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Infertility and assisted reproduction

The purpose of this leaflet is to provide information on the causes of infertility and introduce methods of assisted reproduction.

Definition and prevalence of infertility

Infertility is defined as a situation where a woman has not been able to get pregnant after at least one year of regular sexual activity. Infertility is a common problem affecting up to 15% of couples. There may be *around* 20,000 couples suffering infertility in Estonia.

Infertility can be **primary** (no previous pregnancies) or **secondary** (infertility has developed after a previous pregnancy). 30% of infertility cases are due to the woman's infertility and 30% are due to the man's infertility. In the remaining 40% of cases, the causes can be mutual or remain unclear.

There is a wide range of modern infertility treatment options available. The choice of a specific treatment method depends on the causes of infertility, which require further investigations.

Most common causes of infertility

1. Disorders in egg maturation and release from the ovaries

Disorders in egg maturation and release from the ovaries account for 20-30% of the causes of female infertility.

Egg maturation is regulated by hormones produced by the pituitary gland: **follicle-stimulating hormone** or **FSH and luteinising hormone** or **LH.** FSH stimulates the growth of ovarian follicles, while LH is necessary for the maturation of the egg and its release from the ovary (ovulation). Follicles are fluid-filled sacs in which eggs mature.

If the pituitary gland produces too little or too much of one of these hormones, the maturation or release of the egg is disrupted.

Problems with the maturation and release of eggs can also result from an unhealthy diet, thyroid disorders and chronic diseases.

2. Damage to the fallopian tubes or the lining of the uterus

Damage to the fallopian tubes and the lining of the uterus is the leading cause of infertility in Estonia. Infections, endometriosis and surgeries can damage the lining of the uterus and prevent the embryo from implanting. Eggs are located in the ovaries, where a woman of fertile age matures and releases (ovulates) one or two (rarely more) eggs every month. The distal end of the fallopian tube directs the released egg from the ovary down the fallopian tube, where it can be fertilised. The developing embryo moves along the fallopian tube and reaches the uterus on the fourth day of development, attaching to the uterine lining seven to nine days after fertilisation.

If the fallopian tubes are not passable, the egg cannot move through the tube and meet the sperm, making fertilisation impossible. Damage to the fallopian tubes may be due to an inflammatory process caused by infections (chlamydia, gonorrhoea, etc.). In addition, the function of the fallopian tubes can be impaired by pelvic adhesions caused by surgeries involving the appendix, reproductive organs and abdomen, or due to endometriosis.

3. Endometriosis

Endometriosis is a disease in which tissue similar to the lining of the uterus grows and functions outside the uterus. Endometriosis damages the ovaries and leads to the formation of adhesions in the reproductive organs and abdominal cavity. Endometriosis affects 1-7% of women of reproductive age. The causes of the disease have remained unclear. Endometriosis can be treated with surgery or medication.

4. Changes in sperm count and quality

Causes of male infertility may include:

- congenital abnormalities (undescended testicles),
- hormone imbalances,
- chronic genital tract infections,
- infectious diseases (mumps),
- enlarged veins in the scrotum,
- chromosomal disorders (Klinefelter syndrome),
- damage to the nervous system,
- stress and lifestyle factors.

Sexually transmitted diseases and mutations in the cystic fibrosis gene can lead to damage in the sperm's pathways.

Causes of male infertility may also include:

- toxic substances (heavy metals, organic compounds, alcohol, tobacco, drugs, ionising radiation),
- medications (cytostatic agents, calcium channel blockers, anabolic steroids, psychotropic substances),
- trauma.

Semen analysis

A man’s fertility can be assessed using semen analysis. For the semen analysis to provide reliable results, the patient should refrain from the following for two to four days before sample collection:

- ejaculation (not less than two and not more than four days),
- alcohol consumption,
- sudden temperature changes (hot sauna, bath),
- strenuous physical activity,
- excessive fatigue.

The sample is collected via masturbation in a designated private room at the Centre for Infertility Treatment. The sample may also be collected at home. In this case, the semen should be delivered to the Centre for Infertility Treatment within one hour and kept at body temperature. The man must have an identification document with him.

During the analysis, the concentration, motility and morphology of the sperm are examined. It is also possible to detect infections during the analysis (the number of white blood cells in the semen) and sperm antibodies (MAR-IgG test), which can affect sperm motility. The parameters may change over time, so a repeat analysis should be performed if necessary.

Assisted reproduction

All methods of infertility treatment have one goal – to help achieve the union between the egg and sperm in the most natural way possible and to increase the chances of the egg getting fertilised and growing into an embryo. The ultimate goal is the development of a normal pregnancy in the uterus. Therefore, these treatments are collectively referred to as methods of assisted reproduction.

Assisted reproduction can be classified as **intrauterine and extracorporeal fertilisation**.

Intrauterine fertilisation

Intrauterine fertilisation or intrauterine insemination (IUI) is performed either with the husband's/partner's sperm (AIH) or with donor sperm (AID). During insemination, the sperm is introduced into the uterine cavity.

Indications for insemination include:

- mild male infertility (problems with sperm count, motility or morphology, the presence of sperm antibodies),
- infertility due to a cervical factor,
- unexplained infertility.

Successful insemination requires healthy fallopian tubes; the quantity and motility of the man's sperm are also important.

The success rate of insemination is *about* 10-15% per cycle.

Insemination can be carried out according to a woman's natural menstrual cycle or after ovarian stimulation. In the latter case, ovulation is induced using hormone medications. Better results are achieved when intrauterine insemination is timed with ovulation induced by fertility medication (ovarian stimulation).

Ovarian stimulation attempts to obtain up to three follicles. Tablets or injections are used for stimulation. During the stimulation, an ultrasound scan is performed to monitor the development of follicles.

Stimulation must be performed under the supervision of a doctor to avoid possible complications (excessive development of follicles, known as hyperstimulation).

Around the time of expected ovulation, the man's sperm is prepared and transferred into the uterine cavity using a thin catheter. The procedure is typically painless and does not require anaesthesia.

The procedure takes 10–15 minutes. After that, the woman can immediately get up, go home and continue with her daily activities.

If there are serious abnormalities in the man's sperm morphology and motility, frozen sperm from an anonymous donor can be used. All sperm donors are thoroughly screened for the most common genetic and viral diseases and all sexually transmitted diseases.

If intrauterine fertilisation fails, it can be repeated a maximum of three to four times. If pregnancy is still not achieved, it is possible to switch to extracorporeal fertilisation treatment (IVF and ICSI).

Extracorporeal fertilisation (IVF – *In Vitro Fertilisation* and ICSI – *Intracytoplasmic Sperm Injection*)

The general term for extracorporeal fertilisation treatments is assisted reproduction technology (ART) and the two most common and effective methods of ART are intracytoplasmic sperm injection (ICSI) and *in vitro* fertilisation (IVF). With IVF and ICSI, the success rates after one cycle fall between 25-30%; 15-20% of the women who get pregnant give birth.

The chance of getting pregnant decreases after the age of 37. Therefore, it is recommended to consider pregnancy, even in the case of assisted reproductive techniques, during the first half of a woman's 30s.

The only difference between the two treatments is the way the egg is fertilised. In IVF, the sperm is allowed to penetrate the egg naturally, while in ICSI, the sperm is directly injected into the egg. ICSI is performed under a microscope using special equipment. It is used when the sperm is unable to penetrate through the outer layer of the egg. Once the egg is fertilised, the embryo is transferred into the uterus in the same way as with IVF.

Fertilised eggs develop in an incubator for two to six days until they reach the embryo or blastocyst stage. The embryo is then transferred into the uterus, where it will hopefully implant and develop into a foetus.

One to three embryos or blastocysts are selected for transfer into the uterus. The remaining embryos/blastocysts are frozen if desired and can be used for later transfers within seven years.

For women up to the age of 40 who are insured by the Estonian Health Insurance Fund, embryo freezing and the first 60 days of storage are free of charge. After 60 days, the frozen embryos are stored for a fee according to the price list of the paid services of East Tallinn Central Hospital.

Before undergoing assisted reproductive techniques, both the woman and the man must undergo tests and examinations prescribed by a gynaecologist or general practitioner. The entire preparation process takes place on an outpatient basis and requires five or six appointments with the doctor.

The IVF/ICSI procedure consists of five stages and lasts for 30-50 days from the first day of preparation to the confirmation of pregnancy.

Five stages of IVF and ICSI

1. stage	Ovarian stimulation (preparatory treatment) and monitoring
2. stage	Egg retrieval
3. stage	Fertilisation of eggs
4. stage	Embryo development
5. stage	Embryo transfer

1. Hormonal stimulation of ovaries (preparatory treatment) and monitoring

The goal of preparatory treatment is to stimulate the simultaneous development of multiple eggs, a process known as controlled superovulation.

To increase the chances of pregnancy, it is important to have as many matured eggs as possible for fertilisation. Certain medications are used to prevent premature ovulation. Other medications stimulate the growth of multiple follicles in the ovary.

Injectable hormone medications are given to the woman to stimulate follicle growth and ovulation. An ultrasound scan is performed two or three times during the cycle to monitor follicle growth and medication dosages are adjusted if necessary. Blood tests are performed to monitor the level of hormones in the blood.

This stage of treatment lasts for 10-14 days.

There are mainly two types of treatment regimens used in preparation: short and long protocols. The doctor will decide which protocol is more suitable for the patient. In the long protocol, ovarian stimulation begins on the 21st or 22nd day of the menstrual cycle and the procedure itself takes place approximately one month after the start of stimulation. In the short protocol, ovarian stimulation is initiated at the beginning of the menstrual cycle (on day two to day five of the cycle) and the procedure takes place after two or three weeks.

When the diameter of the follicles reaches over 18 mm, the time for egg retrieval will be determined.

32-38 hours before the egg retrieval procedure, the woman injects a special medication at the time specified by the doctor to trigger the final maturation of the eggs.

2. Egg retrieval or ovarian puncture

The procedure of egg retrieval is performed using a thin needle under ultrasound guidance (a process called aspiration). The doctor identifies mature follicles through ultrasound and then guides the needle through the vagina, first in one ovary and then in the other, to gently extract follicular fluid containing eggs using controlled suction.

All the eggs are collected from the follicular fluid and transferred to an incubator. Not every follicle contains an egg and some follicles may contain eggs that are not viable for fertilisation The number of collected eggs may be fewer than the number of follicles observed during ultrasound monitoring.

Ovarian puncture typically takes 10–30 minutes.

It is performed under general anaesthesia, so the patient should refrain from eating and drinking on the morning of the puncture. The general anaesthesia is short-term and lasts only as long as the procedure itself.

After the procedure, the woman will be observed for a few hours in the hospital.

The sperm needed for fertilisation is collected from the man on the morning of ovarian puncture. On the day of sperm collection, the man should avoid physical exhaustion, alcohol and medication. The man should also abstain from sexual intercourse for two to three days before. All these factors affect sperm quality.

The semen is prepared through a process called "semen washing," during which the most viable sperm are separated.

In the case of male infertility (problems with sperm count, motility or morphology), the sperm can be injected directly into the cytoplasm of the egg (ICSI).

On average, 70% of eggs become fertilised with the IVF/ICSl procedure.

3. Fertilisation of eggs

In **IVF**, after the ovarian puncture, the sperm and eggs are brought together in an incubator set to body temperature. The next day, the eggs are examined under a microscope to determine whether the sperm have fertilised the egg(s).

The developed embryos are transferred into the uterus three to six days later or frozen for future embryo transfers.

In **ICSI**, the eggs are prepared for injection by checking their maturity. In a highly precise procedure, a single sperm is injected directly into the inner part of the egg's cytoplasm – hence the term "intracytoplasmic sperm injection". Approximately 20-24 hours later, the egg is checked to see if fertilisation has occurred.

4. Embryo development

Immediately after egg retrieval, embryos are cultured in the laboratory.

Typically, embryos are transferred between day three (an embryo made up of two to four cells) and day six (a blastocyst made up of about 100 cells) of egg retrieval. This allows for the observation of cleavage (how the embryo cells divide) and the development of embryos, enabling the selection of the most viable embryos for transfer.

5. Embryo transfer

One to three embryos are selected for transfer into the uterus. The main criteria for the selection of embryos suitable for transfer are morphological appearance and the speed of cell division.

One to three of the most suitable (viable) embryos selected in the laboratory are aspirated with a syringe into a thin catheter, which is used to pass the embryos gently through the vagina and cervix into the uterine cavity.

The procedure is guided by a transabdominal ultrasound to make sure the catheter is placed correctly.

After the removal of the catheter, it is immediately checked under a microscope for retained embryos.

The transfer is slightly uncomfortable but not painful, so it does not require anaesthesia. The transfer usually takes about 15 minutes. After that, the woman can immediately get up and continue with her daily activities.

After IVF/ICSI

From the day following embryo transfer, the doctor may prescribe certain medication to help maintain pregnancy.

Two weeks after the transfer, the woman will have a blood test to determine whether she is pregnant. An ultrasound examination can detect pregnancy as early as the 28th day after embryo transfer, when the diameter of the gestational sac reaches 10 mm.

Several factors influence the success of the procedure, including:

- the woman’s age,
- the cause of infertility,
- sperm quality.

Embryo freezing

The doctor aims to fertilise all collected eggs, but typically only one embryo is transferred at a time, occasionally two, very rarely three. The remaining viable embryos can be frozen through a process known as cryopreservation. The embryos are stored in liquid nitrogen at -196 °C and most of them remain viable for a long time. The majority of embryos will survive the process of freezing and thawing. An advantage of cryopreservation is that frozen embryos can be used for future transfers without having to repeat the steps of ovarian stimulation, egg retrieval and fertilisation.

According to the Artificial Insemination and Embryo Protection Act, the embryos can be preserved in frozen form for up to seven years. During this time, they can be used for a new transfer if desired.

Starting from the 61st day, cryopreservation of embryos is subject to a fee.

Frozen Embryo Transfer

Frozen mbryo Transfer (FET) can be used if the embryos were cryopreserved after the IVF/ICSl procedure.

If the IVF/ICSI procedure failed, previously thawed embryos can be transferred into the uterus in one of the following menstrual cycles.

Different protocols, both with and without medication, are used to prepare for the transfer of frozen embryos. The procedure for frozen embryo transfer is the same as for IVF/ICSI. The readiness of the uterine lining for embryo transfer is assessed through two to three ultrasound examinations. Embryos are thawed on the day of the transfer. Approximately 80% of embryos survive the freezing and thawing process. A pregnancy can develop even from a single thawed embryo.

Children born from frozen embryos are no different in terms of development from children born as a result of natural conception.

If, after thawing, the embryos are found to not be viable, no transfer will take place.

Risks associated with assisted reproduction

- Since the probability of having a child by means of assisted reproduction is 15-20% per cycle, **disappointment** due to the failure of the procedure is one of the most significant risks.
- **Multiple pregnancy** carries a higher risk of miscarriage, low birth weight and premature birth.
- The most serious complication is **ovarian hyperstimulation syndrome** (OHSS). OHSS is a condition where the ovaries are overstimulated by fertility medications. It can occur as a result of the administration of hormones. The ovaries may enlarge and accumulate excessive fluid. The ovaries react unpredictably actively to treatment, which results in damage to cell membranes in the body. Symptoms include abdominal pain and swelling, bloating, pressure in the stomach and rectum, nausea and, in severe cases, it can cause breathing or urinary problems. If you experience any of these symptoms, contact your doctor immediately. Generally, this condition requires hospitalisation. In some cases, it can be life-threatening.
- In rare cases, there may be **bleeding** (from the vagina or into the abdominal cavity). This complication can occur during ovarian puncture if a blood vessel is damaged.
- Very rarely, **infection** can occur as a result of hormone therapy.
- Patients may also experience **thrombotic** complications due to the use of fairly high doses of hormone medications. Thrombotic complications are more likely to occur in women with OHSS.
- In addition, assisted reproduction can cause other problems. Going through the treatment process is not always easy and success is not guaranteed. Even those who achieve pregnancy are at risk of treatment failure – miscarriage or fetal loss (as with natural conception).

If you experience any complications, contact your doctor immediately or seek emergency care at the Women's Clinic.

Preservation of gametes before fertility-impairing treatment or in the presence of a fertility-impairing condition

The Estonian Health Insurance Fund will cover the cost of gamete preservation for up to seven years for insured women up to the age of 35 and men up to the age of 40 before undergoing fertility-impairing treatment or in the presence of a fertility-impairing condition. Frozen and preserved gametes can be used for assisted reproduction. Freezing gametes does not negatively affect the effectiveness of assisted reproduction techniques.

Counselling and consent

Before starting the assisted reproduction process, the woman and the man will receive counselling. After that, a counselling report is prepared and consent for assisted reproduction is obtained.

Legal foundations and consequences of assisted reproduction

The legal foundations and consequences of assisted reproduction are established by the Artificial Insemination and Embryo Protection Act (KVEKS), which can be found at: https://www.riigiteataja.ee/akt/1048155?leiaKehtiv.

According to § 84 subsection 2 of the Family Law Act, the court does not establish the donor of the sperm used for assisted reproduction as the father of the child.

For any questions or additional information, please consult your treating physician or midwife.

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