

## What is In Vitro Fertilization?

In-Vitro Fertilization (IVF) is an assisted conception technique available to help infertile couples to have a baby. It involves giving the woman fertility drugs to stimulate egg production, and then retrieving the eggs (oocytes) from the ovaries. In the IVF laboratory the eggs are fertilized with the sperm and cultured in incubators. The embryos are then implanted into the woman's uterus, and if all goes well, a normal pregnancy is achieved.

## When is IVF recommended?

IVF is recommended in different circumstances:

- ❖ Obstruction or other fallopian tube disorders
- ❖ Severe male infertility
- ❖ Endometriosis
- ❖ Unexplained infertility, if duration of infertility exceeds 2 - 3 years
- ❖ Failure of conventional treatments
- ❖ Special programs: Egg or embryo donation  
Carrier / surrogacy  
Preimplantation genetic testing (PGT)

## What is the success rate?

Even if good quality embryos are transferred into the uterus, there is no guarantee that the procedure will be successful. Most embryos with normal development in the lab will not implant or will not develop into the uterus. Good quality blastocysts may have abnormalities and will be eliminated from the uterus through a natural selection process. Most patients will become parents through IVF, but it may take several attempts (IVF cycles) to achieve pregnancy.

Young fertile couples trying to achieve pregnancy have a 20% success chance after the first month of unprotected intercourse, 57% after 3 months and 90% after one year.

With IVF, if the woman is under 35 years old, she has more than 50% chance of getting pregnant in the first cycle. After this age, egg quality significantly lowers every year; after 40 years old, success rate drops below 10%. Risks of spontaneous abortion or foetal abnormalities increase with age, due to the same reason.

In Europe, the average clinical pregnancy rate after one fresh embryo transfer is 34-35%. The Gynera Clinic makes every effort to ensure best chances for success, as confirmed by consistent annual clinical pregnancy rates of more than 45% per fresh embryo transfer, during 2007-2017.

The IVF procedure helps embryos to reach the uterus, but cannot control their subsequent development. As in spontaneous pregnancies, miscarriages (20%) or ectopic pregnancies (2%) may occur.

## What we need to do before IVF?

### Lifestyle optimization

First step to improve fertility and IVF success chances is lifestyle optimization, including elimination of risk factors (smoking, obesity, sedentary life and other potential factors identified by the reproductive specialist).

### Investigations

Prior to IVF, investigations are required to identify conditions that may affect the outcome of the treatment or may increase the risk. These include, but are not limited to: hormonal tests, semen analysis, preoperative screening, infectious disease tests, PAP test, cervical culture, vaginal ultrasound and uterine cavity assessment. Some tests for infectious diseases are repeated during IVF procedure, according to regulations in force.

Women who are not immune to infectious diseases that may affect pregnancy (Rubella, Varicella), may consider immunisation before pregnancy and postponing IVF procedure at least 1 month after vaccination.

In case of healthy carriers of hepatitis B or C virus, procedures can be performed within the couple. Additional precautions and quarantine cryopreservation of cells / embryos are required in this situation.

Patients with chronic or uninvestigated infectious diseases (hepatitis, lues-syphilis) are advised to get an assessment and a medical opinion from the specialized physician before starting IVF.

### Consultation with the reproductive specialist

After completing investigations and information, both partners discuss with the specialist the details of the treatment plan, options and limitations and sign the informed consent.

Some conditions may decrease the chance of success and may require investigation and surgical treatment before starting IVF. Such conditions are: ultrasound visible hydrosalpinx (blocked fallopian tube filled with fluid), large or symptomatic intrauterine polyps, submucosal intrauterine fibroids, uterine synechiae (adhesions).

The patient may refuse treatment prior to the IVF procedure, if she assumes the potential consequences.

## What to expect from an IVF cycle?

### Ovarian stimulation

The main purpose of ovarian stimulation is to obtain multiple oocytes (ideally more than 8-10), to allow further selection of viable embryos. The medication used is complex, covering also other objectives: oocyte maturation, prevention of spontaneous ovulation and other risks, hormonal support of embryo implantation.

Treatment protocols are adapted to individual characteristics and may take 2 to 3 weeks. Fertility medication may be administered at home, by daily subcutaneous injections. Pretreatment or support treatment is usually added, as well.

Stimulation starts at the beginning of menstrual cycle. If, following stimulation, the ovaries have a low response (less than 3-4 growing follicles), the retrieval can be canceled. The ovarian response may be different after a new stimulation, attempted in another cycle.

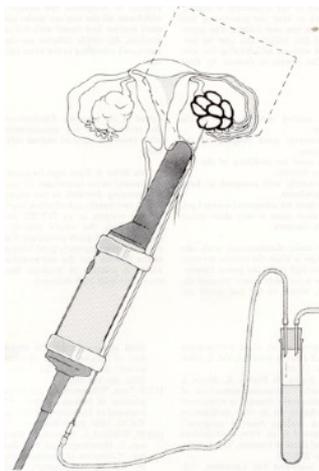
Treatment is monitored by ultrasound and hormone tests to assess ovarian response, possible risks and to determine the duration of treatment, in order to get an optimal number of mature oocytes.

The most important risk of ovarian stimulation is ovarian hyperstimulation syndrome (excessive ovarian response to stimulation, accompanied by high levels of oestrogen and increased vascular permeability). Main symptoms are bloating, abdominal pain, shortness of breath, fluid collection in the abdomen. In severe cases, hospitalization, i.v. therapy, or aspiration of abdominal fluid may be needed. If pregnancy occurs, symptoms are increasing in intensity and last longer. Severe symptoms occur in less than 1% of cases. The risk can be reduced with a freeze-all strategy (cryopreservation of all embryos and transfer in an unstimulated cycle).

Other associated risks are: headache, abdominal discomfort, injection site discomfort, allergic reactions, nausea, shortness of breath; seldom, severe adverse effects such as thrombosis (blood clots), ovarian torsion.

The risk of genital cancers is increased in all infertile women, even in the absence of fertility treatments; there is no evidence that medication would further increase this risk, according to current scientific knowledge.

When most of the follicles are large enough, according to monitoring criteria, medication is given to trigger the final maturation of oocytes before aspiration.



### Oocyte and Sperm Retrieval

Oocyte retrieval is performed by ovarian puncture, under local or intravenous anaesthesia. With a special needle connected to the suction system with controlled pressure, the follicular fluid containing the oocytes is collected in test tubes and is immediately analyzed by the embryologist, in a controlled environment. During retrieval or during treatment, unforeseen events, associated medical conditions or complications may occur requiring additional and/or different procedures than those described above (cyst aspiration, hydrosalpinx aspiration, treatment of bleeding by suture or transfusion). In this case, the doctor acts accordingly, as required in his professional judgement, if there is no restriction specified in the informed consent.

The procedure takes 30 minutes and discomfort is minimal.

Complications of egg retrieval as bleeding, urinary retention, or genital inflammation which may require surgery or blood transfusion are very rare. Abdominal tension, mild cramps or vaginal bleeding are common and do not require treatment. Most patients leave the clinic after one hour, but should not drive after sedation.

Sperm is usually collected by masturbation, but other methods may be needed to recover sperm (from testis or post ejaculatory urine). If producing sperm on the day of egg retrieval may be challenging, sperm freezing in advance should be considered.

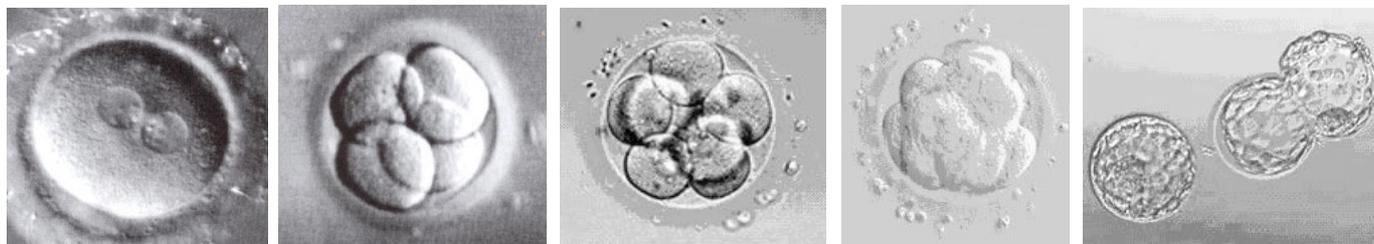
### Insemination & Fertilization

Some of the most important events in IVF cycle occur behind the scenes, in the laboratory. Insemination of the eggs with sperm is followed several hours later by fertilization, when the sperm enters the egg (standard IVF).

After fertilization, the egg looks like a cell with two nuclei, called pro-nuclei (2PN stage).

The pro-nuclei join or fuse within a few hours and the fertilized egg can begin cleaving, or dividing, first into two cells, then into three or four cells.

Embryo transfer may be scheduled at 48-72 hours after egg retrieval, when embryos have 4 to 10 cells, or culture may be extended to 5-6 days, allowing embryos to reach the blastocyst stage.



24 h - Fertilized egg  
2PN

48 h - 4 cells embryo

72 h - 8 cells embryo

Day 4 - Morula

Day 5 blastocyst - left  
Hatching blastocyst - right

Evolution of embryos in the lab is a continuous process of natural selection: some oocytes will fail to fertilize and many embryos will develop abnormally. The selection process continues into the uterus; less than half of the embryos with normal development in the lab will implant, the chance for a successful pregnancy being associated with woman's age.

Extensive culture of embryos for more than 72 hours may give valuable information about developmental potential and allows a more efficient selection of viable embryos. On average, 40% of Day 3 embryos reach, after two more days, the blastocyst stage (implantation stage).

The development of embryos in the lab depends on the quality of reproductive cells collected in that specific cycle and does not always meet expectations or wishes. It is possible that no viable oocytes are found in the aspirated follicular fluid, oocytes may not fertilize or no viable sperm cells are found in the semen. The embryo transfer may also be cancelled if all the embryos develop abnormally in the lab.

Only viable embryos (according to validated scientific criteria) can be utilized in assisted reproduction. Unfertilized cells as well as unviable embryos are discarded or may be used for research.

Micromanipulation techniques may be used in some case. ICSI (intracytoplasmic sperm injection) is a procedure developed to help couples with male factor infertility, previous low or failed fertilization cycles. With ICSI, one sperm is physically injected into the center of the egg, in order to increase the chances of fertilization.

P-ICSI is a variant of ICSI when a special media is utilized for sperm selection. Other micromanipulation techniques (assisted hatching, embryo biopsy) may be recommended in specific situations, according to current scientific knowledge.



## Embryo Transfer

Intrauterine transfer of embryos is usually a painless procedure. Embryos are inserted into the uterus with a special thin catheter under ultrasound control.

The number of transferred embryos is decided by the medical team, based on several parameters and considering the wish of the couple, as well. A higher number of embryos increases the probability of success, but also the risk of multiple pregnancy. We recommend single embryo transfer in women under 35 years old; spare embryos may be cryopreserved. In older women, repeated implantation failure or low quality embryos, transfer of two embryos may be considered to increase probability of success.

Twin pregnancy is not excluded even after single embryo transfer (embryo may naturally divide into two ones).

After transferring the embryos into the uterus, implantation and further development cannot be influenced anymore. The quality and development potential of embryos are the most important variables for the final outcome.

Patients may resume normal activity after embryo transfer, but avoid vigorous physical activity, hot tub baths or sauna.

Progesterone supplementation is recommended during this period, to prepare uterus for implantation. Abdominal tension, mild cramps or vaginal bleeding are common after embryo transfer.

In frozen embryo transfers (FET), the transfer may be performed in the same day with thawing or after culturing embryos for more days, according to embryo developmental stage.

## Embryo cryopreservation (Freezing)

Embryo freezing is recommended if spare viable embryos are available, or if intrauterine embryo transfer involves risks (ovarian hyperstimulation syndrome, intercurrent medical condition, non-receptive uterus that reduces the probability of success).

Frozen embryo transfers (FET) have similar success rates to fresh embryo transfers. Not every cryopreserved embryo will resume development after thawing, but more than 90% of them survive the freezing/thawing process.

FET cycles need monitoring to choose the most favourable day for implantation and to synchronize uterine receptivity with embryo development stage. Ultrasound scan and hormone tests are used for cycle monitoring.

The embryo transfer after thawing is done in a natural cycle, if the hormonal environment is balanced or in an artificial cycle (controlled by medication). The purpose of medication in FET cycles is to create a balanced hormonal environment needed for uterine receptivity and implantation. Medication mimics the natural cycle hormone levels.

## Outcomes and alternative options

Pregnancy test ( serum beta hCG) is scheduled 10 to 14 days after embryo transfer.

An increasing level of beta hCG confirms implantation and a biochemical pregnancy. Two weeks after a positive pregnancy test, ultrasound scan may be scheduled to visualize the gestational sac and confirm clinical pregnancy. If the pregnancy test is negative, bleeding is expected during next days. A follow-up consultation with the physician should be arranged to analyse the procedure and discuss further treatment options.

If probability of IVF success with own oocytes is considered too low (age over 42 years, repeated implantation failure), or treatment risks are not undertaken, alternative treatment may be considered: IVF with donor oocytes, adoption, remaining childless. In severe male factor, donor sperm may be used for IVF or IUI (Intrauterine insemination).

## IVF Pregnancy

Pregnancy after IVF is very similar to natural pregnancy. The same risks and complications may occur, especially in women over 37 years old.

- ❖ Multiple pregnancy (twins) involves additional risks, including miscarriage or foetal prematurity. Blastocyst transfer is associated with a slightly increased risk for monozygotic twins (identical).
- ❖ The risk for miscarriage is about 20-25%, slightly increased compared to natural pregnancy (15–20 %)
- ❖ Ectopic pregnancy occurs in 1-2% of cases — embryos may migrate and implant outside the uterine cavity
- ❖ IVF pregnancies are associated with slightly increased obstetric risks - maternal hypertension, placental abruption (early separation from the uterus), gestational diabetes. Risks are lower after frozen embryo transfers.
- ❖ Medical studies performed so far show a slightly higher risk of foetal abnormalities in IVF babies compared to naturally conceived babies (2-3% of pregnancies). The risk is increased with age and when ICSI was performed for severe male factor. Cryopreservation is not associated with increased risks of abnormalities.

Undergoing IVF or other assisted conception procedures can be emotionally and physically draining, especially when pregnancy is not achieved. Infertile couples are often experiencing depression, anxiety, relationship issues. It is important to seek help from health professionals or contact a fertility support group; talking with others who can empathize with these experiences can also be helpful.

Fortunately, most couples will become parents, even if not always from the first attempt. There is real hope for everyone and it's worth making every effort. Success formula is represented by early seeking for professional help, perseverance and, sometimes, acceptance of alternative options.

