

# DESCRIPTION OF TREATMENT WITH METHODS OF ASSISTED REPRODUCTION AND OVARIAN STIMULATION

**ASSISTED REPRODUCTION PROCEDURES.** This is the name given to the medical activity of collecting gametes (eggs and/or sperm cells) in order to obtain a pregnancy in a woman or to donate them to an infertile couple. Fresh egg and sperm cells are used as well as those collected previously and frozen for storage. The simplest procedure is **intrauterine insemination (IUI)**, in which the prepared semen is put directly inside the woman's uterus, without retrieving egg cells from the woman's ovaries. More complicated procedure is **in vitro fertilization (IVF)** in which egg cells are fertilized under laboratory conditions and the resulting embryos are transferred to the woman's uterus during an **embryo transfer** procedure. Most often, gametes are collected through the so-called **partner donation**, which means using a woman's egg cells and her partner's semen. It is also possible to use semen or egg cells from an anonymous donor, i.e. a person who has decided to donate all or part of the gametes collected from them to another person with whom they are not in a relationship (**non-partner donation**). When the transferred embryo is created from both male and female gametes from an anonymous donor, this is called **embryo donation**.

If a man or woman's health and other circumstances indicate that they may lose fertility in the future, gametes may be collected from them **to preserve fertility in the future** - that is, gametes may be collected, frozen and stored. The Act on Infertility Treatment of June 15, 2015 (Journal of Laws of 2015, item 1087, as amended), together with the regulations, set out in detail the conditions and requirements for carrying out assisted reproduction procedures, including the scope of mandatory laboratory tests and the dates they are due, required consents and patient statements. Their scope varies depending on the type of procedure and the clinical condition of the patients. Treatment with assisted reproduction methods has also legal consequences for gamete donors, the child born as a result of these procedures, and the child's parents. They are available on our website ([www.polmedis.pl](http://www.polmedis.pl) tab *Warto wiedzieć/ Dokumenty do pobrania* [*in English: Please note / Documents to download*] the file [Skutki prawne procedury medycznie wspomaganey prokreacji oraz informacja i ochronie danych osobowych](#) [*in English: Legal consequences of medically assisted procreation procedure and information on personal data protection*] and on the information board in the waiting room. The document includes information on how personal data is collected and protected, on security measures leading to data protection, and about medical confidentiality. Each patient and couple undertaking treatment with the use of assisted reproduction methods is asked to get familiarized with the content of the above documents, which they confirm with their signature put on consents to treatment. The doctors at our centre will explain the legal complexities to you. It is important to note, that these regulations apply to all patients regardless of the source of their funding.

Collection of egg cells, semen and the testicular biopsy procedure are performed under short intravenous anaesthesia.

- 1 ANESTHESIA FOR GAMETE RETRIEVAL PROCEDURE.** Laboratory tests are performed and medical history is taken thoroughly for the purpose of anaesthesia. Based on these, the doctor pre-qualifies the patient for anaesthesia, which may require additional tests/examinations and medical consultations. At this stage, if you have any questions or concerns about the anaesthetic, you should inform the medical team and arrange to speak to the anaesthetist. Immediately before anaesthesia, the anaesthesiologist will take a medical history and decide whether to perform anaesthesia or to postpone it. The procedure is performed under short intravenous anaesthesia and takes about 10-20 minutes. During the procedure the patient is under the care of an anaesthesiologist who monitors the correctness of his/her vital functions and at this time the doctor takes material from the ovaries or testicles in order to isolate gametes from it. Complete psychomotor efficiency returns after about 60 minutes after the procedure. After about two hours of observation, the patient may go home with an accompanying person; you may not drive a car or make important decisions on the day of anaesthesia. In case of suspected complications, the patient is referred to the Hospital. Sometimes you will experience nausea or vomiting, a feeling of thirst and dry mouth after the procedure. In case of pain you can take painkillers: Panadol, Apap, Ketonal, Paracetamol, Pyralgina.  
Preparation for anaesthesia. The patient must arrive for the procedure on an empty stomach, i.e. do not eat or drink anything and do not chew gum for 6 hours before the procedure. Just before the procedure, you should go to the toilet and empty your bladder.  
Complications. Complications are rare. Most commonly they include blood pressure abnormalities, unexpected allergic reaction to administered drugs, nausea, vomiting. In the literature, fatal cases have been reported as very rare.

- 2 COLLECTION OF SEMEN.** Semen may be collected for the purpose of insemination, for use in an in vitro fertilization procedure, for future fertility preservation or

for another infertile couple. The semen donor may choose to freeze and store some or all of the collected sperm cells, or donate them to another infertile couple if the criteria are met. A semen sample is to be collected by masturbation in a room designated and prepared for this purpose. A man may be accompanied by his partner while producing semen. The entire ejaculate, if possible, should be placed into a sterile container. The ejaculate delivered outside the container must not be placed inside it. It is also possible to produce semen at home, and place the sample only in containers provided by your clinic. In this case, the container with the semen sample should be kept in body temperature (e.g. in a pocket) and can only be submitted by the person who produced the semen, or his partner. In case of retrograde ejaculation (ejaculation of semen into the bladder), you should urinate into a sterile container after masturbation. If there is no sperm in the semen, it can be collected from the testicle or epididymis by **testicular biopsy**. The testicular biopsy procedure involves puncturing one or two testicles with a needle and aspirating the contents into a syringe. The material is sent to a laboratory. In the laboratory the sperms are searched for in the biopsy sample.

Preparation for semen collection 3-day sexual abstinence is advisable, but not strictly necessary. Definitely, excessive exercise, alcohol and other stimulants, hot baths and saunas should be avoided in the days before semen production. Deterioration in semen quality can also be caused by recent infections. Therefore, these should be avoided before the scheduled semen production.

Complications after testicular biopsy - the most common complication is a testicular hematoma at the site of injection, an infection. In the event of presence of disturbing symptoms after the surgery, suggesting the occurrence of complications (severe abdominal pain, increasing testicular pain, enlargement of the testicles, temperature, significant bruising of the testicles) the patient should immediately go to the hospital and contact the Centre.

Preparing the semen, also known as semen preparation, includes a number of methods to select the sperm with the best performance parameters and the best fertilization potential from the semen, as well as to properly rinse them to avoid anaphylactic (allergic) reactions after semen administration. The preparation of semen in an in-vitro procedure may involve a number of additional processes to obtain the best sperm.

### 3 **EGG CELLS RETRIEVAL.** Egg cells may be collected for use in an in vitro fertilization procedure, for future fertility preservation, or for another infertile couple.

The egg cells donor may choose to freeze and store some or all of the collected egg cells, or donate them to another infertile couple, if the appropriate criteria are met. Generally, egg cells retrieval is preceded by ovarian stimulation. **Ovarian stimulation** aims to prompt the ovaries to produce ovarian follicles containing egg cells. Usually, between several to less than twenty ovarian follicles are produced as a result of stimulation. During stimulation, a woman takes medications called gonadotropins which cause the ovarian follicles to grow, and drugs inhibiting follicular rupture, called analogues. The course of therapy is repeatedly controlled (every 2-3 days). Based on ultrasound examination and assessment of blood estradiol levels, the dosage of gonadotropins is modified. Sometimes the response to the medications is too weak or too strong and treatment must be stopped. Analogues are started at different stages: in the so-called long protocol even before starting to use gonadotropins, in the short protocol from 1<sup>st</sup> – 2<sup>nd</sup> day of the cycle, and in the protocol with an antagonist during the use of gonadotropins. Both gonadotropins and analogues are administered by subcutaneous injection, usually every day. Sometimes other medications are also used depending on the woman's health situation. When the follicles in the ovaries reach the appropriate stage of maturity (18-20 mm in diameter), which usually takes place after 7-14 days of taking gonadotropins, the patient receives an injection to trigger the maturation of egg cells. About 36 hours after this injection, a follicular puncture and egg cells retrieval procedure called ovarian puncture takes place. Before starting stimulation or preparing for embryo implantation, both partners should have up-to-date laboratory tests, the extent of which is determined by the doctor. In some cases, there is no ovarian stimulation before egg retrieval but only monitoring of the cycle. In this case you can count only on one egg cell.

In the event that previously frozen egg cells from the patient or from an anonymous donor will be used and fresh egg cells will not be collected, ovarian stimulation is not performed. In this situation, the cycle monitoring is performed to determine the day of ovulation or medications are given to prepare the endometrium for embryo implantation.

Egg cells retrieval - puncture Egg cells are retrieved from a woman most often in an in vitro fertilization procedure to create an embryo. They may be collected to preserve fertility for the future - they are then frozen and stored. The patient may decide to use a certain number of the collected egg cells to create an embryo, and store or donate the remaining eggs to another infertile couple. The egg cells retrieval procedure involves puncturing the ovaries through the vaginal vault, under ultrasound guidance, and aspirating the follicular fluid with a needle. Egg cells are searched for in the follicular fluid and placed in a special medium. The number of cells does not correspond to the number of ovarian follicles. It may happen, that there will not be a single egg cell or they may be immature, which is a rare situation. After the procedure, partners should refrain from sexual intercourse; the patient should lead a sparing lifestyle.

Preparation for ovarian puncture (egg retrieval) The patient should not eat, drink anything or chew gum (fasting) for 6 hours before the ovarian puncture. You should take your medication with a little water. The patient should not take anticoagulants unless advised otherwise by the doctor. Do not drink alcohol or use

narcotic drugs on the day of the ovarian puncture or the day before.

Complications after ovarian puncture. In the event of occurrence of disturbing symptoms after the surgery (severe abdominal pain, pain in the collarbone area, fever, fainting, bleeding from the genital tract, rapid heartbeat, dizziness, urinary and stool urgency) the patient should immediately contact her treating physician or the nearest gynaecology department. This may indicate bleeding from the punctured ovary into the abdominal cavity and require surgical treatment. Persistent lower abdominal pain, general unwellness and high temperature in the days following the egg retrieval surgery may indicate inflammation in the abdominal cavity, which requires hospitalization. The above complications are rare (less than 0.5% of cases). Very rare complications include damage to internal organs (intestine, ureter, bladder). The literature reports isolated cases of complications that, as a result of their late diagnosis, led to death.

4 **INSEMINATION AND OVARIAN STIMULATION** is a method that has been widely used for many years. It involves injecting semen into the woman's body. It can be administered into the cervix or into the uterine cavity (intrauterine insemination). The latter is considered the most effective (about 12% per cycle). In certain situations, insemination is performed with semen from an anonymous donor. Sperm is deposited into the uterine cavity using a thin catheter. The procedure is short and painless. This method requires the presence of at least one unobstructed fallopian tube. It can be performed in a natural cycle (to obtain a single follicle) or in a pharmacologically stimulated cycle - which results in the growth of 2-3 follicles. Inseminations in a stimulated cycle are thought to be more effective. The day of insemination must be synchronized with ovulation; spontaneous or pharmacologically provoked. In order to best schedule the date of insemination it is necessary to **monitor the cycle** - that is, to observe the growth of ovarian follicle(s) and other changes in the reproductive organ (e.g. endometrial thickness, cervical mucus). When the follicle(s) have reached the appropriate size (18-20 mm in diameter) the ovulation is provoked pharmacologically or ovulation tests are used to determine the day of ovulation. Insemination is performed as soon as possible before or after ovulation has occurred. Pharmacological stimulation increases the effectiveness of the procedure. However, it carries an increased risk of multiple pregnancy and the occasionally occurring mild hyperstimulation syndrome (**see below for symptoms of hyperstimulation syndrome**). In case of risk of hyperstimulation syndrome, excessive risk of multiple pregnancy (usually when the growth of >3 ovarian follicles is observed), the doctor may decide to stop the procedure and not perform insemination. An excessive response to stimulation may require hospitalization, or even a surgical procedure. According to some researchers, intrauterine insemination is associated with a higher risk of ectopic pregnancy and miscarriage. The risk of fetal abnormalities after using this assisted reproductive technique is similar to that of the population of naturally conceived fetuses. However, the risk of having a child with defects increases with certain medical conditions and also rises with the age of the mother. According to the recommendations and guidelines of the Polish Gynecological Society, in pregnancies obtained by assisted reproduction techniques, patients should be recommended to undergo non-invasive prenatal testing regardless of age. In case of failure, often after a stimulated cycle, menstruation is more abundant and painful.

5 **IN VITRO FERTILIZATION (IVF)** is a method of infertility treatment that involves fertilization of an egg cell outside the woman's body, development of embryos in laboratory conditions and transfer of embryos into the woman's body. Effectiveness of the procedure calculated as obtaining a clinical pregnancy (presence of gestational follicle in the ultrasound image) is about 35%. It depends mostly on the age of the patient.

Therapy consists of the following stages:

- Preparing a woman for egg cells retrieval - **ovarian stimulation**- discussed above
- Collection of egg cells by puncture of the ovaries under short general anaesthesia - discussed above
- Semen collection - discussed above
- In vitro fertilization and embryo culture
- Transfer of embryo into the uterus – embryo transfer

#### **In vitro fertilization (IVF)**

The collected egg cells are stored under appropriate conditions in an incubator. Approximately 2-6 hours after eggs retrieval, an appropriate amount of the partner's semen, specially prepared, is added to them, or a single sperm is injected into the centre of the egg cell - the ICSI (Intracytoplasmic Sperm Injection) procedure. After 18 hours, it is assessed under a microscope whether fertilization has taken place. As a rule, about 70% of the egg cells are fertilized and more than 90% of the fertilized cells divide and develop.

#### **Embryo transfer**

On 2nd-3rd or 5th day after egg retrieval, the embryos are inserted into the uterine cavity using a plastic tube - special catheter. 1-2 or sometimes 3 embryos are transferred. This procedure is painless and does not require anaesthesia; it is performed with a full bladder to facilitate the transfer by straightening the uterus.

After the transfer, the patient remains in the gynaecological chair for about 5 minutes. The implantation of the embryo in the uterine cavity is supported by hormonal medications. From the day of egg retrieval (puncture) until the 12th week of pregnancy or - in case of failure - until the onset of menstruation, hormonal medications - mainly progesterone - are administered. If the embryo implantation in the uterus progresses well, then urine pregnancy tests will be positive at the latest after 14-17 days after the day of embryo transfer.

**Complications** Hormonal stimulation, and the resulting increase in blood estradiol levels, may, especially in predisposed patients, increase the risk of thromboembolic complications that can threaten a woman's life and health. It is therefore important to inform the physician of any coexisting diseases and health problems in the past, and to reduce exposure through appropriate health-promoting behaviours - reducing excess body weight, stopping drug substances, and in particular quitting smoking - before you start preparing for the procedure. In justified cases, preventive use of anticoagulants is necessary already at the stage of stimulation.

Some sources report, that repeated, especially ineffective hormonal stimulation, by producing a state of chronic hyperestrogenism, may increase the risk of certain cancers in women in the future - particularly breast cancer (estrogen-dependent) and ovarian cancer. It remains an open question whether the risk factor for cancer is infertility per se, the therapy, genetic predisposition, or a combination of all of these factors.

**Hyperstimulation syndrome.** Some patients (1-2%) develop hyperstimulation syndrome during hormonal therapy, i.e. an excessive ovarian response to administered drugs, which is manifested by the formation of sometimes large ovarian cysts, leakage of fluid into the abdominal cavity, and a decrease in urine output. This is accompanied by pain and enlargement of the abdominal circumference, sometimes nausea, vomiting, difficulty breathing (dyspnea) and diarrhea. They may require treatment (e.g. administration of human albumin solution) or even hospital treatment. The cysts disappear after 2-5 weeks of pregnancy or during menstruation. Patients at risk for this syndrome, during stimulation must discontinue therapy and follow the recommendations of the stimulation physicians. The occurrence of such a risk does not exclude the patient's chances for the therapy and pregnancy, it indicates an increased ovarian response to stimulation medications and is a threat to the patient's health.

**Fetal malformations.** No higher incidence of fetal abnormalities was found after the use of assisted reproductive techniques mentioned above. The incidence of fetal malformations is similar to that of the population without fertility problems and is approximately 2-3%. The incidence of chromosomal aberrations, e.g. Down's Syndrome, is also comparable to the healthy population and increases with the age of the mother. Therefore, in the case of patients over 35 years of age, prenatal testing between 11 and 14 weeks of pregnancy is recommended. The possibilities of fetal abnormalities also cannot be excluded.

However, it has been found in recent years, that chromosomal aberrations are more common after ICSI procedures - about 1.5% (in the general population about 0.5%). It is therefore recommended that prenatal testing be performed in all patients undergoing ICSI procedures regardless of age. As a result of the treatment, multiple pregnancy, ectopic pregnancy (approx. 0.3%) and miscarriage (approx. 10-20%) may occur.

## 6 FREEZING, THAWING OF EMBRYOS AND GAMETES.

Unused ( surplus ) embryos, egg cells and sperm cells can be frozen and stored at liquid nitrogen temperature. Gametes and embryos are treated with chemicals (cryoprotectants) prior to freezing to prepare them for the freezing process. Storage time was not found to affect the quality of gametes and embryos. During the thawing process, gametes and embryos are also treated with chemicals to restore their vital processes. About 80 % of egg cells and embryos survive the freezing and thawing process. For sperm, the percentage is about 50%. No higher percentage of defects was found in children born from pregnancies obtained after thawing gametes and embryos than in those conceived naturally. Obtaining a pregnancy after thawing egg cells is possible only by in vitro fertilization, and in the case of sperm also by insemination. In case of poor semen parameters before they are frozen, in vitro fertilization is the method of choice. The chances of getting a pregnancy using frozen eggs are lower than from freshly retrieved egg cells.

## 7 INFORMATION FOR OF GAMETE DONORS FOR NON-PARTNER DONATION - TO ANOTHER INFERTILE COUPLE.

A physically and mentally healthy adult person who has the right to perform legal actions may become a Donor. During a medical visit, the doctor makes a preliminary qualification of a candidate and orders additional laboratory tests, including genetic tests. Gamete retrieval is performed in the same way as described above. On the day of gamete collection, the donor must perform the required laboratory tests. Evaluation of the collected cells decides about their quality and applicability. Finally, the normal results of the laboratory tests performed on the day of gamete collection allow the cells to be used. The couple intending to use gametes or embryos from anonymous donors will be disclosed the following data: blood group, eye colour, hair colour and shape, height, weight, body build, race and ethnic group and the results of laboratory tests carried out on the donor. The legal consequences, the scope of information about the donor and how it can be obtained by a person born as a result of non-partner donation or by his/her legal representative described in the document.

Legal consequences of the medically assisted procreation procedure and information on personal data protection are available on our website in the section *Warto wiedzieć / Dokumenty do pobrania [in English: Please Note / Documents to download]* and on the information board in the waiting room. According to legal regulations currently in force, the donor may receive reimbursement of costs set out in the Act on Infertility Treatment (qualifying examinations/tests, travel costs, costs of collecting the gametes, costs of medical visits).