Stockholm PGT Center

Karolinska University Hospital

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Welcome to Stockholm PGT Center!

Reproductive Medicine and Clinical Genetics at Karolinska University Hospital

This publication contains information about preimplantation genetic testing (PGT). This method can be used to help couples with an increased risk of having offspring with a genetic disorder to conceive a healthy child. Assuming that you are already well-informed about the relevant disease and its pattern of inheritance in your family, the information provided here merely relates to PGT as a method, regardless of your diagnosis. Stockholm PGT Center offers PGT to couples at risk of passing on a severe hereditary disorder to their children (e.g. a monogenic disease or hereditary chromosomal abnormality). In exceptional circumstances, PGT may also include the determination of tissue type (so-called PGT-HLA) for which permission from the Swedish National Board of Health and Welfare is required.

Stockholm PGT Center was founded in 1996 as a collaboration between the Department of Reproductive Medicine at Karolinska University Hospital in Huddinge, responsible for the in vitro fertilisation, and the Department of Clinical Genetics at Karolinska University Hospital in Solna, responsible for the genetic diagnostic test. The PGT team is made up of:

- Administrative staff who deal with appointment bookings, respond to general enquiries and communicate with the rest of the team
- Geneticists (doctors and clinical geneticists) and medical technologists who provide guidance and perform genetic diagnostic tests
- Gynaecologists who plan and carrying out in vitro fertilisations
- Midwives responsible for synchronising the different stages of the treatment
- Embryologists and laboratory engineers who are responsible for the handling of eggs, semen and embryos including embryo biopsies in connection with PGT

What is PGT?

PGT is an alternative to traditional prenatal diagnosis and involves testing of embryos for a genetic disorder before they are transferred to the uterus and the start of a pregnancy. This requires in vitro fertilisation (IVF). IVF is a process where eggs are collected and then fertilised with the man's sperm outside of the body. A few days after conception, single cells are sampled from each of the embryos and tested for the specific disease. One of the embryos assessed as suitable will then be transferred to the woman's uterus and hopefully, result in a successful pregnancy. The advantage of PGT compared to traditional prenatal diagnosis is that the pregnancy can be initiated with the knowledge that the unborn child will not inherit the specific genetic disorder, thus minimising the risk of pregnancy termination. The disadvantage of PGT is that it is a long and complicated process.

It can be estimated that at least 10,000 children have been born into this world after PGT. The oldest of these children are now about 30 years old, and so far, no adverse effects of PGT have been reported. However, the number of children born after PGT is still relatively low and the follow-up period relatively short. In Sweden, the use of PGT is regulated by the Genetic Integrity Act 2006 and PGT is currently available in Stockholm and Gothenburg.

The chance of succeeding with PGT

The chance of becoming pregnant following PGT is around 35% for each embryo transfer though this can vary from couple to couple. Factors influencing the chance of succeeding are:

- The age of the woman - it is well known that the possibility of becoming pregnant using IVF decreases as the woman gets older and especially, after the age of 40
- Ovarian response to hormonal treatment
- The weight of the woman - obesity decreases the possibility of a successful IVF treatment
- Smoking
- Genetic diagnosis - the likelihood to find a healthy embryo varies.

Before starting a PGT-treatment the chance of having a successful treatment is carefully assessed. If the assessment shows a very low chance of a successful treatment, PGT will not be offered. In addition, each treatment cycle is followed by an evaluation to determine if a further treatment cycle can be recommended.

Preparations prior to PGT

PGT CRITERIA

A couple may be considered for PGT if:

- The woman's age/hormone levels/ultrasound scan suggest that her ovaries will respond favourably to treatment
- The man is fertile with a normal sperm count
- The couple live together and in a stable relationship
- One or both are carriers of a serious hereditary disease with a high risk of having an affected child
- Single-cell genetic testing is possible
- PGT-treatment funding is available

EXAMINATIONS

The genetic investigations of the couple must have been completed and the genetic mutation or chromosomal abnormality that is the cause of the disease must have been identified within the family. A single-cell test for PGT is then established and this can take anything from one month up to one year. The work-up of the test is most often carried out on blood samples from the couple. In some cases, DNA/chromosome samples are already stored at Clinical Genetics in Solna or a corresponding regional clinic. It is not unusual that additional samples have to be taken from other family members in order to establish the test in a reliable way.

To assess the ability of the ovaries to respond to hormonal treatment, a blood test is taken to measure the serum level of AMH (Anti-Mullerian Hormone) and an ultrasound scan of the ovaries performed for the purpose of counting the ovarian follicles. Anyone undergoing IVF treatment must also be screened for HIV, hepatitis B and C, syphilis and HTLV type I and II. The man will also need to leave a semen sample for sperm analysis.

CONSULTATIONS

Prior to starting PGT treatment, the couple must make an appointment with Clinical Genetics, Karolinska University Hospital Solna and also with Reproductive Medicine in Huddinge. This is usually initiated by a referral from a doctor/GP. Out of area patients will need a referral for outpatient specialist care. Appointments for patients from abroad can be made via Stockholm Care.

At the initial appointment with Clinical Genetics in Solna, the couple will meet a doctor or clinical geneticist for genetic counselling and information about PGT. The possibility to offer PGT depends on the genetic disorder and family circumstances. Usually, PGT can be performed once the diagnosis has been established for the couple in question. However, for a few couples PGT will not be possible due to difficulties to establish a reliable embryo analysis.

When visiting Reproductive Medicine at Karolinska University Hospital, the couple will meet a gynaecologist who will provide information about the IVF treatment, after which, they will also meet a midwife with experience in PGT.

Sometimes, the couple have not yet decided whether or not to go through with PGT, and in these cases the purpose of the initial appointment is to provide information and guidance.

Once the genetic test has been established, the scheduling of treatment is arranged through Reproductive Medicine at Karolinska University Hospital.

Throughout subsequent treatments, the couple will be in regular contact with Reproductive Medicine at Karolinska University Hospital. If required, a second appointment can be made with Clinical Genetics in Solna.

The PGT Treatment Cycle The

PGT treatment consists of 8 stages:

1) Stimulation of the ovaries for maturation of eggs
2) Egg collection
3) Sampling of semen and preparation
4) Fertilisation
5) Sampling of the embryo or a so-called embryo biopsy
6) Genetic analysis and selection of transferrable embryos
7) Transfer of embryo to the woman's uterus
8) Pregnancy test

STIMULATION OF THE OVARIES FOR MATURATION OF EGGS

The ovaries are stimulated with hormones in order for multiple eggs to mature simultaneously. The treatment usually begins with the suppression of ovarian function, otherwise known as downregulation. The treatment is given in the form of a nasal spray 21 days after the first day of the last period. During this time, the woman may experience some side-effects similar to those of the menopause such as hot flushes, night sweats, etc. However, these side-effects will improve and usually disappear once the treatment with hormone injections has started.

If required, an ultrasound scan or blood test is carried out after 14 days of downregulation. Once the down regulation is successfully completed, treatment involving follicle stimulating hormones being injected into the subcutaneous tissue below the naval will commence. The woman and her partner will both be instructed how to manage these injections themselves. The hormone injections stimulate the maturation of the ovarian follicles. During the treatment of hormone injections the woman may experience tenderness in her breasts as well as feeling bloated, nauseated and increasingly emotional. Ultrasound scans and blood tests may be used to monitor and control the effects of the hormone injections to optimise the treatment. The nasal spray treatment continues for the duration of the injection treatment period. The hormone injection treatment usually lasts for 10 - 12 days but may vary individually both in terms of length of time and dosage.

EGG COLLECTION

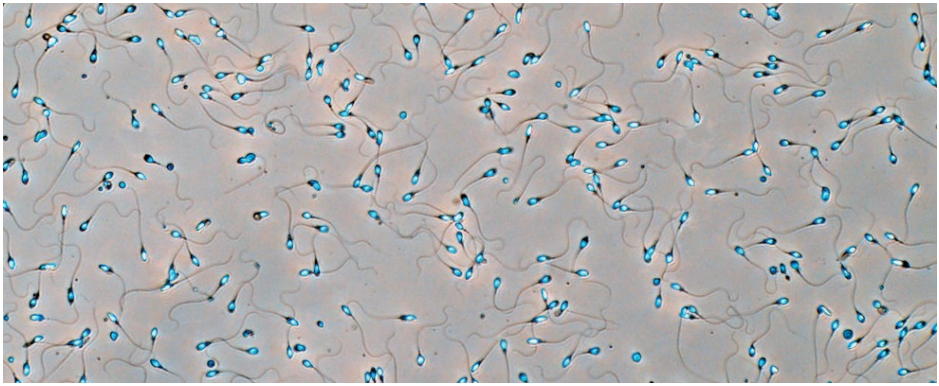
An ultrasound scan will determine on what day the egg collection is to take place. In some cases, the treatment may be interrupted due to under- or overstimulation. Two days before egg collection, in the evening, the woman is given an HCG hormone injection for a final maturation of ovarian follicles.

Egg collection is then carried out 34 - 39 hours after the HCG injection. Sedatives and painkillers will be used to make the woman as comfortable as possible whilst the egg collection is carried out. A local anaesthetic will be used to numb the upper vagina. An ultrasound probe is placed inside the vagina with a fine needle passing along side it. The needle is passed from one follicle to another, extracting the contents from within each follicle, which is then analysed microscopically by laboratory technicians. Every collected egg is placed in a bowl and put in a warming cabinet (incubator).

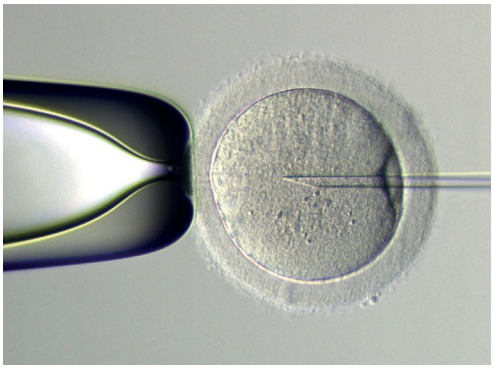
The collection of eggs usually takes around 20 minutes after which the woman is monitored for a few hours.

SAMPLING OF SEMEN AND PREPARATION

On the same day as the egg collection, the man will be asked to leave a sample of semen. This is then prepared and the semen safely stored. At times, a Sperm Retrieval Procedure may be necessary. This is when sperm is extracted directly from the epididymis or testis.



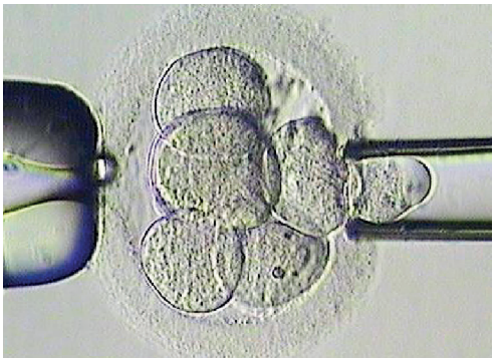
FERTILISATION



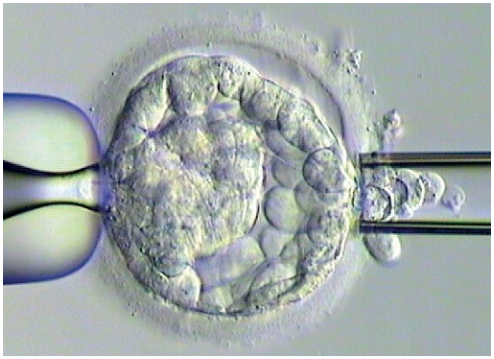
One sperm is injected into each of the eggs. This procedure is called an Intracytoplasmic Sperm Injection or ICSI. Already the next day, the eggs will be carefully examined to see if fertilisation has occurred. Fertilised eggs or embryos are then separated from the remainder eggs for further growth and development.

SAMPLING OF EMBRYOS (EMBRYO BIOPSY)

The embryo biopsy is either carried out on day 3 or day 5 - 6 after fertilisation, depending on the diagnostic method used. One cell (day 3) or 5 - 10 cells (day 5 - 6) are removed from each embryo.

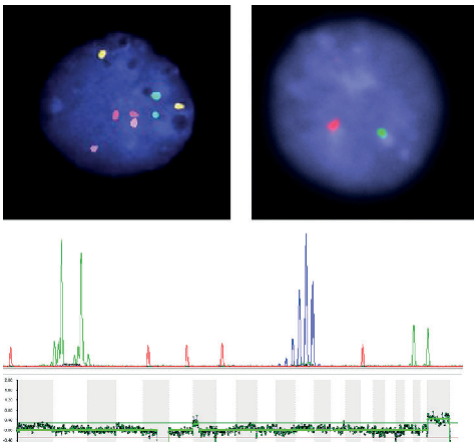


The cells collected are used for the genetic analysis whilst the remaining cells in the embryo will continue to grow and develop in an incubator to eventually form the basis of the fetus, placenta and fetal membranes. Embryos biopsied on day 5 or 6 after fertilisation are frozen immediately after the biopsy.



GENETIC ANALYSIS AND SELECTION OF HEALTHY EMBRYOS

The genetic analysis is performed at Clinical Genetics and the results forwarded to Reproductive Medicine at Karolinska University Hospital. A successful analysis makes it possible to determine which of the embryos have inherited the genetic disorder and which are expected to be unaffected regarding the specific disorder.



We do not endeavour to find out the gender and we do not distinguish between embryos that are healthy carriers from those that are non-carriers - unless considered necessary from a diagnostic viewpoint. The analysis of an embryo biopsy performed on day 3 takes no more than 24 hours. When performing embryo biopsies on day 5 or 6, embryos are cryo-preserved, allowing more time for the genetic analysis.

TRANSFER OF EMBRYO TO THE WOMAN'S UTERUS

Biopsy day 3: Once the analysis result has been received (usually four days after egg collection), one (or in selected cases two) healthy embryo is transferred to the uterus of the woman. If none of the available embryos are healthy, transfer will not take place. However, if there are surplus healthy embryos following a transfer, these may be frozen and stored. Such embryos can later be thawed for transfer to the woman's uterus, if an initial transfer do not result in pregnancy or if additional children and siblings are desired. Biopsy day 5 - 6: All embryos are frozen. Those embryos that are healthy may be selected for transfer to the woman's uterus following a normal ovulation or ovulation induction.

The woman's bladder should be as full as possible during the transfer of the embryo as this helps straighten up the uterus. It also makes it easier to insert and direct the thin plastic catheter that contains the embryo through the cervix and into the uterus. This procedure only takes a few minutes and is usually completely painless.

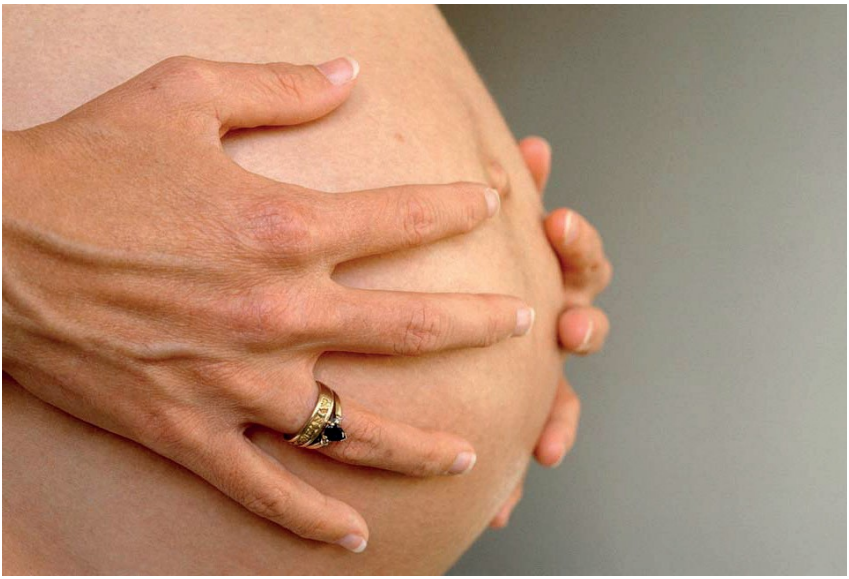
After the embryo transfer, the woman will need additional hormonal support in the form of progesterone. This is given by way of vaginal suppositories immediately after the egg collection or as prescribed by the doctor or midwife at Reproductive Medicine, Karolinska University Hospital. The progesterone medication continues until a pregnancy test has been carried out.

PREGNANCY TEST

Eighteen days after the egg collection and biopsy (day 3) or 13 days after the transfer of a frozen embryo, a pregnancy test is performed. If positive, an ultrasound is carried out 3 weeks later in order to determine the number of healthy and growing fetuses in the womb.

Follow-up and monitoring

WHEN PGT RESULTS IN PREGNANCY



Once the pregnancy is progressing, the couple may ask for an additional prenatal test in the form of a traditional placental biopsy in gestational week 11 - 12 or an amniocentesis (amniotic fluid sampling) in gestational week 15 - 16.

The couple must be informed of the likelihood of misdiagnosis after PGT (see next page), which should be weighed against the risk of a suffering a miscarriage after a prenatal test (0.1 - 0.5%).

The prenatal test should preferably be carried out at Karolinska University Hospital in Huddinge, Stockholm. If carried out at another location, we ask that the sample is forwarded to Clinical Genetics at Karolinska Hospital University for analysis. The analysis takes 1 - 3 weeks to complete, the result of which is always notified by letter and if possible, by telephone.

HOW ACCURATE AND RELIABLE IS PGT?

Cases of misdiagnosis after PGT have been reported but are still rare. Naturally, we do everything in our power to prevent this from happening. However, consideration should still be given to the minor risk of less than 1%.

PLEASE NOTE!

During the PGT treatment, the couple should use contraceptives to avoid a spontaneous pregnancy that has not been genetically screened.

CHILD(REN) BORN AFTER PGT

Couples who have been for an ultrasound scan and have a normal and developing pregnancy will recieve a “Confirmed pregnancy” form. The same form is sent by post to patients from other counties or from abroad. This form should be completed when the baby is born, and sent to Reproductive Medicine at Karolinska University Hospital

The information we need includes: Your child’s length and gender as well as method and date of delivery.

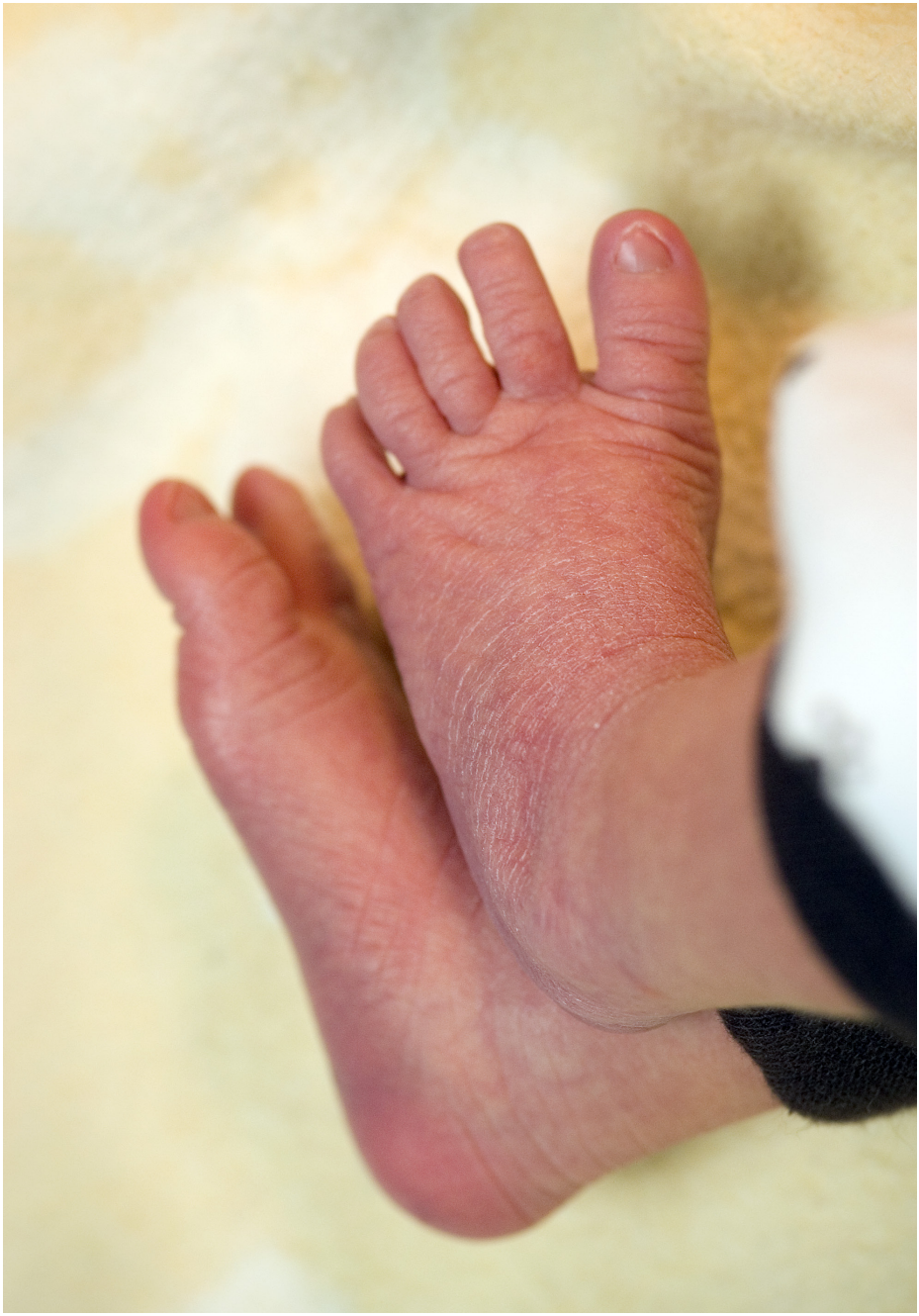
IF PREGNANCY FAILS AFTER PGT

In the event that a PGT cycle was terminated or if pregnancy does not occur, the couple will be invited to Reproductive Medicine at Karolinska University Hospital to discuss the possible reasons for this. Ways of improving the treatment and the couple’s chances for a successful pregnancy are discussed, and whether or not they would like to go through with another PGT cycle. If the probability of achieving pregnancy is assessed as small, the couple will be advised not to attempt another treatment cycle and alternative opportunities of having children discussed. Such alternatives may include traditional prenatal diagnosis, using donor sperm and eggs or adoption.

QUALITY ASSURANCE

Anonymised data relating to all PGT treatments is reported to an international database administered by ESHRE (the European Society of Human Reproduction and Embryology) and its PGT Consortium. The purpose of this is to monitor and assure the quality of PGT.

Please let us know should you wish to have your treatments excluded from the reporting of data to ESHRE.



CONTACT DETAILS

For additional information or to make an appointment, please call the Clinic

CLINICAL GENETICS +46 8 123 727 20 or

REPRODUCTIVE MEDICINE KAROLINSKA +46 8 123 875 06

For overseas patients:

KAROLINSKA UNIVERSITY HOSPITAL

INTERNATIONAL PATIENT OFFICE +46-8-123 475 00

email: ipo.karolinska@regionstockholm.se

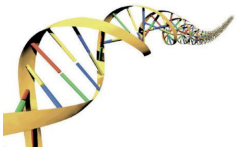
FOR FURTHER INFORMATION

Websites

CLINICAL GENETICS
www.karolinska.se/genetik

REPRODUCTIVE MEDICINE KAROLINSKA
www.karolinska.se/reproduktionsmedicin

ABOUT GENETICS AND HEREDITARY DISEASES
www.socialstyrelsen.se/ovanligadiagnoser



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