



EuroPGDCode:
PGD Folder

PGD Pre-implantation Genetic Diagnosis

One of the state-of-the art techniques of assisted reproduction is PGD, which stands for pre-implantation genetic diagnosis. This technique involves examining an embryo for congenital abnormalities before it implants in the uterus.

1. Who can benefit from PGD?

Until recently, congenital abnormalities could only be detected during pregnancy. This is done in so-called prenatal (literally: before birth) diagnosis, usually by means of amniocentesis or chorionic villus biopsy. Pre-implantation (literally: before implantation) genetic diagnosis is a new method. In prenatal diagnosis, abnormalities are detected after you have become pregnant, whereas pre-implantation examination can diagnose such abnormalities before you become pregnant.

PGD is only offered to couples who carry a *serious* hereditary disorder with a *high* risk of occurrence or reoccurrence. Another condition of PGD treatment is that it must be technically possible to detect the particular disorder in embryos.

To be eligible for IVF combined with PGD, you must not only be suitable candidates for PGD, but you must also meet the azM's conditions for IVF treatment. Prior to admission for treatment, your genetic aspects will be evaluated by the Department of Clinical Genetics, while your eligibility for IVF will be assessed by the gynaecologists of the IVF team. The latter depends on the outcome of hormone tests in the female partner and sperm tests in the male partner.

Each application for PGD is discussed by the PGD committee, which decides whether the procedure can (in principle) be started.

2. How does a PGD treatment work?

The PGD method was introduced in Britain in 1989. It was made possible by developments allowing the DNA and/or the chromosomes (and hence also the sex) of a single cell to be examined. The introduction of special new techniques has made it possible to evaluate the genetic information in an individual cell, and thus to distinguish between embryos with and without a particular genetic disorder.

The tests are performed on embryonic cells, which can only be done as part of an IVF treatment. The IVF procedure is carried out largely as described in our IVF brochure. It involves stimulating the ovaries with hormones, collecting eggs from them, fertilising the eggs in the laboratory and transferring them to the uterus. A successful PGD treatment requires at least eight eggs to be collected from the ovaries. For most of the disorders which allow PGD, fertilisation has to be achieved by means of the ICSI technique, in which one sperm cell is introduced into the egg in the laboratory. The use of ICSI is necessary in these cases because in a 'normal' in vitro fertilisation, other sperm cells than the one fertilising the egg may cling to the egg's surface and

hamper the PGD procedure. For more information on the ICSI method, see our brochure on that topic.

In a PGD treatment, one or two embryos are transferred to the uterus on the third or fourth day after egg collection. If more than one or two suitable embryos are available, you may decide to have the others frozen for transfer at a later moment.

After an egg has been fertilised with the male partner's sperm in the laboratory, it starts to divide. The first division takes place about 30 hours after the egg was collected, and from now on the egg is called an embryo. The division results in two daughter cells, both of which divide a few hours later. At about three days after collection, the embryo usually consists of eight daughter cells. This is the ideal stage for removing the cells required for PGD.

On the third day after fertilisation, one or two of the eight cells of the embryo are removed. This is done by using a very fine needle to make a minute opening in the membrane surrounding the embryo. A slightly larger needle is then used to remove one or two cells from the eight-cell embryo.

The cells thus removed are treated to allow genetic examination. This examination is done within one day, so that the 'healthy' embryos can be transferred to the uterus either in the afternoon of the third day after the eggs were collected or on the morning of the fourth day.

3. What are the chances of success?

The chances of success in terms of achieving pregnancy are largely determined by the success rate of the IVF treatment. For couples undergoing IVF treatment for reduced fertility, the chance of success is about 20-25% for each attempt. It is not yet known whether PGD influences this percentage, but it is expected that the chance of success for couples eligible for PGD will also be around 20-25% per treatment.

4. Which tests can be done?

At present, the offers tests for sex-linked disorders, fragile-X syndrome, cystic fibrosis (CF), spinal muscular atrophy (or Werdnig-Hoffmann disease, SMA type I and type II), Huntington's disease, certain forms of hereditary ataxia (SCA 3), Steinert's disease (myotonic dystrophy) and a number of hereditary chromosomal abnormalities. PGD tests are only used for those disorders for which the embryo is known to be at increased risk, *not* for any other disorders.

Most disorders require prior blood tests on both partners and/or the affected person to assess whether PGD is actually feasible.

Examples of sex-linked disorders include Duchenne's or Becker dystrophy, haemophilia A/B and certain rare syndromes. If sex-linked disorders are suspected, a test is used to distinguish between male and female embryos. Since these disorders normally occur only in male embryos, only female embryos are transferred to the uterus.

If PGD is used to detect fragile-X syndrome, the embryo is checked to see whether or not it has the genetic predisposition for the syndrome. A distinction can be made between embryos (whether male or female) which are affected (that is, show fragile-X predisposition) and those not affected. About half of all couples are eligible for PGD for fragile-X syndrome.

PGD for cystic fibrosis is possible if *both* parents are carriers of the delta F508 mutation. If the parents have one or more other mutations, blood tests will have to show whether PGD is feasible. In PGD for cystic fibrosis, embryos are examined to see whether they are affected (that is, have a double gene for CF) or are unaffected (that is, are merely carriers or have no genetic predisposition for CF). Embryos without genetic predisposition as well as those which are merely carriers are transferred. If you want to, you can be informed about whether the embryos to be transferred are carriers or not.

PGD for spinal muscular atrophy is only possible if the parents have already had an affected child, and it has been shown that one or more genes are missing from both copies of chromosome 5. PGD can then be used to distinguish between embryos which are affected and those which are unaffected. It is not possible to test embryos to see whether they are carriers of SMA.

PGD for Huntington's disease or SCA 3 requires both partners to have their blood tested to see whether PGD is feasible.

In PGD for Steinert's disease, the tests are exclusively used to distinguish between affected and unaffected embryos. The extent to which the disease will become manifest in affected embryos cannot be determined. If one of the parents of a couple is a carrier of a chromosomal abnormality (such as a translocation), PGD will be offered if there is a serious risk of having a child with an abnormal chromosomal pattern, or after repeated miscarriages in the past. The technical suitability of each couple for PGD has to be evaluated beforehand, which takes three to six months.

In all of the above situations, only embryos known to be *unaffected* will be transferred. Embryos which are affected or for which test results are inconclusive, will not be transferred. Should more than one or two unaffected embryos be available, their morphology and cell division rate will decide which ones are transferred.

If a woman who wishes to undergo IVF/PGD is herself affected or is the carrier of a genetic disorder, more elaborate examinations may be required to assess whether she might be at increased risk of complications during the IVF treatment. Only after such assessment will it be decided whether PGD can be performed.

5. How reliable is PGD?

Sex determination is currently highly reliable. This is a very accurate procedure. If two cells are available for diagnostic tests, the reliability is estimated at 98-99%; in other words, the risk of errors is 1-2%.

The reliability of PGD for non-sex-linked disorders is usually around 95%, though it may be higher or lower for individual couples.

Since PGD is a recent development, and any new method has its limitations, patients who become pregnant are offered chorionic villus biopsy or amniocentesis.

6. Does PGD involve any risks?

As far as is now known, the removal (biopsy) of one or two cells from the eight-cell embryo does not affect the development of the embryo. There have been no reports of increased percentages of abnormalities in children born after PGD. It should be emphasised, however, that experience with this new technique is still limited.

7. What is the difference between prenatal diagnosis and pre-implantation genetic diagnosis?

Pre-implantation genetic diagnosis is a new method, which has yet to prove its worth. The main difference between current methods like chorionic villus biopsy and amniocentesis is that these tests check for abnormalities after you have become pregnant, while pre-implantation diagnosis takes place *before* you become pregnant.

It is up to you whether you want to become pregnant in the 'natural' way, and then have prenatal diagnostic tests, or whether you opt for IVF combined with PGD.

8. Where is PGD done and how can I apply for it?

If you think you are eligible for this technique, we would advise you to consult your own genetic counsellor or gynaecologist. If they agree that this would be a suitable treatment for you, you can apply, in writing, to the PGD committee. Further details on the committee are listed below.

All applications are discussed by the PGD committee. You may then be told that PGD is not yet technically feasible in your case or that your application has been refused on other grounds. In many cases it will still be possible for you to be put on a waiting list, pending further technical developments. If PGD is, in principle, available for your case, you will be invited to come tofor a discussion of all aspects of the treatment and the available alternatives. The outcome of the discussion is then once again reviewed by the committee, and you will be given some time to consider whether you still want PGD. If you do, one of the gynaecologists in the IVF team will examine you.

If you are eligible for IVF-PGD, you will be put on a waiting list and you will be called in when it is your turn.