevated risk of congenital abnormalities may therefore be attributable to factors linked to the artificial reproduction process (Kou00, Sch02).

Links have also been made between IVF and certain rare conditions, namely the Beckwith-Wiedemann syndrome (Mah03, Deb03) and a retinoblastoma (Mol03). However, because of the very small numbers involved, the significance of the observed associations is difficult to interpret.

It is not known what role infertility as such plays in the occurrence of abnormalities and what can be attributed to the procedure. There may be a direct relationship between infertility and an increased likelihood of congenital abnormalities. There again, certain aspects of the procedure, such as hormone stimulation, may increase the risk. Researchers suspect that some of the abnormalities are due to genomic imprinting errors (errors in the 'programming' of the genes), like those that characterise Beckwith-Wiedemann syndrome.

A meta-analysis of studies looking at the incidence of congenital abnormalities following ICSI and following IVF found no significant differences between the two (thirteen studies, relative risk 1.00-1.29, p=0.06; Smm02).

Biopsy

In order to perform a genetic analysis of a pre-implantation embryo, cellular material is required. There are three options for obtaining the material: from the blastomere, from the polar bodies or from the trophoblast (Vos01, Ser04). It is possible to freeze biopsied embryos for possible later implantation ('cryopreservation'; Jer03).

Blastomeres

The most common biopsy technique involves removing cellular material on day 3, when the embryo is at the six-to-ten-cell stage (blastomere stage). A single cell is biopsied, unless there are eight or more cells, in which case two are taken. No clear evidence is reported in the literature that this procedure has a negative

effect on in vitro or in vivo embryonic development, or on postnatal development (Vos01, Mag04). The likelihood of a successful biopsy is estimated to be 98 per cent (ESH02).

Polar bodies
Another option is to biopsy the polar bodies. As the ovum matures, a polar body forms, containing a complete set of chromosomes. After fertilisation, a second polar body forms. These bodies are normally lost, but can be removed for diagnostic testing. Because the genetic composition is complementary to the maternal contribution to, respectively, the mature ovum and the embryo, it is possible to deduce the mother's genetic contribution to the embryo. The biopsy of polar bodies has no adverse effect on embryonic development. One drawback of this technique is that the paternal genetic contribution remains unknown; hence, polar body biopsy is suitable only as a means of testing for dominant genetic mutations of maternal origin and for aneuploidies, which are of maternal origin in approximately 90 per cent of cases (Has01). Polar body biopsy is quite common in the USA, but not often used in Europe (ESH02).

Trophoblasts
A third possibility is to extract cellular material from the embryo in the blastocyst stage. By that stage, the embryo has increased to about a hundred cells, and a distinction has developed between the cells that will go on to form 'embryo proper' (the embryoblasts), and the cells that will form the amniotic sac and placenta (the trophoblasts). From the latter group of cells, a relatively large amount of genetic material (up to fifteen cells) is removed, which simplifies the diagnostic test process. This form of biopsy is rarely practical, however, because to date only 10 to 20 per cent of embryos have been found to develop in vitro to this stage. Consequently, the likelihood of successful transfer is too small to justify clinical application of the process (Fin00).

Laboratory diagnosis

The biopsied cells are examined by means of polymerase chain reaction (PCR) or fluorescence in situ hybridization (FISH).

Diagnosis can be complicated by the occurrence of mosaicism, where embryonic cells do not all have a uniform genetic composition. This phenomenon gives rises to uncertainty, especially if only one cell is biopsied, as to how representative the biopsied cell is of the embryo as a whole. A cell which, as a result of mosaicism, is not representative can give rise to a false negative or

false positive test result. A false negative will result in misdiagnosis, as described in a case of trisomy affecting chromosome 21 (Mun98). The likelihood of misdiagnosis can be reduced by biopsying and analysing two cells. The second biopsied cell can also be used to pick up a false negative diagnosis. A false positive diagnosis reduces the number of embryos available for transfer and thus the likelihood of IVF resulting in pregnancy (Fin00). Conventional prenatal tests are sometimes carried out to check whether a false negative diagnosis has been made at the PGD or PGS stage.

PCR

PCR is a process by which a particular piece of DNA is copied repeatedly. Any mutations in the DNA may then be detected by various methods. PCR is useful in connection with monogenetic abnormalities involving a known mutation at a known location. In many cases, the mutation is directly detectable in the copied DNA; sometimes, however, it is necessary to use markers located in the vicinity of the mutation. Because only a small quantity of genetic material can be removed from the embryo, considerable amplification is needed for the diagnostic testing. In the amplification process, great care has to be taken to prevent contamination. The presence of DNA that is not of embryonic origin is liable to mean that the analysis results are unclear or incorrect. Contamination may be caused by paternal DNA (surplus sperm cells), maternal DNA (cumulus cells), or DNA from other people present in the laboratory. As explained in Subsection 3.1, ICSI is used to prevent contamination by surplus sperm cells. Cumulus cells are removed prior to the biopsy. Contamination by third-party DNA is prevented by using 'sealed' laboratory facilities, within which analysis takes place in a special area. As a check, polymorph markers can be examined to confirm that there is no DNA present other than the two paternal and two maternal alleles (Wel01).

There is also a danger of the amplification itself leading to misleading results. Sometimes, one of the two paternal alleles cannot be amplified by PCR (or at least not properly), a phenomenon known as allele drop out (ADO). ADO can lead to an allele with a mutation being overlooked. Misdiagnosis of a gender-related disease following ADO of the Y chromosome has been reported (Har94). In most cases, ADO can be detected by adding PCR markers (multiplex PCR). These markers are invisible if an allele has not been amplified. In recent years in Europe, no diagnosis has been possible in 18 per cent of cases involving embryonic biopsy followed by PCR (ESH02, Table XIA).

No systematic research has been conducted, from which it is possible to say how often the results obtained are unreliable.

PCR has one important advantage over FISH, namely the process speed. Obtaining a result quickly enables a healthy embryo to be transferred to the prospective mother at the earliest opportunity, which in turn increases the prospects of survival.

FISH

FISH is a technique that allows segments of chromosomes to be viewed. Although it is not possible to establish a particular base sequence, the presence of (a segment of) a chromosome can be detected.

In the past, the technique was used mainly in connection with recessive gender-related diseases to detect embryo gender. However, it is increasingly common that the specific mutation responsible for a gender-related abnormality, or the mutation's position on the X-chromosome, is known. In such cases, PCR can now be used for diagnosis.

Nowadays, FISH is used mainly for the detection of aneuploidy (abnormalities in the number of chromosomes, in particular monosomy and trisomy) and chromosomal translocations (where segments of chromosomes interchange positions). Using the existing FISH technique, five to ten chromosomes in a single cell can be examined. For the detection of aneuploidy, PCR methods have now been developed, which not only make the diagnostic testing faster, but also allow a larger number of chromosomes to be examined (Fin01).

The likelihood of a particular FISH-based diagnosis proving unsuccessful is estimated to be 15 to 20 per cent (Har99, Fin00, ESH02).

CGH

One technique of which some researchers have high expectations is comparative genomic hybridisation (CGH; Wil05). This technique is similar to FISH, but allows all chromosomes to be analysed at the same time. By staining the embryonic DNA fluorescent green and standard DNA with a normal karyotype red, and then hybridising the two, any numerical abnormality is highlighted (if the chromosome numbers are equal, no red or green is visible). This technique appears viable once sufficient material has been obtained by PCR, but is currently still experimental (Wil01, Vou02). Researchers have compared the in vitro embryonic chromosome abnormality detection rates obtained using CGH and FISH. Twenty women who had experienced repeated implantation failure participated in the study. With CGH, more abnormalities were detected and

better results were achieved (15 per cent of procedures led to pregnancy, compared with 7 per cent with FISH; Wil03).

Embryo transfer

The last step of the PGD procedure involves transferring those embryos that are not affected by the relevant genetic condition to the prospective mother's uterus. Embryos are selected on the basis not only of their genetic characteristics but also of morphological criteria that are known to have predictive value in relation to the viability and quality of the embryo. Attention is also paid to the shape and appearance of the embryo and the cell division rate. It is estimated that only 11 per cent of embryo transfers lead to pregnancy (see Table VIII in ESH02). To increase the prospects of success, therefore, several embryos are often transferred at once. This increases the likelihood of pregnancy to 23 per cent per transfer procedure (ESH02). However, because complications are more common with multiple pregnancies than with single pregnancies, embryos should ideally be transferred singly (Mac03a, ESH03, Bra03). It appears that the likelihood of pregnancy does not go on increasing the more embryos are transferred. Researchers have developed a model, which can be used to predict the likelihood of pregnancy from the following input parameters: the age of the woman, the development of the embryos in vitro, and the day of transfer (Hun03).

Annex **D**

Information about PGD at the Maastricht University Medical Center

PGD

Pre-implantation genetic diagnosis (Annex to the IVF leaflet)

Contents

PGD stands for pre-implantation genetic diagnosis: testing an embryo for hereditary conditions before it is transferred to the mother's uterus. PGD has been carried out at the Maastricht University Medical Center (azM) since 1995.

Who is PGD for?

In the past, it was possible to check for hereditary conditions only during pregnancy. Amniocentesis and chorionic villi sampling are the most common forms of prenatal diagnostic testing (i.e. diagnostic tests performed before birth). Prenatal diagnostic testing involves checking for hereditary conditions

once pregnancy has been achieved, whereas pre-implantation testing involves performing checks before pregnancy has started.

PGD is carried out only if one or both of the parents are associated with a serious hereditary condition with a high (repetition) risk – and, of course, if it is technically possible to test an embryo for that condition.

To be considered for IVF plus PGD, a couple must not only stand to gain from PGD, but also satisfy the azM's criteria for IVF. Before treatment can be provided, the Clinical Genetics Department has to consider the couple's genetic status. In addition, IVF team gynaecologists have to assess whether the couple can be helped with IVF, by doing hormone tests on the woman and sperm tests on the man.

The request for PGD is then discussed by the azM's PGD Committee, which decides whether a procedure can (in principle) be started.

What does a course of PGD treatment involve?

The object of PGD is to separate embryos that have the hereditary condition that is causing concern from embryos that don't, and then transferring only 'healthy' embryos to the mother's uterus. To obtain embryos for the selection process, it is necessary to follow an IVF procedure. The IVF procedure is largely as described in the leaflet 'IVF, Test Tube Fertilisation'. It involves giving the woman hormones to stimulate her ovaries, then performing a surgical puncture to collect the ova. These ova are fertilised in the laboratory before the resulting embryos are transferred to the woman's uterus.

For the PGD treatment to have a reasonable chance of working, at least four to eight ova have to be extracted from the would-be mother's ovaries. In most cases (depending on the condition that the PGD is intended to prevent), fertilisation is brought about using a method called ICSI. This involves introducing a single sperm cell to the ovum in the laboratory. Fertilisation has to be brought about this way, because testing for the relevant conditions can be difficult if other sperm cells, besides the one that has fertilised the ovum, remain attached. More information about the ICSI method is provided in the leaflet 'ICSI Treatment'.

Once an ovum has been fertilised in the laboratory by a sperm from the woman's partner, the ovum begins to divide. The first division typically occurs roughly thirty hours after the ovum has been extracted. Once an ovum has started dividing, we call the resulting group of cells an embryo. The first division results in two daughter cells, which themselves divide a few hours later. This continues, so that, about three days after extraction of the ovum, the embryo usually consists of eight daughter cells. This is the ideal point at which to remove some cells for PGD.

On the third day after fertilisation, one or two of the embryo's eight cells are removed. Removing material in this way is called biopsy. It involves using a very fine needle to make a small opening in the membrane surrounding the ovum. A slightly larger needle is then used to suck one or two cells off the eight-cell embryo.

The cells removed from the embryo are treated to make them suitable for genetic testing. If the tests find that the biopsied cell(s) is/are clear of the relevant genetic condition, it may be assumed that the embryo from which the cell(s) came is healthy.

The genetic testing is completed within a day, so that the 'healthy' embryos can usually be transferred to the would-be mother's uterus on the afternoon of the third day after ovum extraction, or the morning of the fourth day.

In a PGD procedure, one or two embryos are transferred. If more than one or two of the embryos created are deemed to be suitable for transfer, the 'extra' embryos may be frozen for future use, subject to consultation with you.

How likely is it that PGD will lead to pregnancy?

The likelihood of success (i.e. pregnancy) depends mainly on how likely it is that the IVF treatment will lead to pregnancy. On average, couples who receive IVF treatment because of fertility problems have about a 20-25 per cent chance of pregnancy. The likelihood of pregnancy for couples that undergo PGD is roughly 20-25 per cent per treatment.

What can be tested for?

At present, the centre at Maastricht can test for gender-related conditions, fragile X syndrome, cystic fibrosis (CF), spinal muscular atrophy (Werdnig-Hoffmann disease, SMA type 1, SMA type 2), Huntington's disease, certain forms of hereditary ataxia (SCA 3), myotonic dystrophy (Steinert's disease; only if the man has the disease), and a number of hereditary chromosome abnormalities. In PGD, the laboratory looks only for the particular condition that there is known to be an elevated risk of. Where most conditions are concerned, preparatory blood tests have to be carried out on both of the would-be parents and/or the family member who has the condition. The purpose of these tests is to make sure that PGD is actually possible.

Gender-related conditions include Duchenne/Becker muscular dystrophy, haemophilia A/B and some rare syndromes. When PGD is carried out in connection with a gender-related condition, distinction may be made between male and female embryos. Generally speaking, only boys get these conditions, so only female embryos will be transferred to the uterus.

When PGD is carried out in connection with fragile X syndrome, the embryo is tested to find out whether it has a predisposition to the condition. Distinction may be made between embryos (male or female) that are affected (i.e. have the predisposition) and embryos that aren't. PGD can be used to help about half of the couples who are at risk from fragile X syndrome.

PGD can be used for CF if both parents carry the deltaF508 mutation. If the parents carry (an)other mutation(s), preparatory blood tests are needed to find out whether PGD is possible. In PGD for CF, the laboratory checks to find out whether the embryos are affected (i.e. have a double predisposition to CF) or unaffected (i.e. completely clear of the mutation or carry it without being liable to develop CF). When transferring embryos to the uterus, it is not possible to distinguish between carrier-embryos and completely clear embryos. You can get more information about the transfer of carrier-embryos.

PGD can be used for spinal muscular atrophy if both parents are known to lack a segment of chromosome 5 that is responsible for hereditary predisposition. PGD can then distinguish between embryos that are affected and those that aren't. It is not possible to tell by PGD whether an embryo is a spinal muscular atrophy carrier.

Where Huntington's disease or SCA 3 is concerned, preparatory blood tests need to be carried out on both would-be parents to find out whether PGD is possible.

In PGD for myotonic dystrophy, distinction is made between embryos that are affected and those that aren't. PGD can't be used to find out how serious the disease would be in the person that the embryo might develop into. At Maastricht, PGD is used for myotonic dystrophy only if the man has myotonic dystrophy. If the woman has Steinert's disease, PGD is not carried out, because women with this disease may develop complications if they undergo IVF treatment. Under such circumstances, the alternatives to PGD will be discussed with you.

PGD can be used to assist couples where either the man or the woman carries a chromosome abnormality such as a translocation, if there is a high risk that the couple will have a child with an abnormal chromosome pattern, or a high risk of repeated miscarriage. Each couple has to be assessed individually to ascertain whether PGD is technically possible for them. This usually takes six to twelve months.

Where all the above-mentioned conditions are concerned, only embryos that have been found to be unaffected are considered for transfer to the would-be mother's uterus. Embryos that are found to be affected or for which the test results are indecisive are not considered for transfer. If more than one or two unaffected embryos are available for transfer, a choice is made on the basis of the embryos' shape and division rate.

If a woman who requests IVF/PGD has or carries a condition herself, more thorough testing may be needed to find out whether there is a risk of her suffering complications if she undergoes IVF treatment. A decision about whether to go ahead with PGD is made only once it is clear whether the woman is at risk.

How reliable is PGD?

At the moment, an embryo's gender can reliably be determined. If diagnostic tests are performed on two cells, the reliability is estimated to be 98 per cent. In other words, there is a 2 per cent chance that the result will be wrong. The reliability of diagnostic testing for conditions that do not involve gender determination is about 95 per cent in most cases. However, the reliability for an individual couple may be higher or lower. Because PGD has only recently been developed and every new method has its limitations, clients who become pregnant following IVF/PGD are offered chorionic villi sampling or amniocentesis as well.

Does PGD entail any risks?

As far as anyone is aware, the removal of one or two cells from an eight-cell embryo (biopsy) does not affect the embryo's development. Nor is there any clear evidence that children born following PGD are more likely to have abnormalities than other children. However, it is important to understand that relatively little experience has so far been gained with this new technique.

Where does PGD take place and how do you go about getting it?

In the Netherlands, PGD is currently carried out only at Maastricht University Medical Center. If you think that you may qualify for PGD, we advise you to begin by talking to your own clinical geneticist, gynaecologist or GP. After that, a written request may be made to the azM's PGD Committee. Contact details are provided below.

Each application is discussed by the PGD Committee. In some cases, the Committee may respond by telling the couple that it will not be (technically) possible to help them in the short term, or that their request has been turned down for some other reason. If PGD is in principle possible, an appointment will be arranged in Maastricht to discuss all aspects of the treatment and the available alternatives. Following this discussion, the findings may be considered by the PGD Committee again and you will be given time to think things over and decide whether you definitely want to go for PGD. If you opt to have PGD, one of the IVF team gynaecologists will need to carry out an examination. If IVF plus PGD can go ahead, you will be placed on a waiting list. When it is your turn, you will be invited to attend the Center.

The PGD Committee's Medical Coordinator is Dr C de Die-Smulders. Her phone number is 043 387 7855. If you have any questions, they should be addressed to Dr de Die-Smulders.

Written requests should be sent to:

Maastricht University Medical Center
Clinical Genetics Department
Attn. of Dr C de Die-Smulders
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6202 AZ Maastricht

How to get there

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